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| **Podcast** | “The reason why I was doing science all these years is because I just love doing it.” Medicine laureate Victor Ambros grew up on a farm with seven siblings. Throughout his career, he has seen collaboration as a crucial part of science.  In this podcast conversation with Adam Smith, Ambros talks about his scientific journey and how much his father has influenced him. He also shares his experiences on imposter syndrome and gives some advice on how to deal with it.  This conversation was published on 12 June, 2025. Podcast host Adam Smith is joined by Karin Svensson.  Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.  Victor Ambros: I think I’ve learned that if there’s something peculiar, new, unusual and unprecedented, it is almost certainly part of some broader phenomenon.  Adam Smith: How can you be on the lookout for something that you are not expecting to find? In Victor Ambros’ case, he discovered a mechanism for silencing genes in the worm. He was studying that at the time he thought might just be a peculiarity of his worms, but turned out to be of central importance for biology. Now there are many drugs in clinical trials based on that finding. But this question of how you keep your eye out for something, but you dunno what it is central to the stories of so many Nobel Prize laureates and great scientists in general. So please join me for this conversation with Victor Ambros, where we might learn something about what it is that makes you the sort of person who can spot the unexpected.  Karin Svensson: This is Nobel Prize Conversations and our guest is Victor Ambros, recipient of the 2024 Nobel Prize in Physiology or Medicine. He was awarded for the discovery of microRNA and its role in post transcriptional gene regulation. He shared the prize with [Gary Ruvkun](https://www.nobelprize.org/prizes/medicine/2024/ruvkun/facts/). Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundacion Ramon Areces. Victor Ambros is the Silverman professor of natural sciences and a professor of molecular medicine at the University of Massachusetts Chan Medical School. In this conversation, he speaks about growing up on a farm with seven siblings, his knack for upcycling bad and broken guitars into serviceable instruments and the mysterious and important silencer at the center of his Nobel Prize-awarded research. But first, he talks to Adam about the uncomfortable art of receiving a prize.  Smith: You speak very interestingly about the award of prizes to individuals. You have emphasised in so much that you’ve said about the importance of teamwork in science and the sort of social nature of it and the collaborative nature of it. The focus of attention on you as a Nobel Prize laureate is very great. How do you feel about it?  Ambros: I had so many prizes that I’ve had practice of kind of trying to reconcile of the way I view myself, and then how the prizes seem to represent a viewpoint about me that I think is exaggerated. But I’ve come to understand that, ‘Victor, it doesn’t matter if you think you don’t deserve this prize? All these other smart people do. So your job is to be gracious and try to do the best you can out of the circumstances’. Really, it’s an opportunity then to actually speak to how science is done, speak to the collaborative nature of it and the importance of circumstances. I’ve had a career where I’ve always seemed to end up in really great circumstances and great labs, and working on a project that ended up identifying microRNAs. But I didn’t choose the project because I thought it was going to come up with fundamentally new biology. I chose the project frankly because Bob Horvitz said, ‘this is a good project for your postdoc’. I said, ‘yeah, it looks interesting’. It’s like that kind of random walk leads you ultimately to a place like this. You have to acknowledge that I didn’t get myself here. Then I try to emphasise, the reason why I was doing science all these years is because I just love doing it. The goal was just to keep doing it. If your goal is to keep doing it, then you probably will achieve that goal. If your goal was to win a Nobel Prize, you’re not likely to do so. These are sort of obvious things in a way, these principles, but it’s perhaps helpful for younger scientists to be encouraged to just focus on what they can do.  Smith: Yes, it was a long project. At times it was more active, at times it was less active, but you certainly kept it in focus the whole time and put resources into it when you felt there was an opportunity. I think that sense of commitment is actually quite unusual.  Ambros: I work at an institution here at UMass Chan Medical School where up and down the hallway there are folks as dedicated and incredibly bright and have fantastic projects going. I think that’s what’s so important and encouraging about the scientific enterprise, is that there’s no shortage of talent, maybe a shortage of opportunity at various levels and so forth. The thing about the Nobel Prize and the way the Swedes pulled it off, is that you really felt intensely that this was a celebration of science, but a celebration of science for all the reasons how we understand science. It wasn’t like, ‘Oh, you’re the next Richard Feyman, so sign this book’. No, this is Victor Ambros signing this book. Let’s not make any illusions here. That’s what’s so cool about science, this random person can end up here.  Smith: That’s beautifully put. Has it felt like that all along? Have the various things that have happened to you since October, sort of fitted in with that?  Ambros: The spirit in Stockholm was all that. Actually, in my darkest hours, let’s say years ago, I might have thought, ‘well, what would it be like to win the Nobel Prize?’ Because people would come up to me and say something like that, and I would think, Jesus, that would be so scary, so awful. Because I would have to pretend, I’d feel like it was a lie? But instantly, when I walked onto campus that morning, everybody was so happy. Strangers were coming up to me. I realised what this is about. It’s about making people happy about science and about their institution. The University of Massachusetts got all excited. Everybody on campus was so genuinely happy for us, and happy for the institution. The state of Massachusetts is happy. So you realise, this is what it’s all about. I’m just the excuse for folks to be happy about being involved in science. The same thing in Sweden, and then we visited Washington, went to the Swedish Embassy down there. It was wonderful. In other words, it did not feel like a lie, which I was so happy about.  Smith: I remember students once boldly asking a laureate in Poland, ‘do you suffer more from imposter syndrome now that you’ve got the prize?’ The answer was yes and no but apparently in your case, the community’s happiness at your prize must be very sustaining.  Ambros: Yes. My imposter syndrome is better after this, and I don’t know why.  Smith: For all the reasons you’ve outlined.  Ambros: I think having a purpose. There was a purpose surrounding this Nobel Prize for me. The purpose is my voice could be heard when I make statements about how science is great and how scientists are wonderful, how there’s lots of talent but not enough opportunity. The kinds of things that I would kind of walk around mulling about previously. Now I could say something and people will listen. That gives you purpose. Maybe that’s the problem with imposter syndrome, is the disconnect between who you think you are and your apparent purpose.  Smith: I think when they choose laureates, I don’t think that any thought goes into what kind of ambassador they’re creating. It’s all about the science. But in your case, it’s a fantastic ambassador to create somebody who goes around and spreads that particular message, especially at such a time. This is a difficult time for science.  Ambros: Yes. This has been quite a thing because 7 October occurred before the election in the United States, right? There was still optimism. Then the election happened, and then that felt really bad and foreboding. When we were in Stockholm, people were talking about this, and I would say, ‘yes, it’s going to be real test for the States. We’ll see’. I was kind of slightly optimistic that we’d be able to manage things. But then when the new administration came into power, they just instantly started blasting away at everything.  Smith: All the thing we valued.  Ambros: Yes. The whole fabric of the US. We discovered that the way the US government works is based on human decency. That these guys, any of these presidents could have done all this before if they weren’t at least decent and took their oath to the Constitution seriously. These people are actually deliberately disruptive in the way that every authoritarian coup that we’ve ever seen across the globe. They got the manual right there on the resolute desk of the Oval Office, how to take over a country and develop an authoritarian regime? Maybe we shouldn’t be surprised at all they’re doing now that we understand the motivation. Now we’re in a situation where there’s a crisis of funding, and then there’s a tax on the universities. Totally unprecedented. We’re learning how to pull together in ways that we didn’t previously. I think there’s a sense that we’re going to figure out how to do this and reset, how to reset the country, reset our universities, and reset academia and so forth. Pharma, I don’t know about them, they have to figure out how to reset too, so that we’ll come back stronger after this.  Smith: That’s very hopeful because the initial kind of response, everyone was just reeling from it. A lot of people had so much to look after that they had to look after themselves a bit. But you are hopeful that there’s a community resistance building.  Ambros: Yes, that’s right. I’m hopeful about that. There are signs that that’s the case.  Smith: I suppose your status now puts you more front and center as a spokesperson for this. Are you happy to be that person?  Ambros: I’m not happy that Victor Ambros is that person, because he’s not particularly articulate. But I’m willing to do whatever I can and with guidance from others. I’m hopeful that as a community of, let’s say Nobel Prize laureates, we can have a voice. We’re exploring how to do that. We’ve all reaching out through letters and so forth to Congress and to the public. There’s that happening. But those are gestures where there’s a letter signed by 2000 scientists that’s in the category of “you better say something”. Because if you don’t, what does that mean? We don’t have the illusion that any one gesture or one thing is going to sway anything. So there’s an acceptance of the fact that this is going to take some time by reiterative and perhaps building resistance, public resistance from different quarters repeatedly, and growing voices. It’s going to take time to do that.  Smith: It’s interesting that you point out that one could come back stronger, that there could be benefit at the end of all this.  Ambros: We have to. There’s no choice. Because what’s the other thing you say? Well, let’s give up on the USA, we’re not going to do that. Hell no. This is our country. It’s not theirs, obviously, because they don’t accept the basic premise that we are the Constitution. It’s not theirs. They can’t take it from us. That’s the attitude we have.  Smith: Just in passing, it reminds me of a line in a Laurie Anderson song. She says ‘Our America, you saw it, you tipped it over and you sold it’. That kind of encapsulates the approach it occurred to me.  Ambros: Because the thing is, the US is a terrible country in so many ways. What we’d spend our lives trying to do is to make it better. If you spend your life trying to make it better and really always having hope that it can get better and seeing signs of how it can, and that we make these steps, then that’s what our investment is. That’s how we acquire ownership of a country. That’s what I mean by it’s our country. It’s not like I say, ‘Oh, everything about the US is exactly the way I’d want it to be. That’s why I say I own it’. No, it’s because we’ve been the ones who’ve been trying for decades to make this country better and better and be what it can be? Now these guys come in and sort of tip it all over. That’s just unacceptable. Somehow we have to succeed in resisting,  Smith: I guess it’s good to be reminded what you’re about once in a while.  Ambros: Yes, trying to get better, not trying to get worse.  Smith: Pretty simple. When you speak so nicely about teamwork and collaboration, one has to mention that you grew up in quite a team. It’s pretty unusual to be one of eight children these days. It must have been quite an experience. What’s it like growing up amongst seven siblings?  Ambros: It was a farm in Vermont, so the closest neighbours were quarter mile away. We were on our own a lot, although we had a lot of chores around the farm, so I milked the cow every day. It was a big family, so there’s a lot of kids around. You didn’t get much personal attention. I really valued time hanging out with my dad, I admired him a lot and I learned a lot from him. He’s very handy, and could fix and build anything. He’s like a hero of mine. Even though I was in a large family, I would have some time with him hanging out, helping and stuff like that. Then there would be a lot of time for solitude, where you just go wandering in the woods. Believe it or not, I had a gun so I could go out and shoot things with that gun.  Smith: That does sound like boys heaven.  Ambros: Yes.  Smith: What did you shoot?  Ambros: I would shoot at things, but never really hit them.  Smith: Your parents had immigrated to the US from Poland?  Ambros: My dad did. My mom was American.  Smith: He’d had a horrible and incredibly difficult war.  Ambros: Yes. We always felt like daddy never had the opportunity that he deserved. Our opportunities, by contrast, were really great. Therefore we had to achieve. That was sort of the sense, because his education was stopped in high school when the war broke out. Then he was a slave labourer for Nazis for three years or something. He never got back to school. But he taught himself languages and he was very well read. Just briefly, I remember talking to him about Anna Karenina, the book that I’d read when I was like 65 years old. The first time I read it and I said, ‘Oh, this is an awesome book’. I went to my dad and he said, ‘yes, I read that book’. We started talking about it and we started talking about scenes in the book with beautiful description, unbelievable invoking these movies in our head. And I said, ‘When did you read that?’ He says, ‘When I was 20 or something’. He had read it in Russian. So the two of us were talking about the same book. I had just read it and he had read it 50 years before in a different language. An amazing experience. So that was the kind of person he was. He had an incredible memory and very widely read. When I was growing up, I was thinking, ‘I’ve got to show daddy that I’m really taking this opportunity that he’s given us and really going with it’.  Smith: It’s a lovely reversal of something that often happens with parents where they tell their children, we didn’t have the opportunities you’ve got, and the children squander the opportunities. But in your case, it was different. The children seemed to be telling the parents, we didn’t get your opportunities, so we’ve going to make use of it.  Ambros: To be fair, he did sit me down, like when I’d screw up. He’d sit me down and say, when I was your age…  Smith: Well, it worked in your case.  Ambros: Yes, it worked.  Smith: Running a farm is no easy thing. Did he like being a farmer? I guess that wasn’t where he thought he’d end up.  Ambros: No, he didn’t. I think my dad wanted to be an architect or an engineer. He built all the buildings on the farm himself. Then finally farming. It just didn’t pay. We had a farm, so we had all these vegetables and so on, and we had chickens, pigs and everything. All the food that we needed was basically grown on the farm. So my parents didn’t have a lot of expenses besides cars and stuff like that. We didn’t go to private school, but still it was not paying bills finally. He quit farming, but just kept a cow for me to milk every morning. Then he eventually became a cabinet maker. He had a business in town where he made cabinets, other furniture and things like that. He was a super amazing woodworker. That’s me and my brothers learned woodworking from him.  Smith: What a beautiful thing. There’s this woodworker called James Krenov, who was a American woodworker, but also of Russian descent. He wrote beautiful books about cabinet making. I’ve read them and have thought how extraordinary to be able to create such beautiful things. He used to say something about the fact that when asked why he did it, he said because I just want people to have one beautiful thing in their house. Most people can’t have many beautiful things, but if they just have one beautiful piece.  Ambros: Yes, that’s right. I’m sure that was part of what motivated my dad. He did have a flaw though. His flaw was, in his mind, there was a maximum amount anybody should pay for a piece of furniture. Like a table shouldn’t cost more than whatever, a bureau shouldn’t cost more than whatever. It didn’t matter how much time and expense he put into it, he would not build what it was worth. He was always struggling right on the edge of solvency. But he had a business that employed four or five people at its peak. They all had a wonderful time and learned a lot of stuff from him. He was an important person in his community. Actually, at one point he had like three people in the shop were members of the volunteer fire department. Whenever the alarm goes off, they have to drop what they’re doing and run to the fire. My dad was the only business only employer who paid the volunteers for the time when they were away fighting the fire.  Smith: Wow. I just love his approach to how much things should cost. It’s the absolute opposite of surge pricing. It’s wonderful.  Ambros: But we fancied ourselves, astute business people, so we would say, ‘daddy, you got to charge what the going rate is and stuff like that’.  Smith: He’d already set the precedent that you listened to him and he didn’t have to listen to you, I guess.  Ambros: Exactly.  Smith: That sounds an amazing man. And your mother was a writer?  Ambros: She was, yes. Her pen name was Melissa Mather. She was a farmer. My dad and she were partners on this farm, and she actually helped with farming sometimes during certain seasons. She’d be out there on the tractor driving around. But she wrote books. She wrote a memoir called ‘Rough Road Home’. It was about city lady moves to the country, starts a farm and the house is run down and there’s neighbours around and they’re interesting quirky neighbours. Then she wrote a couple of novels and they did sort of moderately well, she was successful enough to her income from that contributed significantly to the family.  Smith: You were growing up in the beginnings of the space age.  Ambros: The space age was definitely a big deal. Sputnik was when I was maybe six or seven years old. I remember going out there and we’d spot it going over. Then the space race got going and it was just really enthralling. It was also risky. It was an adventure to watch it, to observe it as a youngster.  Smith: That’s interesting. You bring up risk. A lot of interesting scientists live on the edge of thinking the possible. It’s a sort of risky thinking. Sometimes it goes way out there as somebody like the chemist [Barry Sharpless](https://www.nobelprize.org/prizes/chemistry/2022/sharpless/facts/), who just seems to be able to think the unthinkable. But it’s funny because academic life probably doesn’t seem to most people like a risky life, except for you might lose your job. But there does seem to be an appeal in risky thinking.  Ambros: It’s really cool that most of what you do in academia, academic research is driven by yourself. You’re an entrepreneur. The ideas come from your own head and from talking to people around you and from your students and stuff like that. You put that together into this ongoing research program, it’s fueled by these periodic grant applications to the government. You try to manage that successfully. It’s completely up to you. It’s totally in your own hands. That’s kind of amazing in a way that so many people with different kinds of backgrounds and different sort of psychologies manage this, the amount of risk that you feel can vary person to person. But it definitely goes through cycles because when your grant is up for funding, that feels like you’re really out there and you’re really risking everything. Then it gets funded and then for four years you kind of like, ‘Ah, I can relax and sort of, we’ll do what we find interesting and we’ll do the best we can and so forth and see where we are in three and a half years.’ It’s an interesting cycle. But my research program has always been fairly inexpensive because I work with this nematodes C Elegans. Folks who work on mice or other vertebrates, there is huge cost to just doing their routine work. I feel like they probably feel much more vulnerable. You have to get more grants than just one and it never seems to be enough. I sense that it’s tougher in different fields depending on what your particular field is, how vulnerable you feel.  Svensson: Adam, let’s unpack some things about Victor Ambros’ research. He was awarded the Nobel Prize for discovering microRNA. What is microRNA?  Smith: MicroRNA is really short RNA. I guess you’ve heard about RNA?  Svensson: Yes, I’ve heard about DNA and I know that RNA is.  Smith: Keep going.  Svensson: It interacts with DNA right?  Smith: Don’t worry. It’s not a test.  Smith: DNA is the code in our cells, which tells the body what to make. Mostly they make proteins. Between the DNA and the protein is the RNA. DNA makes RNA and RNA makes protein. An RNA is basically a way of transferring a code from DNA to the ribosome, which then makes the protein. So Victor Ambros found a very short sequence of RNA that was coded for by DNA, but it didn’t then encode a protein. What it did, it turned out, was to switch off another piece of RNA. It acted as a repressor of the expression of a protein. This was in his worm that he studied C Elegans. A microRNA is a tiny bit of RNA that switches off the expression of a protein. It was an entirely new function for RNA when it was discovered. Nobody expected that this mechanism would exist, but there it is.  Svensson: Later on in this conversation, he talks about the microRNA Let-7. Why was that an important discovery?  Smith: While he was doing this work on Lin-4, Gary Ruvkun in a lab just a couple of kilometers across the river in Cambridge in Massachusetts, was studying a gene called Let-7 also in the worm. The same worm C Elegans. He discovered microRNAs for Let-7. It was thought at an early stage by both Amrbos and Ruvkun that what they discovered was a worm phenomenon. This was something that went on in their little C Elegans and it was peculiar to C Elegans. But a few years later, Ruvkun in particular, discovered that this microRNA functioned across species. It’s a common mechanism to all animals. It was first discovered for Let-7. So Let-7 became very key because of the ubiquity of the Let-7 microRNA that was found everywhere. They realised that this thing that they thought was worm specific was actually happening throughout nature.  Svensson: So at the center of this story is that minute worm, this C Elegans. Why is it such an important animal?  Smith: C Elegans is a much awarded worm. It’s accrued quite a lot of Nobel Prizes. It turns out to be a really strong experimental model system to work on. There’s only about a millimeter long, and it’s reproduction cycle, I think is three days. If you are trying to change things in the worm, you can rapidly change things and get new worms with their new characteristics. Geneticists like Ambrose and Ruvkun can make alterations to genes or study genes and quickly do experiments and quickly get results. It’s small and tractable, but it has behaviour, although it’s very tiny, it still feeds. You can study feeding behaviour and see whether it likes what it’s being fed or doesn’t like. If you change a gene, you can see that it stops wanting to eat this or whatever. It’s an animal which you can study as an animal yet it’s extremely malleable.  Svensson: But I always thought the fruit flies were the favourite animals of geneticists.  Smith: Those are also very useful model system. They’ve been a traditional sort of bulwark of geneticists for many years. C Elegans came along a bit later as a model, but has also proved to be very strong. It also has the beautiful characteristic of being transparent. You can see what’s going on inside. If you label cells, they glow and you can just look at the worm and there they are. It’s really God’s gift to geneticists, cell biologists and molecular biologists, and this whole group of people who are devoted to C Elegans and love their worms very much. Let’s listen to Victor Ambros talk about why he chose to work on C Elegans.  Ambros: What was so striking about it was it felt like it was simple and accessible. Rightly or wrongly, I got the impression that, ‘Oh, this is an organism, maybe where I could find some traction, because it’s relatively new, there’s a lot of opportunities, and it felt like there were questions that might be addressed with this animal’. Bob projected this idea, there’d be some unique perspective that would be drawn from studying this animal. Because your focus would be, let’s say, on development in terms of these minute high resolution events, like when a cell divides, and then when its daughters become one thing versus another. What kind of signals were controlling these decisions with temporal resolution. It felt to me like it would be a system where there might be some opportunities to really make an impact because it’s new and because the questions, at least as articulated by Bob, was somewhat different from the questions that were presented by more complicated animals.  Smith: If you look back over the discovery process and the realisations you had along the years, is there something you’ve sort of learned about the art of discovering something very fundamental?  Ambros: Yes, I think I’ve learned that if there’s something peculiar, new, unusual and unprecedented, it is almost certainly part of some broader phenomena, suite of phenomena. I think we have generally as a science, we’ve learned that there’s deep homology amongst organisms. But what’s, almost the case, is that that homology is also accompanied by incredible diversity and adaptation of those things. Argonauts, the protein that’s at the core of microRNAs, is an example because now folks have discovered Argonauts in all kingdoms of life. They seem to be always programmed by small nucleic acids, whether it’s RNA or DNA. They’re performing all sorts of different functions. You have these deeply conserved, fundamental molecular mechanisms and then incredible adaptations of that mechanism for incredible diversity. That’s one of the things of course we love about biology, that the organisms are all related, but they’re so all incredibly different. It’s just unbelievable diversity somehow, even amongst animals. It’s astonishing diversity among, and we’re all using sort of the same sets of genes.  Smith: Do you have a favourite example that has surprised you of how microRNA have been found to be involved?  Ambros: I think it’s still a mystery. Gary Ruvkun discovered Let-7 to be perfectly conserved across all the bilaterian animals in all the genomes. Essentially you can find a Let-7 gene that has exactly the same sequence as the Let-7 gene in C Elegans. Now, of course, in all those genomes, often there’s other Let-7 family microRNAs. But the point is our bilaterian ancestor had Let-7 with that sequence in its genome. Everybody since then has had to have it. We don’t know why or how, you asked me some surprising realisation. I feel like what’s equally exciting is these mysteries persist that Ruvkun Let-7 why and how.  Smith: That lovely question. Why are things as they are?  Ambros: Yes. If we can’t explain it on first principles, it means there’s something there to be discovered. That’s the point. The more we can understand about the conservation of Let-7, the more biology we’re going to learn.  Smith: Your partnership with your wife Rosalind has been a very important part of your work. You’ve been working together for a long time. She was the first author on the 1993 paper. The project is one you’ve done together. It is fascinating to have such a partnership that is both sort of home and work. How do you work together? How does it operate?  Ambros: I would say the operating principle is that Rosalind her perspective on no matter what is going on, whether it’s at home or at work or in the science, is probably sort of the wisest. I can be off fantasising this or fantasising that or imagining this and that. That’s sort of what I do. Then she’s a steadying influence. Whether it’s in those projects we did with Rhonda Feba, it just the technological acumen and the persistence that Rosalind brings to the experiments, right? She can pull off experiments and get data where it requires a lot of physical labour. These were hard experiments to do. She was developing films while experiencing labour. The beginnings of labour for our second child. She’s also the steadying influence at home. She’s the person who’s keeping track of everything, keeping track of all the kids’ needs, juggling in her mind, all that stuff. At the same time managing the lab, personnel in the lab and also doing experiments. I’m sort of in awe of just the basic capabilities that she has. She has a memory that’s way better than mine. That’s another thing I draw on. The theme maybe is that the two of us are almost indispensable for each other. There’s so much we can point to in our lives that was the result of an actual partnership. As difficult as it can be, any partnership is difficult and especially a marriage can be difficult. There’s just so many things going on from so many directions. It’s not always easy to agree. It’s not always easy for me to see the wisdom of her perspective initially? It’s been almost a miraculous kind of experience, I must say. We’re still together and yesterday we hung out with our kids and four grandchildren. Despite the fact that things are really so chaotic in science in the country here, it’s great to be able to have that dimension at home to our lives. It’s always been there. No matter how messy things have been in the lab or how frustrating and so on. It’s impossible to state how fortunate I am to have Rosalind. None of this would happen without her at all.  Smith: Thank you very much for talking about it, because I think it’s almost always the case that somebody who does amazing work has somebody back at home, kind of managing life and making things work. But it’s quite unusual that that person also interacts so much with the work. You and Rosalind have this almost unique set up, but it’s extraordinary. It’s also interesting to explore your relationship with Gary Ruvkun because in a very different way you two have been working together at times and then competing almost at times. Although friendly competition always, I gather. You obviously spark off each other beautifully since your time as postdocs in Bob Horvitz’s lab.  Ambros: Yes, it was really quite an experience because I was his first postdoc, and then Gary came. Gary was a molecular biologist. He was already accomplished molecular geneticist and biologist. He taught us how to prepare DNA, how to prepare RNA from worms, run these gels and really clone things and vector. Then we did a project together in Bob’s lab and published a paper. Then we started our separate labs and we talked about kind of collaborating, but I think it just didn’t seem practical, especially since our labs were physically separated when I moved to Dartmouth up in New Hampshire. It was more like, Hey, we’ll stay in touch. We had this thing called the Boston Area Worm meeting, which occurred every month or so. People from all over New England would come together and talk about ongoing projects. There was lots of opportunity for us to stay in touch. When we published those papers together in 1993, that was the result, not of a collaboration, but just of a communication of the projects that were going in our respective labs. I try to emphasise that when I’m going around and proselytising; collaboration is wonderful, but communication is actually pretty great too. We never really felt we were competing. At least I didn’t because there was so much room in the field. There’s just so much room for investigations. I think we’re more or less informally making sure that we weren’t doing the same thing, but he would do screens that were super inventive that we never would’ve thought of. Gary’s a wonderful colleague because he’s incredibly imaginative, he’s amazing. He has a sense of humour, which sort of permeates the way he generates ideas, even scientific ideas. It’s almost never, do you have a conversation with Gary that when you don’t walk away saying, I got to think about that. That sounded crazy, but there’s something to that.  Smith: Yes. You don’t have to be right all the time. Being crazy sometimes is okay.  Ambros: Yes, it sounds crazy, but they’re usually not crazy. That’s what Gary is doing.  Smith: I was told that you like repairing guitars. In the context of your father and his ability to build barns and cabinets, building scientific stories is a creative enterprise. Do you find that you are somebody who likes making things generally and putting things together?  Ambros: Yes. By the way, that’s one of the things that Rosalind and I really enjoy doing together, sort of restoring furniture. We get something super cheap and then you fix it up and it’s actually really nice. The guitars are a way to do woodworking, but on a small scale, you don’t have to have the biggest machines. I don’t really make furniture. I make a guitar because it’s just like nice, manageable scale. It’s like super interesting as a woodworking project because this instrument has to hold itself together against the tension of the strings. Then it’s supposed to sound good too. There’s a lot of opportunity for being really precise, but also being inventive. Then restoring guitars is kind of nice because you can get these old guitars that cost $40 when they were new, and then you can take them apart and then rebuild them with sort of better wood or bracing. Then it’s a nice serviceable guitar that costs practically nothing and it sounds really good. Now it has a new life. It was $40 originally, but then the strings sort of started to tear it apart.  Smith: I love the idea of giving this upgrade, putting some love into it.  Ambros: Yes, this thing’s going to be around now for indefinitely. It was a piece of junk and you don’t care. It sounds not bad, it plays not bad. Then I also made some from scratch too, which is really interesting too.  Smith: That sounds pretty advanced woodworking to me.  Ambros: That’s like a rite of passage. You fix a guitar, then you can get kits and assemble it. You can step into this hobby like that and then graduate to making more and more of it from scratch.  Smith: Okay. I’ll just finish by telling you something that James Kevron wrote in his book. He said he used to get all these off cuts of wood from dealers cheap, but often they were interesting woods and he kept them in his wood store and he’d just go and stand with them and caress them and wait for them to tell him what they wanted to be.  Ambros: That’s so sweet. That’s right. I have a piece of wood that my dad found under the floor of a house that he was renovating. It was an 1820 house and there was a piece of flooring under there. When he died, I inherited it. It’s a piece of cedar or something that went into that house in 1820, and it has over 170 lines of rings on it. I’ve made two guitars out of it so far. Talk about the wood calling out to you for a purpose.  Smith: Absolutely. You are giving that wood a voice even.  Ambros: Yes, that’s right in this case.  Smith: That’s very nice. I’m really grateful to you for this conversation. It’s very nice to explore all these different facets of your life.  Ambros: I’ve enjoyed it very much.  Svensson : You just heard Nobel Prize Conversations. If you’d like to learn more about Victor Ambros, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries. Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize outreach. The producer for this episode was me, Karin Svensson. The editorial team also includes Andrew Hart and Olivia Lundqvist. Music by Epidemic Sound. For another podcast with a six string connection why not listen to our episode with a 2022 chemistry laureate and fellow guitar lover, [Morten Meldal](https://www.nobelprize.org/prizes/chemistry/2022/meldal/facts/)? You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | 0501 = VA  Victor Ambros: Hello?  Adam Smith: Hello, am I speaking with Victor Ambros?  VA: You are, morning!  AS: Good morning, very early morning I know, many congratulations on the news!  VA: Thank you, sorry that my phone was in the other room this morning so I didn’t hear any earlier calls.  AS: Not at all, I mean, you haven’t yet spoken with Thomas Perlmann from the Nobel Committee, I guess?  VA: No, I have not.  AS: Did you actually receive the news by being called by a journalist?  VA: I received the news by being called by my son! Yes, a journalist called my son. Right, and so my son called.  AS: That’s a nice call to make to your dad.  VA: I bet, yes!  AS: It must all be a bit bewildering, getting the news just as it’s all breaking, so everybody is all trying to reach you. But if I can ask, what are your initial thoughts?  VA: Well, I mean, my initial thought was great surprise because I had understood the prize to my good friends [Craig Mello](https://www.nobelprize.org/prizes/medicine/2006/mello/facts/) and [Andy Fire](https://www.nobelprize.org/prizes/medicine/2006/fire/facts/) for RNAi, I considered that to be an appropriate prize which encompassed microRNAs. I had kind of put the idea aside, although people from time to time do mention, “Oh you might win a Nobel Prize,” but I always dismissed that as, you know, “No, no, no, it’s ok. It’s all been covered, and appropriately.”  AS: Well, this is also the fourth Nobel Prize for the nematode.  VA: Yes, and that gives me incredible pride, and the fact that Ruvkun is the other awardee, is incredible, because Gary is such a good friend. I mean you ask me what my first sense was, it’s surprise, and secondly of course it’s a kind of muted joy because, you know, whenever this kind of thing happens to basic scientists, especially scientists working on the nematode, I think it’s a wonderful thing for everybody doing this kind of work. We see it as a, in a way, as a celebration not really of the particular scientist in this case, but of the way of doing science, you know. Curiosity driven, genetic studies of a complicated phenomenon and what you hope is you’ll learn a little bit more about how the phenomenon works – and it’s always amazing when the findings are new enough to be of interest broadly.  AS: I wondered whether that ability to be on the lookout for new phenomena and really take them seriously and investigate them – that’s a special art – is it something that you think was a particular benefit of having worked with, for instance, [David Baltimore](https://www.nobelprize.org/prizes/medicine/1975/baltimore/facts/) for your PhD, [Bob Horvitz](https://www.nobelprize.org/prizes/medicine/2002/horvitz/facts/) for your Postdoc. Did that train you in the art of looking for the unexpected?  VA: Yes, yes, very much so. I mean I was fortunate enough to work with a series of fantastic scientists, Bob and David, and before that I worked with a postdoc named Edward Gruberg, and Gruberg was a fantastic mentor and really got me alerted to the fact that you can find out new things doing sort of routine experiments, and he also taught me how to read the literature and therefore train myself to be aware of what’s known and what’s not known, so that you can notice what’s new.  AS: It’s also a celebration of the versatility of RNA this prize isn’t it, I mean, yet again, something unexpected.  VA: Yes, that’s actually very exciting to consider that, you made a really good point. I just got back from a meeting in Ottawa, which is a meeting of the Riboclub, and there was over 500 people there, and they celebrated the formation of RNA Canada, which is the nation wide network of scientists and others promoting research around RNA, or else agriculture, climate change and so forth. We all know that RNA is fascinating, and incredibly versatile. It was, the whole meeting was kind of like a celebration of RNA, especially when I went to the posters, there was poster sessions with young people doing incredibly diverse kinds of work.  AS: I guess today will help to boost that message. I long to know what your son actually said to you when he called you?  VA: (to someone off the phone) Hey Candy, what did Greg say? “Have you been getting calls from Sweden? You should answer the phone,” he said.  AS: That’s nice! Ok, well, thank you very much and once again congratulations.  AS: Bye. |
| **Interview** | How has your childhood influenced your scientific path? [1:53](https://www.youtube.com/watch?v=fcfPsIukw0A&t=113s) – Where does your passion for science come from? [2:50](https://www.youtube.com/watch?v=fcfPsIukw0A&t=170s) – Did you have any scientific heroes as a child? [3:37](https://www.youtube.com/watch?v=fcfPsIukw0A&t=217s) – What fascinates you about space? [5:27](https://www.youtube.com/watch?v=fcfPsIukw0A&t=327s) – What do you love about science? [7:12](https://www.youtube.com/watch?v=fcfPsIukw0A&t=432s) – What’s your advice for young scientists? [10:13](https://www.youtube.com/watch?v=fcfPsIukw0A&t=613s) – Do you have any advice for scientists dealing with failure? [12:28](https://www.youtube.com/watch?v=fcfPsIukw0A&t=748s) – Have you ever experienced imposter syndrome? [15:54](https://www.youtube.com/watch?v=fcfPsIukw0A&t=954s) – How did you meet your co-laureate, Gary Ruvkun? [17:06](https://www.youtube.com/watch?v=fcfPsIukw0A&t=1026s) – How would you describe Gary Ruvkun? [18:13](https://www.youtube.com/watch?v=fcfPsIukw0A&t=1093s) – How important is collaboration in science? [21:02](https://www.youtube.com/watch?v=fcfPsIukw0A&t=1262s) – What is diversity so important in science? [23:57](https://www.youtube.com/watch?v=fcfPsIukw0A&t=1437s) – Can you tell us about the guitars you build? |
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| **Podcast** | “When we’re doing genetics, we are tapping into that mythic power of change.” In this conversation with molecular biologist Gary Ruvkun, we discover his scientific journey and find out that the world of genetics still has many fields left to explore.  A natural storyteller, Ruvkun also shares some of his favourite tales with us – from his gap year in Latin America to how his grandparents emigrated to the United States. For Ruvkun, travelling has given him more stories than he could have ever imagined – and he tries to share them whenever he has the chance.  This conversation was published on 26 June, 2025. Podcast host Adam Smith is joined by Karin Svensson.  Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.  Gary Ruvkun: When we’re doing genetics, we are tapping into that mythic power of change. We’re exploring the plasticity of biology.  Adam Smith: I really like that quote from Gary Ruvkun describing the astounding power of genetics to explore so many mysteries of biology that have previously been hidden and are opened up by this extraordinary field. So many great scientists talk about the importance of getting the right tool to address the question you are interested in. Of course, one normally thinks of that in terms of a specific technology, a specific technique. In this case, Ruvkun is referring to the whole field of genetics and its power to open up biology. This is a theme that we very much explore in the conversation. So do join me please in listening to Gary Ruvkun.  Karin Svensson: This is Nobel Prize Conversations and our guest is Gary Ruvkun, recipient of the 2024 Nobel Prize in Physiology or Medicine. He was awarded for the discovery of microRNA and its role in post transcriptional gene regulation. He shared the prize with [Victor Ambros](https://www.nobelprize.org/prizes/medicine/2024/ambros/facts/). Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces. Gary Ruvkun is Professor of Genetics at Harvard Medical School. He talks to Adam about how traveling rough helped shape his career. The blurry line between plants and people, and his suspicion that life on earth originated in space. This conversation takes place in the early summer of 2025, in the midst of a clash between the U.S. presidency and some of the most respected institutions in higher education.  Smith: This brave stance that Harvard is taking must be a source of pride.  Ruvkun: It is a source of pride. And Alan Garber, who’s the president of Harvard, is a friend of ours and I kept saying, “Boy, if I was you, I would quit like a year ago”. But now he’s in there pugilistic as hell and hiring good lawyers. Harvard knows its way around the legal profession. They’re doing a good job and yes, I think Trump picked the wrong fight.  Smith: Let’s hope so. Anyway, strange place to start.  Ruvkun: It’s everywhere. It’s like a gray cloud over this town.  Smith: Yes. And presumably your students who are also worrying whether they can stay and all the rest of it.  Ruvkun: Yes. We’ve had meeting upon meeting about this stuff and what it means to their careers.  Smith: Terrible distraction from the business of being curious and getting on with it, which is what led to all these wonderful things. And that’s the thing about your prize. They’re all celebrations of curiosity driven research, but in a way your discovery so unexpected, so marvelous and so sort of unintended. It’s such a lovely example of how things come out if you just keep looking.  Ruvkun: Yes. It’s also very much empowered by the genome projects and that is a case of government support. England did a third of it. The U.S. did a third of it and it was very efficiently done. The people in charge of it were very aware that it was expensive and they did it in record time. It really starts in the late eighties. It starts with [John Sulston](https://www.nobelprize.org/prizes/medicine/2002/sulston/facts/) in England who’s this quiet guy working on worms in his little room with a lab of one or two.  Smith: Exactly. Deeply unassuming.  Ruvkun: Part of this Nobel Prize business is going over my manila folders of things. I have handwritten letters from him in 1984 because he’s helping us do a what’s called a chromosome walk to get to the gene which this Nobel Prize noted. He’s helping us do it as well as a hundred other people do the same thing. He realises that he’s set up a framework. Just he and Alan Colson, two guys working together, both incredibly competent workaholics at the LMB. He sent me letters saying, “Here’s a 50 kilobase region, it’s next to this 50 kilobase region. This is in the region of the gene. Good luck”. He sent the same letter to other regions and other persons, a hundred people were be getting this. Then he ramps up to do the genome project and goes from a lab of two to a lab of 200 again in this totally soft spoken way, demanding public release of the data every night.  Smith: It’s a beautiful story, actually. Prize after prize strings together, all of this.  Ruvkun: Yes. I got to see Sulston at the Nobel Prize.  Smith: Did you come in 2002?  Ruvkun: As a guest, not as an honoree. I was a nobody. But I was a guest, not of him, of [Bob Horvitz](https://www.nobelprize.org/prizes/medicine/2002/horvitz/facts/), who was my postdoc advisor. Bob came to our Nobel Prize six months ago and Sulston at the after party was wearing American cowboy chaps, and fake pistols at some kind of pistol range that the Karolinska grad students set up. Sulston was a party animal so he was partying heavily that night. It was really fun.  Smith: The Brit wheel out. In your case in particular, I suppose your curiosity came at a good time coinciding with the development of the technology. One thing I wanted to ask you about was the animal you work on, C. elegans allows you to be so explorative because its turnover is so fast and it’s so accessible. Does it allow you to be more inventive, more curious?  Ruvkun: Oh yes. The fact that it’s cheap to work on means everything. Our genetics is incredibly fast these days. What used to take a mega lab of 20 people with Howard Hughes Medical Institute support, which I don’t have, I’m still jealous of people who have that. But it used to take a big lab sort of 20 years to flesh out a pathway with genomics and genome sequencing. Now we get our mutants in a week, we get the genome sequences of them a couple of weeks later and we stare at the genome sequences and figure out what our mutations are. One person can flesh out a whole pathway. I have three examples of postdocs who did sort of a 20 year operation in two years now. That’s all because of genomics. The genetics is ever more powerful now.  Svensson: Hey Adam. I now feel very excited about genomics, but I’m not entirely sure what it is.  Smith: Genomics is simply the study of all the genes in an organism and the way they interact with their environment. I say simply that’s a pretty complicated thing to study. But yes, it’s exciting.  Svensson: And Gary Ruvkun pays tribute to an important person in this field, John Sulston. Why was he important?  Smith: For a start, he worked on this beloved organism of Gary Kuvkun, C. elegans, this roundworm nematode. It’s about a millimeter long and there’s a community of people who work on it. John Sulston was one of the early exponents of working on this worm. He got his Nobel Prize for studying the lineage of particular cell type in those worms. Then he was thrust into the public eye by becoming the leader for the British side of the Human Genome Project. Starting just before the millennium, and produced about a third of the sequence of the human genome. He not only led that project, he also fiercely defended the need to keep the data from the Human Genome Project in the public domain. He’s much celebrated for being a real advocate for public accessibility of science and data.  Svensson: A pair of scientists that often mentioned by Ruvkun and others in connection to this is [James Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/) and [Francis Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/). What was their contribution?  Smith: Their original and much fated contribution was their proposal of a structure for DNA, the double helix, which together with[Maurice Wilkins](https://www.nobelprize.org/prizes/medicine/1962/wilkins/facts/) got them the Nobel Prize in 1962. They’ve continued to be hugely influential figures, very different people and very much on all geneticist mind.  Svensson: Both of them seem a little bit bonkers, don’t they?  Smith: Yes. Maybe it takes a bit of being bonkers to be a great scientist. I think that’s probably true. But I think it certainly applies to them. Francis Crick, I suppose he might have been a little bit bonkers in later life to go off and work on consciousness because you couldn’t have picked a harder problem. And I think it’s fair to say that he didn’t get very far, but nobody gets very far with consciousness. It’s early days. But his contributions to whatever he was interested in were always very thought provoking. He absolutely adored asking questions. He’s very famous for asking questions at seminars. They could be brilliant questions. They could be very simple questions, but he liked to ask questions. Then when it comes to Jim Watson. I think bonkers again would work. A very influential scientist respected by so many people. He has brought a great deal of criticism upon himself, also for his very controversial statements about so many issues frequently based in his understanding of the science. But going into areas that most people just would never talk about. He speaks on issues such as the genetic basis of race, which is incredibly controversial. That has made him a very contentious figure in science.  Svensson: Another really interesting character in this field is of course Gary Ruvkun. Can you explain a bit about why he got the Nobel Prize?  Smith: He and Victor Ambros were co-discoverers of this system of regulating gene expression (previously completely unknown) by very small species of RNA called microRNAs. When they found it, they thought it was perhaps a system that was peculiar to their worms. These beloved C. elegans that they study. But, in particular, it was Gary Ruvkun’s work a few years later that showed that this was far more ubiquitous than that. It’s present in practically all organisms and is a really important way that the cell uses to regulate gene expression at the post transcriptional level which means that after the messenger has been produced from the DNA that’s going off to tell the cell what protein to make you then stop that in its tracks using these microRNAs. The ramifications are enormous and there are potentially all sorts of therapeutic approaches based around that.  Svensson: This is also part of the great collaboration within genetics, isn’t it?  Smith: Yes, it is. In their case, they were working in parallel and finding common ground and talking to each other and collaborating where necessary. That’s very common, especially among the worm community. There’s a great common feeling in a sharing of information.  Svensson: And the love of the worm.  Smith: Yes. The love of the wormhole binds people together. We all need common interests right?  Svensson: And pets.  Smith: And pets. I don’t know if they go as far as that. These things don’t live very long. I wouldn’t invest all your emotional baggage in a worm. Anyway, let’s listen to Gary Ruvkun talk about how geneticists continue to build upon each other’s work.  Ruvkun: Now the beauty that very few people appreciate but more should, is that we get our mutant hits. Almost every time it’s a list of 20 genes that I know nothing about. But because of the tree of life, somebody has worked on a homolog of those genes in a plant or a frog or a bacterium. You just have to be willing to sort of dive into what the other genetic systems and genome systems tell you. It’s so educational. Reading the literature becomes even more important.  Smith: It’s still referencing back to that Sulston sharing his thoughts with you, it’s still very much a community of sharing.  Ruvkun: Except this is publishing, right? They don’t know I’m looking at their papers.  Smith: No, not quite, but it’s kind of an extension of that community.  Ruvkun: Yes. The currency of biology is on the order of 20,000 genes, which we have and a worm has and a plant has, but they have basically that same currency. Half our genes are shared with plants. There’s 500,000 molecular biologists like me, and we’re all studying the same 20,000 genes. Every gene’s been studied somewhere.  Smith: Does it surprise you that that we’re also alike? We’re so alike with plots and everything else?  Ruvkun: No, it’s sort of been hinted at from the very first time people started using nucleic acid sequences. The ribosomal RNA is sort of the clock that’s used to all the trees of life that you constantly see everywhere. Every third paper has a tree of life. That tree is generated by doing phylogenetic comparisons of ribosomal RNA. In fact, just for the people in the humanities who might be listening to this, this idea of trees that Darwin is so famous for, the linguist figured this out for languages before Darwin. I think we stole it from the comparative linguistics people, as a community.  Smith: Am I right in thinking that it makes you a little suspicious when you look at the tree of life that life did not originate here on earth?  Ruvkun: Yes. That’s my take on it. It is totally uncelebrated by people who think about the origin of life on earth. I constantly talk at NASA about this stuff and go to various origin of life conferences every so often. But that whole community really thinks I’m stupid on this idea.  Smith: How nice. Let’s talk about that then. It sounds like we’re getting into the wacky side of things. It’s fun.  Ruvkun: It’s panspermia, which is the idea that life spreads between planets, has a checkered past of scientists who go psychotic late in life, believing that life came in from other places.  Smith: Fred Hoyle was a great champion of it, wasn’t he?  Ruvkun: He was. He sort of believed viruses came from space. But Francis Crick also believed that life came from outer space and he was never wrong about anything.  Smith: Maybe even he would’ve been right about consciousness if he’d had enough time to look at it.  Ruvkun: Yes. That was a bad life decision to work on consciousness. The failure rate for that is infinite.  Smith: I fear that’s true. There are other great scientists who like the idea of life from elsewhere.  Ruvkun: Yes. It’s not well celebrated. The reason I like it is that if you go to the base of the tree, most people would say bacteria, they’re pretty primitive, but they are far from primitive. They have the ribosome, which is the heda making proteins. They had already figured out the genetic code. They’re not like this sort of clunky, barely working horse drawn carriage. They are a full on everything we associate with life they have. That’s present as soon as the earth cools down.  Smith: Given what we know now, what do you think would be the way of backing up the idea of panspermia?  Ruvkun: Finding DNA on other planets outside the solar system and good luck on that. But like the people who look for messages from extraterrestrials, they look for them to send the number Pi or the number E, but really you should just look for a ribosomal RNA sequence. If I was going to send a message of who we are, I would send out the E coli 16 sRNA sequence that says everything about who we are on Earth.  Smith: Yes. Possibly too much though.  Ruvkun: Yes. The other view is you should send out a shark’s genome sequence to say we are tough motherfuckers.  Smith: Space has always intrigued you, in fact you and Victor Ambros were both very much switched on by the space race in the U.S.  Ruvkun: Yes. In fact we went to the Stellafane homemade telescope Congress in Vermont about 10 years ago. You show up at 10:00 PM and everybody who’s made a homemade telescope is pointing it at something else. You walk from one telescope to the next and it’s all night long in Vermont. It was fantastic.  Smith: Wow. Have you made a homemade telescope?  Ruvkun: I made a homemade telescope, yes.  Smith: Gosh, is it hard?  Ruvkun: I was sort of working as a tech, this is before grad school in San Francisco. There was something called the San Francisco Sidewalk Astronomers run by John Dobson who is famous for the Dobson telescope that he designed which is totally simple. It’s not an equatorial mount, you make it with plywood and it’s very hard to aim at anything. But he ran telescope making courses in San Francisco in his basement in a really crummy neighbourhood of San Francisco. He taught us how to grind our own mirrors. Again, I didn’t know any of this. It’s in a concrete tube. It’s about six feet tall. The funny story of that scope is when I was moving to Boston for graduate school, 1976, I happened to stop and see a friend in Detroit and then went through Canada, which looked like the shorter route with my Dodge van. Coming in at Niagara Falls, the guy opens up and looks in the back of the van and finds a basket of weavings from South America and figures I’m running drugs. But the first thing I take out is my six foot tall telescope. He goes, “What’s that?” This is the customs guy. I said, “Oh, that’s my homemade scope”. He goes, “You can go” because he’s like no way you’re running drugs if you made your own telescope.  Smith: You are a nerd. We can see.  Ruvkun: Exactly.  Smith: You mentioned the Dodge Van and South America. You are the sort of person who builds telescopes in your basement or in somebody else’s basement and is endlessly curious in the laboratory. You sound like you were sort of set for science from the very beginning, but you did take time out and do other things. I know people are intrigued by this because nowadays people are so directed and feel they haven’t got time to stop and all the rest of it.  Ruvkun: My generation, remember I graduated from college in 1973 and that’s the hippie dippy generation. Everyone’s going back to farms. I planted trees in Oregon living in my van. I found that job by going to Max’s Tavern on peanut night in Eugene, Oregon. There were like, a lot of people were talking, this place was hiring.  Smith: I like the idea of peanut night. What is peanut night?  Ruvkun: They serve peanuts and beer. There’s all these peanut shells on the floor of Max’s tavern. Max’s still has peanut night, by the way. Even today in Eugene, Oregon. Then I went and worked for a year. But that was part of sort of going back to nature. I never wanted to be a farmer and live on a commune that never attracted me one bit. Maybe for a day, but never for a life. Then going to Latin America, that was really probably driven that my dad worked in Latin America a lot. He built steel mills and cement factories and he was a big industrial guy. He had an engineering firm and he was in charge of Latin America for this Kaiser engineers, which is a big company in Oakland, California. He would go to Latin America all the time. My mother actually learned Spanish to be the good wife. We did our homework together when I was in high school and she was like underlying Don Quixote for her homework. She was getting her college degree when I was getting graduated from high school.  Smith: But that’s fantastic that you were just sort of co-learning as co-scholars.  Ruvkun: My parents sort of let me be, they were unhappy with my citizenship grades, “he’s a bit of a troublemaker kind of thing”. They didn’t like that because they were both very un-troublemakers. They wanted me to improve in that regard.  Smith: Keep that quiet in the current climate.  Ruvkun: Yes.  Smith: Okay. But you survived citizenship.  Ruvkun: Yes, that all worked out. I had been an electronics nerd in high school. Ham radio was a big part of what I did. That was part of my social network. There were a bunch of nerdy kids who would be on the radio talking to each other. That was a community. It wasn’t worldwide, it was sort of more local people, San Francisco and Oakland. But they were really inspiring to me more so than the kids I went to school with. That became a community. It’s almost like a early social network.  Smith: Yes, of course. You needed a certain technical prowess to be part of it.  Ruvkun: Yes. It was vacuum tubes, which sucked.  Smith: I suppose I’m attracted by the idea that you weren’t at that point in life at least, so driven that you couldn’t take time out to see other things to travel in Latin America. To plant trees and just sort of, I suppose discover who you were.  Ruvkun: It taught me a lot about navigation. I don’t mean physical navigation, but just sort of complicated journeys and how to take care of yourself and how to not get taken advantage of. It gave me a library of stories. I have a thousand stories I can tell and I’ve told many of them. They mutate over time. Like the bus driver that we knocked out in Bolivia because he was drunk. He started swinging at me when I said “Esquina esquina” which is what you call out in a city bus, which means next corner. This was an intercity bus and he’s going, “No esquina”. But he was clearly drunk. It was a fiesta in this small town outside of Cochabamba, Bolivia. He throws a punch. In my retelling of the story, I kicked him in the chest and knocked him out. But in fact it was the guy I was traveling with. There were three of us traveling. He did that, which I only discovered by rereading the letters I wrote to my family about these things.  Smith: It’s a fantastic story whichever way you tell it. But isn’t it interesting how things mutate?  Ruvkun: Yes, in my favour.  Smith: Yes, maybe that’s the general direction. Maybe that’s the evolutionary pressure there.  Ruvkun: By the way, the people on the bus was a marching band because it was a fiesta and they were laughing their heads off that the gringo had just knocked out their bus driver. They just thought this was the funniest thing ever.  Smith: One has to ask, was the bus moving at the time when this happened?  Ruvkun: No, no, no. He had pulled over to let me out and then some guy with epaulettes and he was dressed up like a marching band. He took over driving the bus three more hours back to town. These are adventures, right? These are stories and they’re survival. There’s survivor bias that I didn’t have a head on collision because I was smart enough to say pull over.  Smith: Absolutely. It may be too much of an extension, but I suppose when you get into real science and you’re having adventures with your mind, you are then telling stories about them and it’s all kind of the same thing.  Ruvkun: It’s navigating the unknown and being comfortable with it. Travel I think is really important.  Smith: What was it though that taught you to be as inventive a scientist as you are and as questioning a scientist? I think it’s fair enough to say that you don’t take safe paths, that you tend to live a little bit on the fringes, testing out slightly outside ideas.  Ruvkun: When I got to graduate school in 1976, I was in way over my head. There were people who knew a lot more of the sort of nuts and bolts of molecular biology than I did because I hadn’t had that level of a background. But so many examples of superb science and both my professors and my fellow students. It was beautiful to me that in Stockholm four of the people I hung out with in grad school were there with us. We came of age together and learned what it is to be scientists. I always think that training was sort of like a hundred seminars that I went to. Not just of people who were at Harvard, these are people who came as guests. It helps to have a name like Harvard that they would all say yes to give a talk there because it was sort of one of four or five centers in the world. At that moment there was sort of just a few places that were really great at molecular biology. Now there’s hundreds that are really great. That’s because the field is a hundred fold bigger and better than it was. But it used to be just a small number of places where it was being invented at that moment. I didn’t realise it at the time, but in fact when I’m writing up the things I’m working on now, it’s all about the genetic code in our newest projects. The code was only eight years old at that point. It had barely been discovered because DNA was 1953. But figuring out like what are the 61 letters of the genetic code that all happened in the mid 60s. I took a course in it in 1970. It was four years old when I took the course. It was all new. I didn’t know that.  Smith: You say when you arrived as a graduate student it was all a bit overwhelmingly good. There were just marvelous people around you. How did you, if you like, build the confidence to realise that you fitted in and knew that this was the place you wanted to be? I think a lot of people find that they go and they’re a bit overwhelmed by the pace of ideas and just how good people are.  Ruvkun: Yes. I didn’t feel like I was way better than everyone else. That’s for sure. I was sort of part of the pack, but it wasn’t a huge pack. It’s not like there were hundreds of students floating around. Everybody had a name and it was a very finite number. There’s like a dozen labs each with say a dozen people. The labs got much bigger later as the explosive discoveries happened. Not just at Harvard but many places. There was lots of moments of, “I’m not assured of success, right?” I think I had good instincts of picking systems that are fast and cheap. What things cost makes a big difference. If you do stuff with mice, you’re paying whatever it is, $5 a day just to keep them housed. You spend a lot of time writing grants just so your mice can eat. Our little worms are incredibly cheap. By the way, that was part of Sidney Brenner’s genius. He was a bacterial geneticist and he goes, “I want to work on an animal that I can do bacterial like genetics”. He picked the worm for like 10 different reasons for that. I am happy he did. I barely knew the guy. I exchanged a hundred words with him in my whole life. I very much appreciate his taste in science  Smith: That’s the phrase. That’s really what I was trying to get to with you. What gave you good taste in science?  Ruvkun: It’s connoisseurship, right? It’s like how do you know what’s great? You just know it. It’s seeing lots of good examples.  Smith: So with Victor, when you published, was it -93, your 22 nucleotide microRNAs? You knew that that was absolutely extraordinary.  Ruvkun: No, we didn’t know that at -93. We knew it was kind of interesting, but we were worried that it was a weirdiness of worms.  Smith: I suppose that’s where I was getting to. Within the worm it was an extraordinary thing to have discovered.  Ruvkun: We expected it to be more normal. Because we were doing genetics and we had a gene that did a process and we kind of thought it would be like other genes doing other processes. We hoped it would be as cool as the homeo box in Drosophila.  Smith: Right. It took time for it to sort of be universally realised that it is so important. It was your work later that really extended the application across all filer. But I just wondered whether you were sort of surprised by the fact that people didn’t jump on it more at the time.  Ruvkun: There was a little bit of the language that was used in worm developmental genetics with the lineage was very bizarre to other developmental biologists. We were jumping into a field that had been around for a hundred years but using our own sort of private language. There was an installed base of developmental biologists who were not geneticists except for the fly groups were somewhat resistant. There was an arrogance of the C. elegans group. Part of that was so many British accents, sorry. There was a certain resistance, but it wasn’t nasty. But it was just a sort of natural resistance. I wasn’t sort of surprised but then, as soon as we showed that it was conserved in humans, that helped a lot. Then the small RNAs being involved in RNA silencing and plants (David Balkan’s wonderful work) happened at that exact moment. That was sort of a double mushroom cloud that said, “Oh my god, there’s a tiny RNA world that’s doing all kinds of things we didn’t imagine”. That all happened at 1999 and 2000, that’s when the whole thing exploded.  Smith: It did indeed. On this gap between the publication and the wider acceptance, what I’d been thinking about was that the publication of the proposed structure of DNA in -53, when people talk about it, they talk about it as if the world changed that day. But it didn’t. It really didn’t. One measure of that is that there wasn’t even a nomination for the Nobel Prize for that work until 1960.  Ruvkun: I did not know that. We had a lab reunion to celebrate the Nobel Prize like a month ago. Part of my preparation for talking to everybody in the lab was to go over the citations of all the papers we’ve published because we publish in a lot of different fields besides microRNAs. We do insulin signaling and other things. I was interpreting it before I was going to present it to them. I said, “No, I need to look up Watson and Crick and see what that was like”. It was astounding that the number of references to it, if you go to the citation index was about a dozen a year until 1960. There was just nothing. I thought for sure that it would’ve been celebrated. Everybody believed it. I think it was just so convincing. There was nothing to talk about.  Smith: Everybody was disheartened.  Ruvkun: What I was trying to use that for was to normalise for the number of molecular biologists because if your field in 1960 was one, 1000th the size, which I think is about the right number, then basically one citation is worth a thousand today. I just thought we should at least have that in our minds when we talk about this sort of thing. But I was stunned by that. Then the late citations on Watson and Crick, they’ve probably been canceled because of Watson’s horrendous eructations on intelligence and stuff. Jim is a friend of mine, I go and visit him. To me being in the same room with Watson, I get goosebumps. You couldn’t write a more poetic life story to discover the double helix and then be in charge of the genome project. How does that happen? It’s amazing.  Smith: It is.  Ruvkun: There were small RNA meetings right at the moment of the explosion at Cold Spring Harbour. To have him in that audience listening to it, it was so poetic to me. It was like Yahweh was in the audience.  Smith: You’ve mentioned a little bit about your childhood. Your family had come from Russia, is that right?  Ruvkun: Both sides, my mother’s parents and my father’s parents, I don’t think they spoke Russian. I think they spoke Yiddish at home. For sure English was a very distant second language to them. So my parents grew up, I would guess speaking Yiddish. But we would go to Sunday dinner, I guess it was at my father’s parents’ house probably every Sunday or every other Sunday. It was about an hour’s drive out of Oakland, California. Stockton is where they were, which is not where you expect to see a bunch of Jews. They had a junkyard that was next to the house and they had a truck and they had a section of the yard for sinks and a section for engines. Being in the junk business during the depression was a good business. They weren’t wealthy but they weren’t poor.  Smith: That would’ve been my heaven as a child to be taken to a junkyard.  Ruvkun: Yes, it was good. I liked the porcelain section, I don’t know why.  Smith: There must have been such treasures to be found.  Ruvkun: My father and his father would go around with his model Ford through the Central Valley buying stuff. I’ve never heard stories of antisemitism. I think grandpa was respected for his honesty. There were stories again, I don’t know that my grandmother, during the depression, would give people food for off the back steps? There was a whole sense of outreach and community that they had. Then my dad went to Berkeley as an undergrad. He comes from the Stockton high school system, which is probably not all that elevated. He thought he had gone to heaven getting to Berkeley at age 18. That’s California at its finest. The tuition at Berkeley at that point, this is in 1937, it’s probably $50 a year. It was nothing. My tuition when I went to Berkeley, guess why I went to Berkeley? Because my dad went to Berkeley. My tuition was $600 a year.  Smith: Gosh. That’s how it should be.  Ruvkun: No scholarship. That’s just what tuition costs if you’re a Californian resident at that point. Now, I guess it’s 20,000 a year, something like that.  Smith: It sounds like they were good people, your grandparents and parents.  Ruvkun: Yes. Then my mother’s parents in Seattle again spoke Yiddish at home. I think they were illegal aliens because they came in through Canada somehow. Their entry papers have them coming into Canada through Winnipeg, which is as far as I know, is not on the ocean. I don’t know how the hell you get from Riga, Latvia (I think is where the ship left from) and how you get to Canada in 1905 in Winnipeg. I got no clue. At one point, 10 years ago I apologised to my cousins in Seattle, my mother’s side of the family for not being able to spell the name Gervidge properly. That’s my mother’s maiden name. They said, “Oh no, there’s a reason why you can’t spell it. Grandpa would misspell it on all the census forms so that the angel of death couldn’t find him”. That was the story. But the revisionist history says he was trying to not get deported.  Smith: Yes. I go with the first explanation.  Ruvkun: But I don’t know how a Russian Jewish family ends up in the Central Valley. There’s not a large Jewish presence.  Smith: This ability to survive in different environments and work hard and be good and down the generations, it has its effect.  Ruvkun: People who have the boldness to emigrate 10,000 miles, that’s a selection of type. My mother came with her sister to San Francisco at age 16 or something like that. She graduated high school really young. I just learned that last year. I had no idea that she was like sort of a precocious kid in high school and never thought to go to college. YWCA is where proper Christian women would go and there was a Jewish equivalent, the young Hebrew Women’s Association. So they were in San Francisco and my mother went with her sister Ann, who was a great seamstress and she wanted to be a Hollywood seamstress. Somehow going to San Francisco wasn’t quite going to Hollywood. Maybe they didn’t know the difference.  Smith: Close.  Ruvkun: So they lived in this young Hebrew women’s thing in downtown San Francisco. Then met my father’s sister and one thing led to another. Then my parents got together and they got married. My dad proposed to my mother on 7 December, 1941 because they were sitting in his 1934 Ford in Alameda. They heard on the radio that Japan had attacked and my dad goes “So what do you think?” This was his proposal of marriage.  Smith: It’s a hell of a moment to choose.  Ruvkun: I think she said yes. I only heard this like five years ago.  Smith: Going around telling people at that moment everyone must have been somewhat distracted by other things that were happening.  Ruvkun: Yes. He was working at the Kaiser shipyards in Richmond, which was a humongous thing. That was a bold move by Kaiser to bring assembly line technology to building liberty ships, which were really important for the Lendlease Act that saved England. Richmond went from nobody being there to a hundred thousand workers in like a year. How do you do that? They would have a train leaving Penn Station in New York and there’d be a ad in the newspaper. Here’s the hourly pay, the train’s gonna fill up. This is your job if you go to Richmond. The train would carry 2000 workers a week or a day, I don’t know what it was. But that’s how they got their ship builders.  Smith: Wow.  Ruvkun: What he was doing there was very important because they built 800 ships that brought all the arms to England for the Battle of Britain. When he walked the streets of the Bay Area in 1943, all the young men were gone. He felt like he was a coward. So he enlisted in the Navy and what he did in the Navy wasn’t nearly as important as what he was doing in Richmond. But he felt good about it.  Smith: Your current work, the microRNA field, has blossomed enormously. Now microRNAs are in clinical trials for various diseases. This turns out to be an incredibly important regulation mechanism. But you continue to find new bits of biology. I suppose that I would say that your system keeps on surprising you in wonderful ways. Describe what that’s like, to work with something that constantly tells you something about the way that life works.  Ruvkun: I think geneticists undersell genetics. The metaphor that we use to describe genetics is that a geneticist figures out how something works by breaking it in a thousand different ways. What that misses is that the important things about genetics is not so much that your DNA encodes how to build an organism, but it encodes how to build an organism that can respond to a million different insults. Both physiologically in terms of what the organism, like me as a person, I can survive or you can survive. But also how you can produce variants that might be able to actually not go extinct. The tree of life is full of extinction in branches that died, the dinosaurs, etc. But there’s a lot of different branches that have ramified. Its adaptability is why we are here and why everything so complicated is here. When we’re doing genetics, we are tapping in to that mythic power of change. So it really undersells it to say we’re breaking things in a thousand different ways. It’s much more, we are exploring the adaptability of organisms in our hands. That’s why when I do genetics, often the mutants we pull out or sort of genes that would be downregulated to respond to this or that insult and we’ve just insulted the worm or a bacterium or a plant in a way that it’s kind of evolved to be able to handle. We’re exploring the plasticity of biology. Genetics is just way more interesting than we’ve given it credit for. We’ve taught it wrong for a hundred years.  Smith: I’ve never heard that description before. It’s beautiful. You are, in a way, inviting the organisms to show their colours to show what they can do.  Ruvkun: Yes. How much variation they can handle and they can do it. We are so adaptable. Organisms do go extinct but some don’t. I’m totally enthralled with it. Our genetics leads us in totally interesting ways. Right now I’m back to exploring Francis Crick and the wobble hypothesis. That’s a long time ago. How base pairing of tRNAs that they use wobble base pairing to be able to read degenerate codons. This is 1966 papers. There’s a lot more to the genetic code than we’ve given it credit for. So I’m back with Francis Crick and working on wobble and that all came out of our genetics.  Svensson: I think I need some more help here. Adam, what is the wobble hypothesis?  Smith: Yes. We’re going to have to get into a bit of biology for that. When information is being transferred from the DNA where it’s stored, to producing proteins in the cell, which has gone to make us what we are, we go through this intermediate step where we produce what’s called the messenger RNA, which is the intermediate step between the DNA and the protein. In order to read the message in the messenger RNA, it needs to interact with another sort of RNA, which is called transfer RNA. The message in the RNA is contained in these codons, which are three nucleotide base sequences always described as three letter code sequences, which contain the information for an individual amino acid. Those three letter codes have to interact with three letter codes in the transfer RNA. You’d have thought that for that registration to take place, you’d need a one-to-one correspondence between the codes in the tRNA and the codes in the messenger RNA. There are 64 possible codes in the mRNA so you would expect that you need 64 possible codes in the tRNA. Turns out you don’t find 64 tRNAs, you find maximum 45. Somehow you don’t need as many as you thought. The wobble hypothesis proposes that the tRNA doesn’t actually need to be all that precise in reading the mRNA.  Svensson: So it wobbles basically.  Smith: It wobbles in molecular terms in that third base pairing. So the first two bases, they can’t wobble. They have to precisely align. You’ve got your tRNA coming up to your mRNA numbers one and two, they have to precisely lock in with a kind of Lego-like fit. But for the third one we can afford a little bit of wobble in that interaction. It can move around so we can fit with this one and it can also fit with this one.  Svensson: It made me think of dancing, bits of pieces sort of moving.  Smith: Many chemists do think of their interactions between molecules as dancing. It’s a really nice way of putting it. I think there should be more dance in chemistry.  Svensson: To something completely different then, Gary Ruvkun has also worked on ideas for COVID vaccines.  Smith: Yes. I gather that during COVID when he was just stuck at home, it occurred to him that work he had been doing on protein glycosylation, which is modification of proteins and the way that that can lead to editing of the proteins had of potential relevance for COVID because the spike protein on the virus was known to also be glycosylated. He published a paper in bio archive and then he presented to the team developing the vaccines on this piece of work that he never expected to have any input into at all. But that’s the nice thing about science that you never know where it’s going to lead you. Let’s hear Gary Ruvkun himself speak about why he spent lockdown doing this work.  Ruvkun: Comparative genomics, computational biology you can do at home when you’re locked at home. It was a way to deal with it. I also just knew that there’s ain’t nobody else thinking this way about it and it might not be right. I’m not trying to trumpet it more than it deserved.  Smith: There ain’t nobody else going to think about it in this way – is that the kind of guiding principle in the lab? Is that what you’re trying to find unoccupied territory where you can perhaps be original?  Ruvkun: Yes, I like having open space to ourselves and not people sort of nipping at our heels. I’m not interested in competing with people because then it’s obvious. If 10 other groups are doing it, you’re not adding that much.  Smith: Would that be your advice to people if you’re going to go into this?  Ruvkun: Yes. There’s a ton on herd behaviour in life in general, but for sure in science there is a lot of it. If you do genetics you get sent into territory. The thing about genetics, there are 20,000 different ways to go because there are 20,000 genes. I know a lot maybe about 1,000 genes, 5%, but 95% I don’t know squat about but I know how to look it up.  Smith: Good advice. Thank you very much indeed. We’ve been all over the place. A bit of a traveling conversation.  Ruvkun: Thank you, Adam. This was fun.  Svensson: You just heard Nobel Prize Conversations. If you’d like to learn more about Gary Ruvkin, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries. Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was me, Karin Svensson. The editorial team also includes Andrew Hart and Olivia Lundqvist. Music by Epidemic Sound. If telescopes are your thing, check out our earlier episode with 2018 physics laureate and stargazer [Andrea Ghez](https://www.nobelprize.org/prizes/physics/2020/ghez/facts/). You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | 0502=GR  Gary Ruvkun: Hello?  Adam Smith: Hello, Am I speaking with Gary Ruvkun?  GR: Yes you are.  AS: This is Adam Smith calling from the website of the Nobel Prize.  GR: Hi, Adam!  AS: Hi! Many, many congratulations!  GR: Thank you!  AS: So you just got the call from the committee a few minutes ago, what happened?  GR: I heard what sounded like an authentic call from the Nobel Committee! [Laughter] There’s always a chance that it’s one of my friends.  AS: Yes! Have your friends played pranks on you in the past?  GR: Well, I best not say. But you know the call from Stockholm is mythic in the world of science, and I’m sure it is in literature too, and maybe even the peace prize people pull pranks on each other; although I doubt it!  AS: We think they might be too serious for that sort of thing yes.  GR: I think they’re very serious.  AS: What were your first thoughts when you heard?  GR: Well, just surprise and you know “Oh boy, it’s going to be a fun ride!”  AS: Yes, when you and Victor Ambros made the discovery of an entirely new mechanism for regulating gene expression, the thought must have occurred to you that it was Nobel worthy.  GR: No. No, no, no, at that moment it was just the quirky, what we were working on, it was really interesting. We were young faculty members wanting to make sure we were successful at the next stage of our careers. We weren’t thinking that this is going to win a Nobel Prize, we were thinking this is really interesting. As the field exploded, which is just a joy to watch, then there was a sense that this is the sort of field, the sort of sea-change that gets awards and things. But that took a long time and was an unbelievable pleasure to watch, to participate in. The talent that got attracted to the field was magnificent. And the meetings with, you know, two hundred or three hundred people were electrifying, and still are great.  AS: It’s really lovely to hear the way you say how exciting it is to see the field build, because in some ways you might think the opposite, you might think, “I like having these niche areas to myself,” and it’s great. But it emphasises the social side of the whole thing.  GR: Oh yes, there’s a lot of interchange.  AS: One nice thing about you is that you took this career break between an undergraduate and a graduate, and going to grad school. You just went travelling, planting trees. It’s nice for people, it’s not nonstop, you can take time to reflect.  GR: Oh yes, and that was an era where this linear path to career, career, career, was sort of not the norm. Although I wouldn’t advocate it for everybody because there was a lot of carnage in the process in my generation. But yes, for me, I lived in my van for a year in the mountains of Oregon, planting trees and then traveled all through Latin America. I think one of the things is that I had a lot of stories to tell. You know it helps to have entertaining stories. I think for people coming to my lab, this is like a different experience talking to me.  AS: Let me finish by asking how much you think it made a difference training with the right people? Because when you did your postdoc training with [Wally Gilbert](https://www.nobelprize.org/prizes/chemistry/1980/gilbert/facts/) and [Bob Horvitz](https://www.nobelprize.org/prizes/medicine/2002/horvitz/facts/).  GR: Yes, they were super important.  AS: How much did they teach you if you like just to keep your eyes open for important questions. I suppose that might be the key?  GR: Well, these are role models for how to be a scientist and how to think about big problems. I was inspired by them and even by people I didn’t know, people I would see in the hallways. As an undergrad I studied physics at Berkeley, and I was surrounded by these mythic physicists who were so important. It’s a sea-change that you don’t expect coming right out of high school and all of a sudden you’re seeing people at the top of their game and it’s all they think about.  AS: What an amazing introduction to science, extraordinary. Thank you so much Gary.  GR: Thank you Adam.  AS: Do you think it’s possible that you could send me a photograph? Is there somebody with you that could take a photograph of you right now and send it to me?  GR: Oh God, I’m having a bad hair day, but I can do it within two or three hours. How’s that?  AS: Honestly, we’ve had laureates in pyjamas, we’ve had laureates in all sorts of lovely scenes.  GR: Ok, we’ll take a picture.  AS: Lovely! Thank you so much.  GR: Thanks Adam.  AS: Congratulations again.  GR: Thank you, bye. |
| **Interview** | Where does your passion for science come from? [2:31](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=151s) – What fascinates you about space? [3:25](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=205s) – Why do you love travelling and what can you learn from it? [5:48](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=348s) – What were you like at school? [9:40](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=580s) – What should aspiring scientists do while they are at university? [12:55](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=775s) – How did you meet your co-laureate, Victor Ambros? [14:55](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=895s) – How important is collaboration in science? [16:42](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=1002s) – Do you have any advice for scientists dealing with failure? [18:23](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=1103s) – We know you love to cook. Are there any similarities between science and cooking? [20:32](https://www.youtube.com/watch?v=Gj1qTh0E5L4&t=1232s) – How did you celebrate after the Nobel Prize announcement? |
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| **Podcast** | **“If I get an award, I have an opportunity to thank people. I also thank the people who tried to make my life miserable because they made me work harder and become more resilient”** Working harder and becoming more resilient seems to be the story of Nobel Prize laureate Katalin Karikós’s life. Despite facing a number of enormous challenges, she has never lost hope or focus. Instead she is convinced that it is better to focus on yourself and not to despair when life doesn’t go as planned.  In our podcast conversation Karikó, our 2023 medicine laureate, shares some of her best practices for overcoming obstacles and never giving up. As an added bonus, she also gives us some insightful parenting advice.  This conversation was published on 23 May, 2024. The host of this podcast is nobelprize.org’s Adam Smith, joined by Clare Brilliant.  Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.  Katalin Karikó: If I get an award, I have an opportunity to thank people. I also thank the people who tried to make my life miserable because they made me work harder and become more resilient.  Adam Smith: Speaking with Katalin Karikó, I was just so struck by how incredibly positive she is about everything, whether it’s disappointments in the work, or awful colleagues, or rejections, or losing a job, it’s all good. What a wonderful way to live. I mean, personally, I’m constantly set back by things that don’t go the way I hope they would be, but doesn’t seem to phase her at all. What an extraordinary ability she has and it comes over in abundance listening to her talk. So do stay with me for this conversation with Katalin Karikó.  Clare Brilliant: This is Nobel Prize Conversations, and our guest is Katalin Karikó, recipient of the 2023 Nobel Prize in physiology or medicine. She was awarded for discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19. She shared the prize with [Drew Weissman](https://www.nobelprize.org/prizes/medicine/2023/weissman/prize-presentation/). Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was producing cooperation with Fundación Ramón Areces.  Katalin Karikó shares her time between the private sector and academia as a senior vice president at BioNTech and an adjunct professor of neurosurgery at the University of Pennsylvania. In this conversation, she talks about raising an Olympic champion, getting up early to make breakfast for her lab team, and how a book by Janos Selye, the Hungarian-Canadian scientist, who coined the term stress, formed her whole approach to the ups and downs of life. But first, Adam and Kati discuss how she sees her place in the battle against Covid.  Smith: In his will, Alfred Nobel indicated that he wanted the Nobel Prize to go to those who had brought the greatest benefit to mankind, as he said, and humankind as we say now. Benefit to humankind is a difficult thing to define, but in this case, the benefit of the vaccination program during Covid was absolutely apparent. I just wanted to start by asking how it feels to walk around and know that most of the people you are passing in the street have been injected with a vaccine that most likely you were instrumental to developing.  Karikó: I perceive things differently. I feel that all of those who came before us, all of the science and what I learned from them and my colleagues here at the university or at BioNTech, everybody just worked together. I don’t feel that I did it. I felt that everybody did their part and I was just one of those. That’s how I feel. Otherwise, it would be overwhelming, probably. But that’s how I felt always. As I mentioned many times, I was not craving recognition that somebody would know that I did something. It was, for me, it was enough that I knew even without any pandemic, I knew that what I was doing is good, and one day it will be helpful for people. That’s why I went to Germany. I commuted for a decade to make sure that this product will enter to the clinic and will help somebody. I wanted to stay as long as I could see somebody will be helped. I just put one thing, and many, many people that did important things.  Smith: Certainly so many people were involved, and it’s a communal effort. And that’s, I suppose the wonderful thing about science. But nevertheless, it’s unusual to see the direct benefit of your work in the way that you and the others who’re involved in this program have been able to. Can I just get you to reflect a little bit on the impact of the work?  Karikó: The biggest feeling, what I was generated within, inside it was that, this Meadowbrook, elderly home where they get an covid infection broke out just one week after everybody received one injection. Then they send me the letter that when the first person get infected, everybody thought that one third of the people will be gone, and nobody died. Then they made this Katalin Karikó appreciation day and they were celebrating. They had a T-shirt, and they want to be grateful to somebody. They send me pictures when the children of those elderly people could visit the home. And the joy, I was happy that I was part of it. I know that they celebrated me, but I can tell you that it was more important than any award, including the Nobel Prize, reading that letter, seeing those pictures.  Smith: That’s lovely. I suppose, yes, it’s a very interesting point that people wanted somebody to thank. When I think of in the UK, people standing on the streets applauding the NHS on a weekly basis, they were just wanting to say thank you to somebody. How lovely to be the person they’re saying thank you to sometimes.  Karikó: I am most thankful to those people who were working in the hospitals, all of the healthcare workers, because they risk their life. They went every day taking care of the patient, and they didn’t know that they can infect it or infect their own family. They risk the most and they are the real heroes.  Smith: Your story has become very famous. People know you as the person who believed in the power of mRNA therapeutics against considerable adversity and stuck with it. Is there a simple answer to the question of what gave you the resilience to stick with your beliefs?  Karikó: I think that learning how to handle stress, to not pay attention and not to divert when I believe in something. It was all coming from when I was 16 years old and I was reading Janos Selye’s book about our life and stress. I am not a religious person, so we didn’t get some word from the church or what to follow. That was what I really followed in my life. It was like some stoic philosophy that I just focus on what I can change and all of this outside, opinions etc, I just take it as learning. Like if it is hurtful, I learn that I won’t do and won’t tell anyone about it because it’s hurtful. Everything is learning. Even from very early on when one of my teachers said that he will make sure that I won’t get accepted to the university. He will arrange that I realised that not everybody’s rooting for me, and also that I had to even work harder to make sure that I will be the best and they will still accept me.  Karikó: If he would say to me when I was 18 that he was sure he will arrange it was very difficult to get into the university, he will arrange that I will get accepted. Somewhere I would just sit back. That’s why if I get an award and I have an opportunity to thank people, I also thank to the people who tried to make my life miserable because they made me work harder and become more resilient. That’s how you process stress because stress can kill you as Selye demonstrated. He coined the word stress for the human feelings. You have to learn how to make this negative stress to positive, because the positive we need, the anticipation and excitement we need that otherwise we wouldn’t get up in the morning. You have to learn and practice. It’s not easy. Selye described that when you are angry, the fastest way you can release your anger and the stress is revenge. He said that you should never do that because it hits you back and it escalates and it gets worse, and you never get down and quiet. He said, you have to find something to be grateful for the same person. You are just ready to make a revenge because the gratitude is also get back to you.  Smith: It’s amazing to me that you learnt this when you were 16 because of course there are examples of this, this idea of what doesn’t kill you, makes you stronger and being grateful for adversity. But it takes forever to learn. Yet you at the age of 16 decided you were going to read about it and learn. What drove you to be so if you mature about yourself at 16?  Karikó: Actually in the high school, we sent a letter to Selye, he’s Hungarian, and we couldn’t speak English. We learned Russian in the school, and we sent him letter and he responded. We get so excited. His book was published in Hungarian. We read the book and then in the biology after-school program, we discussed what this mean, what we have to do. It was not just, I am reading by myself. We discussed with the other students and with the biology teacher. We also sent letters to [Albert Szent-Györgyi](https://www.nobelprize.org/prizes/medicine/1937/szent-gyorgyi/facts/). He also responded. That’s why I feel responsibility in these days to respond to high school students and help them because you never know.  Smith: So you were already very switched on at the age of 16. You were interested, curious, ready to be a scientist.  Karikó: In elementary school, I was already competing in biology and I was in a very small town and I was third best in the country.  Smith: Okay, so did that come from within?  Karikó: We had garden and we had animals. I was just curious with many of the other kids and, of course, great teachers. My parents also encouraged us to study because they had no opportunity. My father had six elementary years and my mother had eight years.  Smith: Your father was a butcher, wasn’t he?  Karikó: Yes, he was a butcher. I watched when he caught up the animals and I was told that I was curious, I want to see what is inside now. The animal is not running. What made it run?  Smith: What about your mother? What did she do?  Karikó: My mother, she had just studied elementary, but then when we were born, she attended night schools and she became a bookkeeper. She was always reading books. Then she was very computer wise, she was 80 years old. She got her own laptop finally because she wanted her own, she could look up everything on the internet. She could set up the VCR for example, to watch one channel and record on the other one. She was technically great.  Smith: I don’t think I can do that.  Smith: She was a great believer in you as you mentioned during our lovely conversation in October, on the day that you heard the news of your award, you mentioned that she believed you were going to get it every year.  Karikó: Yes, she would. My mother told me, Kati, you know, next week is announcing, who gets to Nobel Prize? I will listen, you might get it, they might say your name. I told her, don’t worry.  Smith: Mothers are always right, right?  Karikó: Really 10 years ago I was kicked out from Penn after 24 years. No goodbye party, nothing, just get out. I walked to the parking lot and thinking what next? Because that’s what I emphasised to young people: these things happen to you. You don’t have to think too much about why things happened to you because this is other people’s decision and you have to focus on what I do next. You have to spend all of your focus energy on that, otherwise you are just bitter.  Smith: So even on that day in 2013, you remember the lessons you learned when you were 16 and you were able to take the positive from it and think, okay.  Karikó: I was 30 years old. I was terminated in Hungary in my position when I was 40 years old in -95, I was demoted from faculty position at Penn and I became senior research investigator. I kept working like nothing happened. Literally. I said, the bench is here I am in the United States of America, where else, if not here I could do what I want. So I still had the bench.  Brilliant: Katalin Karikó’s work is focused on mRNA. Can you explain to us in simple terms what mRNA is, Adam?  Smith: I’ll give it a go. We are all taught that the DNA in our bodies contains the information that creates everything we are. mRNA is a single-stranded messenger molecule in that pathway of information flow. It transfers information from the DNA to the ribosome, which is the machine in cells that makes the proteins that make us.  Brilliant: Why is this mRNA messenger molecule potentially useful as a therapeutic?  Smith: Well, you can see that in all sorts of therapeutic applications, it might be good to tell the body to make a particular protein. You might want to do so for some particular disease, or in this case you might want to do so because making proteins is an essential part of the pathway to producing vaccines in many cases.  Brilliant: How are proteins used for producing vaccines?  Smith: A vaccine is trying to get the body to produce antibodies that it will then use to stop an infection by some agent. In this case of the Covid virus, what you want to do is to give a piece of the covid virus that isn’t dangerous to the body, get the immune system to recognise that piece, produce antibodies, and therefore be ready for a real attack by the covid virus later. You can produce those proteins in the body, those non harmful proteins in, in various different ways. One way is to give the body the mRNA that makes the protein, have the body produce that protein, have the immune system recognise it, and then have these antibodies ready for when the real virus attacks. The protein for Covid that has standardly been chosen as the one that gets the immune system going is the spike protein on the outside of the Covid virus.  Brilliant: How did Karikó and Weissman’s work help with this process of developing the Covid vaccine?  Smith: What they noticed was that mRNA that’s made outside the body in the lab evokes its own immune reaction if it’s given to somebody so that it doesn’t get to do its job because the body immediately recognises it as an invader, as foreign and eliminates it. They found a way round that they recognise that the problem was that the mRNAs that are being made in the lab aren’t chemically modified in the same way as those that are made naturally by cells. They worked out what kind of modification they needed to make in order to produce lab built mRNA that was acceptable to the body and could get on and do its job and produce proteins.  Brilliant: That sounds like a really important discovery. I think they published this in a paper back in 2005, but it didn’t get much attention at the time. Why was that?  Smith: No, I think they were quite struck by the thunderous silence they encountered. People did see its importance, but it didn’t fly in the way that they thought it might. I suppose the answer is that research findings take time to filter through. People are not particularly looking for that at the time. People are not recognising its importance, not seeing how to apply it. If you think of the 1953 paper in nature announcing [Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/) and [Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/)’s proposal for the structure of DNA, that’s always talked about as a truly groundbreaking moment. Indeed it was, but it also took time for the implications of that paper to be really widely felt. It wasn’t, for instance, until 1960 that Watson Creek were nominated for the Nobel Prize. That’s seven years later. You might have thought if the impact was so enormous, that might have happened sooner. I guess it’s just a case of things take time to filter through and be understood. The delay in the importance being recognised was certainly not ideal for Kati Karikó.  Brilliant: Yes, it’s really interesting to see the similarities here. How did Katalin deal with delays like this and other setbacks in her career?  Smith: Yeah, she certainly had a lot of setbacks, which seems deeply unfair. But she speaks very candidly and interestingly about the way she dealt with the rejection in setbacks she encountered at Penn. Let’s listen to her.  Karikó: I don’t blame even those people who evaluated, I don’t know who did because there are 10 names there, but I can imagine they had children, they have teams and they have to submit grants and write papers and they look at there and it was probably was not well written or something and they didn’t understand. That’s the other thing. I always, when I get back any rejection, I always thought that, when I was reading that, probably would say, oh, they are stupid. They didn’t understand. They just said, oh, they didn’t understand. Probably I didn’t write well so they couldn’t understand it. This is a practice, it’s not coming easy because people has easier to blame somebody and it is easier to say that, oh, they should, they should accept my paper, they should accept my grand, my husband should be that my children should do. People always want other people to do what they should do. For example my neighbour should be quiet. You cannot change that. You always have to say, okay, what I can do, I can move out in the neighbourhood.  Smith: It’s such a powerful philosophy and I envy you the strength to keep applying it in every circumstance. But when it comes to your own research, you must have had really strong belief that you were right. Because if people are telling you, no, we’re not funding this, you might begin to listen to them and think, hang on, maybe they’re right. But that didn’t occur to you. You were sure that you were on the right track.  Karikó: Every time when the response came back, I already could see something improvement. So, now I have a new cap and then with this one I get more protein and so I can further improve the process. Because the criticism was that the RNA that grade quickly, I was told that it could be a medicine if it has a shelf life of two years. Of course at that point we mix the transit and the RNA and two minutes we have to inject because otherwise it gets aggregates. It had to be somehow frozen and taken out a liquids so that two years later. That’s what I have to work on. People are making decision above my head but in the laboratory I was in full control and it’s like in the 21st century, I did most of this thing myself. There were no technician, I had no money to hire anybody. I was making all of the solution and culturing the bacteria, making the RNA, culturing the cells, putting, evaluating. When I was doing, I was always thinking, aha, if it’s not coming out what I expect, maybe this or this had to, it is good if you do these things. I was 58 years old, I did all of this still myself, all of these experiments.  Smith: It’s a great gift not to be precious about sort of being in charge about being director and having people working for you and everything, but actually just accepting that it’s okay to do these things yourself. Because obviously it worked better in your case.  Karikó: Yes. During the pandemic many group leaders realised they are just managers. They are managing, they have to bring in the money because they had to be pay all of those coworkers. The joy is really to do an experiment, expect something to happen and wonder what could that be? That’s the joy.  Smith: I remember another great experimentalist, Nobel Prize laureate [Oliver Smithies](https://www.nobelprize.org/prizes/medicine/2007/smithies/facts/) saying very proudly, I’ve never been a director.  Karikó: They ask me many times; tell me how you can be successful. I believe that is not the success. It is that you are happy. That’s number one thing. Whatever you are doing, you have to feel happiness. You have to have a physical and mental health. And for that one, I exercise every day today, yesterday, every day. Once I run the marathon, but you don’t have to go that far. Just like even in Germany, six kilometer every morning I went before I went to work. And for handling stress, you have to practice it and you have to enjoy. If you ask my husband, all of this frustration seems from outside, he never could see me come home and complaining about this and that. He always was convinced that I am having so much fun that he said, you are not going to work. I am going there to have fun.  Smith: You seem to have got various of the secrets of life worked out here. Live as you want to live, don’t be pulled in directions you don’t want to go because of what’s going on around you.  Karikó: The people I could see also, they are living up to an expectation of something. They think that that’s what they expected from them and then not their life. I met my husband, he’s five years younger and my mother, she said, that’s okay. Let’s say 17, you are 23, that’s fine. But when he’s 40, you are 45 years old. The woman is then an old woman. A 40-year-old man is a young one. So I told, okay, I will divorce when 45 and that’s it. There’s nobody who could influence me, to tell me that it is not right to do something. That’s what I tell the people because, then they don’t have regret. It was my decision.  Smith: The move to Germany, to BioNTech, was forced upon you by the fact that you had to leave Penn. It was hard because you had to commute between the US and Germany. But it turned out to be a good thing.  Karikó: Yes, I enjoyed it very much there. It seemed that the goal was to make a product which will help somebody otherwise we can go home and it’s over. It was more meaningful than more paperwork and more references. It was great that we all worked together. It was not a competition. I could see the people here in academia, they didn’t even start something and they were, oh, I will be the first out, door last. There we just have to do work together and everybody helped, and this doesn’t matter. I was there and I worked day and night really because my family was here and I was alone. I spent the whole weekend working. I remember Saturday, Friday, or midnight at morning and I was still reading because I read a lot during that time. I had a team finally, and they were all great scientists.  Smith: That is quite a privilege to, despite the hardship of being away from home, be suddenly given time to yourself again, and be allowed to just use it as you wish.  Karikó: Yes, it was great. I was assisting my team so that every morning I brought breakfast for the team and then I was the last one to leave. I was the first and I was the last, I was cheering for them. I tried to assist them with what they needed and always led them to come up with what we should do next. Because if you tell somebody this is what you should do. That is not the same as if they come to the conclusion themselves. Then they are much more enthusiastic to do it. My team, even today, nobody has left. My team is still there.  Smith: Listening to you that’s not so surprising. You sound like an inspirational leader.  Karikó: They should not respect somebody because they were put above them or something. When they said boss to me, I said no, I am a colleague. As a team, we work together and we discuss and internally we fight about how to do things. Externally, one thing I fought for getting everybody promoted to associate directors. I finally had to go to the union. They asked how it could be that my whole team should be promoted? But I thought that everybody’s independent, they could lead a team, but they wanted to stay in my team.  Smith: It worked.  Karikó: It was successful. Everybody was promoted.  Smith: That’s a very good solution to the problem of staying put and not getting promoted. Just take everyone along with you.  Karikó: Yes, they are doing great. I’m so proud of them. That was one prior to the pandemic, when we realised one day that changing a little thing has tremendously changed the translatability of the RNA. We get so much more protein and we have to figure out why, because we had a clinical product already, and then it was like, okay, so we can do this and this. Then when we discussed, I didn’t have to say that you should come Saturday or Sunday. Because this was very urgent, so everybody said that they will come. Everybody said so that we had just sorted out.  Smith: What a joy to be part of an enterprise like that. Talking of the working relationships with your team, let’s think about how you worked with [Drew Weissman](https://www.nobelprize.org/prizes/medicine/2023/weissman/facts/), because you are quite opposite characters. You obviously hit it off enormously well. What was the secret of your successful relationship?  Karikó: We were experts in a different field, so we were constantly educating each other. I learned immunology from Drew. I learned immunology in school, at the university but that was already out, the field was changing so quickly. I was not paying that much attention to immunology before that. I learned all of these things from him and I was helping him set up his lab. We never worked in the same lab actually, not even in the same building. We were in different departments, so we educated each other. When we had to perform the experiment, we decided that we would do that. He didn’t get the much money at the beginning, so he prepared the dendritic cells himself. Then I performed the experiment made RNA, and so then what the experiment meant, and then we would have different views on it.  Karikó: I remember at the beginning when we discovered that modification. If the modification was not present in the RNA, we got so much interferon. He as a physician thought maybe the lupus patient has so much interferon because they might not modify their RNA, so he ran away and get some sample from lupus patient that we looked at the RNA. I isolated it and okay, not, but I would not think that much about this patient. I had other things to think about, many technical problem we had to solve, like the purification. I remember New Year’s Eve and New Year’s Day, I was there in the lab because I always thought about how to purify the long RNA. Nobody figured out how to, but that I get an idea.  Karikó: I told my husband that I could park right in the door, nobody was there. You try many things and it does not work out that way. Eventually after two years, we did figure out how to purify it again. Drew and I discussed and he tried things and he came up with the HPSC, changing different columns, what we should do. He was very involved and sometimes I said ‘I give up on that’. He still did it and then I said ‘okay, maybe you are right’. So Drew in the laboratory when we looked at data and he was just like me, cut into my words and he was very talkative and what we should do. What did it mean?  Smith: It sounds like two people really enjoying each other’s curiosity, which is exactly what science should be. You’ve received so many prizes now and a lot of public recognition. Do you think your role has changed because of all that?  Karikó: I have to say that at the beginning when I had to give interviews, I didn’t know what to say. I was just like, sometimes I couldn’t say anything. Then I realised that that receiving prizes and these prizes is very divisive because there are so many people, I should break the prizes into pieces and give it out to the people. In the same time, the attention is on science and the scientists and it is celebration. It is important that science is celebrated and the people get more knowledge on what scientists are doing. Many people at the beginning ask me to share my story. I asked my daughter if I should tell my story, Hungarian and English, and finally she found an agency and that’s how my book was born. That kind of describing of how much fun is the scientist? I also, in these different occasion, I want to emphasise that when they said, oh, you struggle, I don’t want to describe the scientist life as a struggle, because then people run away. It was not struggle. It is fun. Getting grant and support and other things, yes, you have to work for it, but this is not like a pain or something. It is every time I learn so much, I love to write. I did not emphasise to colleagues actually at Penn because people not really like it. But I learned so much because I had to think about what will be the outcome, what it means. I had to read, read, read and learn. When I get different awards, I first try to emphasise that science is fun. To be a scientist is something you get paid for, enjoying your time there. Also encouraging the young ones that science is maybe what is good for them. That’s one thing, and I try to help and be a cheerleader for other scientists. Because many people can associate to my story because usually you are not getting promoted and immediately becoming successful. Because I went down, down, down, I expressed all of these things and I am an alien. I am a woman, a woman talking with an accent. More people could feel, and they were just happy that, okay give them hope that you just keep focusing and not complaining that much.  Smith: Would it have been a fulfilled and happy existence if it hadn’t worked? If you just chased your curiosity, gone down and down and down and found another thing to do, but somehow at the end of it, you hadn’t seen it all come right?  Karikó: I could see that RNA entering clinical trial because it happened already in prior to the pandemic. For me, it would be satisfactory how many times, when I was flying and I could look down and people, even cars disappear because everything is so tiny. I always thought, hundred years from now, nobody will remember we ever existed, you know? So this fight for recognition was never in me. I could see that, okay, people are using this Moderna. I was there, I was so happy. I was reading at the beginning that they discovered the modification. I said, okay, it’s not really they, but who cares? Something happened. They are using for clinical trial and something is happening. I was happy, honestly didn’t complain to anybody that, oh, they are using, no, it was good. It is good that they are using for and pushing it and who cares?  Smith: I was here and something happened.  Karikó: Yes, I was part of the process and when they will have cure or something, I said, oh, I did my part. For me it was enough that I would know and not the whole wide world.  Smith: It is such a pleasure to speak to you and it is inspirational. You seem to be somebody who really knows yourself. You know what you are about. I think it’s quite rare to have such a clear vision of how to steer your way through life and remain on an even keel.  Karikó: Many times during award ceremonies I often say to the girls that they can be mothers and my daughter also turn out quite right…  Smith: It’s an understatement as an Olympic champion.  Karikó: Yes, so now the grandchildren, that’s the thing for them. Mommy got two Olympic gold medals. Grandma got a Nobel Prize. What should she do?  Smith: Now that might be a worry actually.  Karikó: Yes, that’s what important, I told the potential parents of young scientists that don’t over assist your child, no tough love. You have to love, but you have to let them contribute to the family life. Just like when I was a child, with my sister, we did many chores, but it was like we didn’t feel that it was work. It was like we are part of the family and we were happy that we could do, and we were so proud that we could do things. My sister could cook. She was in elementary school and my parents had to work long hours. Of course I was the assistant because she’s three years older, so I just peeled a potato or made the fire because we had stove and she was cooking and so on.  Karikó: My daughter was the same, she learned that she had to get up and dressed, you have to go to school and when a child could see me and my husband working diligently, that’s what they will remember. That’s what they want to follow. You can tell them to do your homework. You are watching tv. You are not doing enough, then they see that. Like my parents, I was so proud of them for what they said to me. Not everybody’s like that. These kind of straightforward, honest people were my parents and I thank them a lot. Not just for the genes I got.  Smith: How nice. I think, yes. It’s just going back in conclusion to that amazing statement you make, that you thank everybody along the way. Those who contributed, those who helped, those who hindered, everybody made you what you are and made you made it all possible.  Karikó: I think that, in the first, I don’t know, 10 years of your life, whatever influence you see your parents, how your siblings, your school, the teacher, that’s how you are shaped. Then when you are teenager in high school you are a rebel, but then eventually you will be that person.  Smith: That’s a very nice point to stop on. I think that all of those with rebelling teenagers will hold onto that thought. It’s been an enormous pleasure speaking to you. Thank you very much indeed for giving your time.  Karikó: Thank you.  Brilliant: You just heard Nobel Prize Conversations. If you’d like to learn more about Katalin Karikó, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Claire Brilliant. Music by Epidemic sound. If you’d like to explore the journey of another laureate saving lives through their research, listen to our earlier episode with chemistry laureate [Carolyn Bertozzi](https://www.nobelprize.org/prizes/chemistry/2022/bertozzi/podcast/). You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | 0503=KK  Katalin Karikó: Hello?  Adam Smith: Hello, may I speak to Katalin Karikó?  KK: Speaking!  AS: Hello, this is Adam Smith calling from nobelprize.org  KK: Yes Adam!  AS: Many congratulations on the award of the Nobel Prize.  KK: Thank you, thank you very much.  AS: Where are you and how did you hear the news?  KK: I was sleeping, and actually my husband picked up the phone. I am at my home in a suburb of Philadelphia in Abington township. And I was away in a conference in Cold Spring Harbor, and just Saturday returned. We celebrated 50 years of recombinant DNA technology. I met all of those people there, 80s, 90s that did the basic work, and I just came back.  AS: A lovely gathering. And on hearing the news – I mean you’re no stranger to awards of course, they’ve been coming so thick and fast recently – but what were your first thoughts on hearing this news?  KK: That somebody is just joking!  AS: How were you reassured?  KK: It was kind of very scientific and too much information was in it that somebody would just make it up. But you never know in these days.  AS: Now you know for sure!  KK: I’m not … [unclear] a hundred percent sure!  AS: Yes, maybe it’ll never sink in, who knows.  KK: Yes!  AS: Apart from the doubt and the reassurance, what does it mean to you?  KK: Adam, if you know about 10 years ago, I was here in October because I was kicked out, from Penn, was forced to retire. Then my husband supported me and said that, you know, when finally visited in Germany and found that maybe BioNTech is the right place, then he said “Just try it and I will make sure that you don’t regret.” Looking back in my life he supported that I would go, and for nine years I commuted to BioNTech in Germany. I did all these experiments actually, with my own hands, I was 58 years old, I was still culturing plasmids and feeding cells, so it is very unlikely.  I have to say that my mother, she passed away 2018, but my mother listened always to the announcement of who gets the Nobel Prize because she told me, “Oh next week they will announce, maybe you will get it.” You know I was laughing, I was not even a professor, no team, and I told my mom, don’t listen, and she said, “Yes but you know, you work so hard.” And I told her that all scientists work very hard.  AS: How wonderful to have someone who believes in you to such an extent.  KK: Yes, she believed, and my daughter she watched me work hard, and she became two-times Olympic champion.  AS: Olympic champion in what?  KK: Rowing, and she is a five times world champion, and I went to this, she was inducted in the hall of fame, she was rowing here and there, and I was always introduced like “She’s Susan’s mom.” I was Susan’s mom. And now that my daughter came several times to the awards ceremony with me, and she was introduced as “Kati’s daughter.”  AS: I must say, for me it’s a great delight to be talking to Susan’s mom on this call! But I suppose the message in all this is that persistence can pay off, in the end.  KK: Yes, to persevere, and I believe the first 14 years of your life, your genes, your parents, your teachers, your friends, they shape you, the person who you will be. I also, as a woman and a mother, I try to tell fellow female scientists that you don’t have to choose between having a family, you can have it, you don’t have to over assist your child, your child will watch you and they will do, because that’s what counts, the example that you present.  When I was 16 years old, I read the book from Hans Selye. Hans Selye is a Canadian scientist, but he was Hungarian so his book was translated to Hungarian. His mantra was that you have to focus on things that you can change. Many young ones are giving up because they can see that their friends or their colleagues are advancing, and it seems that they do less and somehow, they get higher salary and promoted. I told that if you notice that then you already took away your attention what you can change. Because you cannot change that. And I told that when I was terminated, I didn’t spend time feeling sorry for you and saying things like “Why me?” You have to focus all the energy you have to spend, to seek out, “What next? What I can do.”  AS: Indeed! Let me just ask you very briefly about your working relationship with Drew Weissman. You strike me as very different characters.  KK: Yes, he is like you know. I brag, I am more talkative. But when you would see us looking at the data, we cut each other’s words! What it means, you know, we’re very ‘alive’. About the experiments, and we were very similar. But then yes, once Drew showed me “You know Kati, from A to B you zigzag, zigzag, zigzag, zigzag! And I am just like, straight.” But I told him that when I zigzag, I learn so much!  AS: Indeed, zigzagging seems to have been very productive! It’s been so lovely to have this relaxed conversation, I am afraid that it’s so early in the morning, but your day is just going to get busier and busier from this point on, good luck with it all, and thank you very much indeed.  KK: Thank you very much.  AS: Bye.  KK: Bye. |
| **Interview** |  |
| **Q1** | What brought you to science? |
|  | Honestly, I have to say my high school teacher, who said that ‘You could be a scientist’, and he said it so many times that at the end I believed it and I imagined myself that I will be a scientist and imagine going to work and every day figure out something. I had never seen a scientist, I grew up in a very small town, and I decided that I will be a scientist. Somebody is believing in you, maybe that’s the inspiration. |
| **Q2** | What do you enjoy most about science? |
|  | Science is fun, to be a scientist, this is a fun job. What is exciting is that there is a complexity, and then it is you who can solve it by reading articles or doing experiments and put together things which maybe nobody did. Then you realise what’s going on. The joy that you were the first one to know that this is how things happens. That’s one. It is very similar to be like a detective or an investigator on a crime, but the end of it, you don’t find a perpetrator, you find a solution, and maybe that solution would help somebody. That’s what is the beauty about it, maybe somebody who’s sick and then your discovery can contribute to their healing. |
| **Q3** | How have you maintained your focus despite all the obstacles you have faced? |
|  | **I have to say that people judged me unsuccessful when I felt very successful, because in the laboratory I was in full control of doing experiment, getting question asked and then getting the answer for it. Of course, you never get the answer because when you do an experiment, you get more questions instead of the answer. But this is what is exciting. It seems that not getting funded and there are other difficulties. But actually, when you are a scientist, you constantly have to fight the failures and solve problem difficulties. You keep repeating, you don’t understand, so it is like scientists are those who can get up and keep working with the same enthusiasm. That’s actually some defined success that you can stand up and you can keep on with the same enthusiasm as before.** |
| **Q4** | What advice do you usually share with young scientists when they are facing obstacles? |
|  | I have seen that the young scientists are comparing themself to the others, seeing that they are maybe less hard workers, and they are advancing. I say, ‘Don’t do that. You have to focus on what you can do’. If you already took away your attention and paying attention on somebody else, you won’t succeed. You have to focus on what you can do, what your project is. I also tell them, to be a scientist is not for everybody. If you like to follow instructions, maybe you have to go to the military. You like to be in the spotlight, like I am right now, you have to be an actress or maybe a reporter. Because a scientist is usually thinking in the laboratory and is not in the spotlight like I am. You have to enjoy no matter what kind of work you are doing. That’s the most important.  I tell them also that physical and mental health is very critical. I used to exercise every morning. I was running six kilometres, even when, 10 years ago, I worked in Germany and on the Rhine, I ran six kilometres, once I even ran the marathon. I was 50 years old, I set up the goal to make it, and that’s it. You have to learn how to handle stress. That’s also very important. I was very lucky that I learned from Hans Selye who was Hungarian, and he was studying stress. In Hungary, when I was 16 years old, I read his book and learned how to handle it. The mantra is, I can tell the young one – and even the old one if they don’t know about it – is that you have to focus on what you can do. Not that what your boss should do, your wife should do, your neighbour should be quiet or something. You have to decide what you can do about that, that’s what is taking away all of the stress |
| **Q5** | Was there a specific mentor who influenced your career? |
|  | My father was a butcher, and I heard that when I was little, I was curious when he opened the pig, and I want to see what is inside, whereas my sister and my mother did not want to see that. I don’t remember that, but they said that I was standing there seeing that now, this animal was moving, now, it’s not moving, what made this animal move? I don’t know, but definitely the teachers. I am very grateful to them, because in elementary school already we had excellent teachers, and we went to … Like with the biologic teacher, we just went to outside in the fall, and he picked up the leaves and said, ‘Oh, it is yellow. Is it the yellow it became because it was green before, or maybe the yellow was behind the green and the green is gone?’ He made us think, ‘Hm, or the red leaves, where is the red coming from?’ I am very grateful to them. In elementary school I already competed in different biologic competitions, and at eighth grade, I was the third best in Hungary. |
| **Q6** | How was it to visit your home country Hungary after the Nobel Prize announcement? |
|  | When I went back to Hungary, to my alma mater, it was a beautiful sunny day, and several hundred people were there and they were cheering, and I was just so surprised. Then in the evening a few thousands were there and every time they said, ‘Say something’ and in the moment, I just remember that when the announcement was made, and on that day we went to the university, there was a flash mob. After that Drew Weissman went to his team to celebrate, I went home. Then I told the people there who were waiting, in Hungary, I told them, ‘Now, I am here. I want to celebrate with you’. Because the city Szeged also is very important because I studied there for five years, and that was one time I met my husband there, we married, my daughter was born in Szeged. All the happy times that I was in this city, so happiness belonged to that city. I told them so, and they were cheering to any word I said, they were cheering. |
| **Q7** | What do you plan to do with your prize money? |
|  | It is most likely I will spend the money for education and helping students. I don’t really like to brag about things, but all the award I got in Hungary, I never took out from the country. I gave to organisations helping underprivileged children. I, myself benefited from that because my parents had just elementary school education and going to the university, even getting a high school diploma I was in the first in the family. My sister also got a high school diploma and she also got a PhD in economic, but we were from there. I think that those children whose parents may be not educated enough to see that the future brightness of their children should be followed up in higher education. There are programs there, so I gave money for that. Also at the university, my alma mater, University Szeged, some prize money I channelled there. Even other awards, like Princess of Asturias, to the local kids I gave the money back. |
| Q8 | How was it to move from Hungary to the US? |
|  | I was born 68 years ago in Hungary, and up until I was 30 years old I was living in Hungary. I got my education, my PhD, I started research on RNA, even lipids, I did study. Moving to the United States was not easy because I lost my position in Hungary. I tried to find a job in Europe and I applied for a couple of jobs, but I couldn’t apply for finance because we were behind the Iron Curtain and eventually, I had to go all the way to America. I am one of those scientists, I never dreamed about going to America. Everybody was talking, ‘Oh, America’. I was very happy in Hungary, but I had to go. I ended up in Philadelphia, and the system was at that time in the communist Hungary that you are allowed to leave the country with $50 per person, and because I got a job offer, I even was not eligible for the $50. The family, my daughter was two and a half years old, my husband, we had a hundred dollar, so that was difficult to imagine that we are arriving and for one month how we will survive. We had a Russian-made car, and that we sold to my colleague, and then on the black market, we exchanged the Hungarian currency to pound. We got like 800 pounds because they had just pounds, not the dollar, and that’s what we got. That’s how we started in America. Imagine that you go there in 1985, you don’t have a credit card, you have no cell phone, iPhone, we didn’t have any, at that time nobody had. I had nobody there I knew, no family member ever got to America and then no classmate, no teacher, nobody. You just have to learn so quickly how to survive. |
| Q9 | What was your first impression of the US? |
|  | It was a cultural shock. When arriving immediately they said, ‘Now you have to select a bank’. I said, ‘Why? I don’t need a bank. I never had in Hungary, a bank’. They said, ‘How did you get the salary?’ I said, ‘Oh, it was in an envelope. It was counted all of the last pennies in it’. They said, ‘Oh, we don’t do that’. Everything was a shock because going from Hungary today to there would be very different. But in 1985, it was unbelievable. |
| Q10 | What does Hungary mean to you today? |
|  | I grew up there, my sister lives there, my mother, she passed away five years ago, but she lived there, I have relatives there and I grew up there. But of course, that Hungary which I left is very different now. I have to say that when I worked the last 10 years in Germany, I felt in Germany more a Hungarian. I could see things there that reminded me of my home. Of course I am happy to go back and talk to fellow scientists and meet my colleagues and fellow students, but it is different. That’s the same way even for United States, because when I was working in Germany and going back, now I go back to University of Pennsylvania, I worked there for 24 years. I worked there, and I don’t know the people, they are changed. Of course the campus also changed a lot. |
| Q11 | Tell us about your co-laureate Drew Weissman and your collaboration. |
|  | I used to work at the cardiology department, which belonged to the cardiology section, which belonged to the department of medicine. But then from there, I moved to the surgery department, which is a different building, an adjacent building, but I know the code for the Xerox machine only in the medicine. Surgery, where I worked, had no Xerox machine, and we always had to Xerox copy the scientific articles. I keep going back to the prior place, and then I could see this guy I had never seen before. I introduced myself because I kind of like to brag and I told him what I am doing while he was xeroxing. He’s very quiet, so I mentioned him that I work with mRNA, and he said that he came from Anthony Fauci’s lab. At that time it didn’t ring any bell for me, for Fauci was not in the television all the time. Then he said that he wanted to make a therapeutic or prophylactic vaccine for HIV, and we started to talk more. I told him that I can make mRNA for him. He gave me the genes and I cloned and I made RNA and we started to work together. So it is true, we met at the Xerox machine, but that part that we were wrestling and fighting, that was not true. We looked at the data, scientific results, then we were not different. We cut each other words, what does it mean, what we should do, no, we should do that, we were talking like that. But otherwise, he’s quiet more, according to his wife he has a limited number of words he can say one day, and when he goes home, he already used up all. He’s a physician, so when we looked at some data, he was thinking about some disease-related thing, and I was more thinking about the basic science because I am a biochemist. We educated each other. I learned from modern immunology vaccinology from him, and he learned the RNA part. That’s one thing, that where the innovation can come. You might have a big team and you are investigating some phenomenon from many different directions, huge team can do that. Or there are two persons who are on different fields, they understand each other, they respect each other and educate and then they come up with something. Oh, I can do that, I can do. Then they proceed. |
| Q12 | What advice would you like to share with young scientists? |
|  | The number one thing: you have to enjoy what you are doing. It is important. You have to realise that you like the things, what you have to do in the rest of your life, as if you select as a job. I mentioned the health is important because you remember the airplane, you have to use the oxygen first on you. If you are not okay, then you cannot help others. You have to be happy, healthy, and stressless. You have to take care of yourself and then you can help others. The young ones, we can go on and on how many things I could tell them about how they should proceed, but the most important thing is that they have to enjoy what they are doing. I have to say what is important if they decide they will be scientists. What I could see is that you have to solve a problem. You are working on this problem. What is the thing is that you publish because you’ve discovered something, and then somehow you want more discovery, more money is needed, applying for fund. Then finally somehow publication is coming because we need more money, we need the promotion, and the goal will be somehow is advancing your career to promote tuition and other things, and the prestige, and somehow the original goal becomes a tool to reach that. You are publishing because you have to get your PhD degree, you need more grant, more money. If you stay with the focus on solving scientific problems, you’ll never be disappointed. When you move to this one and you don’t get the promotion, then you’ll get the disappointment because this will not depend on you, maybe on some other organisation or superiority. But here the problem is always there, you can always work on it. |
| Q13 | Is diversity important in science? |
|  | It is important in science to have women because we are thinking differently. We are multitasking, guys cannot do that very well. People have different views, different thinking as I mentioned, like somebody’s a physician or there is a basic scientist and they are thinking differently. If they work together and respect each other, then a new invention can be done. That’s what I think is important, so I try to emphasize that women are important for science, and the science need more women because at the beginning there are many women graduating schools and they have their dream, but the difficulties might come when they have a childbearing age and they want family. I was lucky in Hungary because we had high quality, affordable childcare, so I could stay at work and I was confident that my daughter was taken care of when I was working. I can see in many countries that if you are not having enough financial support, then you have to give up your job because that little baby is crying there and you have to take care of it. Your dream is just a potential, giving up seems a solution to take care of your child. But if a government is listening, then we have to talk to them how important that would be because more women could do more discoveries, |
| Q14 | Do you see any similarities between sports and science? |
|  | It is kind of like setting of a goal. When I was practicing for the marathon, my daughter was biking next to me, ‘Mom, come on, come on, you can do it, you can’. Even when it was the race, she volunteered to give out water, hardly could wait when I will reach that water stand so she can give me the water. The race was in November, in March I started to practice. You are not getting up in one day, ‘Okay, today I run a marathon’ – you will be dead, you cannot run. She could learn that you have to do the preparation every day, do something towards that goal. That’s what setting up goals is what is important, for everybody, a child, old people, everybody has to have a goal and then work towards that and when you reach that, you are setting up a new goal. That’s like they told me, that you get a Nobel Prize, and that’s what you can do after that. I mean, that’s not a goal. A goal is that I am doing my research and then when I am done with certain things, then I set up a new goal – it cannot be a goal to get an award, because anyway it does not depend on me. I told that always I have to focus on what I can do, and those are other people’s decision. That’s for the firing and terminating my position. I also said that it was other people’s decision and I have to focus on what I can do instead of feeling sorry for myself Why me? There were other people could be fired. Why me? No, don’t spend your time because you are feeling down and feeling sorry for yourself. You focus on, okay, now what should I do? Because you can make a decision, and that’s what important. I mentioned that it is not necessary that you have to be happy if you are terminated in a position. I was not happy, but did not spend time on being sad, but I have to do something next. |
| Q15 | When did you learn the importance of setting up goals? |
|  | In the process, as I mentioned, in elementary school when I was writing about Linné, it was for the high school advertise that you can write an essay. Every day I was reading something, writing something, and you work towards and submitting that essay. That’s already the win. I never get any award for that, and that is not important. I set up a goal and accomplish, and then the next goal to set up, and maybe my daughter, watching me, learn that. That’s what I say to also the parents. You don’t have to over assist your child; they like to be independent. Rather than what you are showing that you go to work, what is important, how you talk to other people, that’s what they watch. They could learn from that. You can tell them certain things and they can see that you are acting differently. They notice that and they will take on that. So, if you work hard and you enjoy your work and your child want to do that also. |
| Q16 | Did you realise how important your research would be during the COVID-19 pandemic? |
|  | I worked at BioNTech and BioNTech signed with Pfizer in 2018 to develop mRNA-based vaccine for influenza. We already worked two years, -18 and -19, and we did all of the studies and were ready for start a human trial for influenza. The technology is such that you just have to change – I should say just, but, still is a process – change template and then you can make the different kind of vaccine, and that’s what happened. We were ready with all of this preparation for another fight, another disease. But here we had to have prophylactic vaccine for the sars covid 2, and the influenza was ready, so a lot of preparation was done for a different virus, but it is now, it’s phase three trial. The vaccine for influenza is very important that the RNA, because it is always from the four nucleotides, contains the four nucleotides, so we can have a multivalent vaccine. The influenza, again, influenza A and B and different many different proteins encoding RNA can be in one shot. Right now, not even just the influenza, but even the covid vaccine and respiratory CCR virus, it’s one shot because you can combine them. If it would be protein based, you cannot do that because they will stick to each other and then will have an aggregate because the protein can be charged negative, positive or hydrophobic hydrophilic, and you cannot mix them. But the RNA, you can do it and the subject will synthesise the protein, and then those proteins will teach the immune system. That’s what the enemy is, you have to recognise. |
| Q17 | How does it feel to know that your research has saved millions of lives? |
|  | I have to say that I myself, I never felt that I did. I relied on the work on many other people, I was doing research for 20, 30 years. I learned from reading articles from people who are not with us anymore, and I learned from it. I had colleagues and so many, many people who contributed. I feel that we did it. We scientists, with all of my colleagues at Pfizer, BioNTech as well as University Pennsylvania, and those scientists who worked on the field. That’s how I feel, and I have to say, I was lucky. I never had this craving of recognition. There are some people who want to be recognised. For me, it was enough that I know that what I did and what is important and not that other people would know. For me, I feel that a lot of scientists, hundreds and thousands of scientists, contributed to the knowledge, because the RNA was discovered 60 years ago, and during those 60 years, many things happened. I will present that on my presentation and the Nobel presentation lecture. I will tell you that how many things was discovered and was contributed by scientists. As a scientist, I felt that I didn’t expect it that what I am doing will be that important. I know that it is important. I know that one day maybe other scientists will take on and reaching in one day a level that somebody will be helped. |
| **ID** | 0504 |
| **Biographical** |  |
| **Autobiographical** |  |
| **Podcast** | **“When I was a young kid, my father would tell me, you can do anything you want when you go to work. The most important thing is to enjoy it. I found that”** How can we ensure that knowledge and science is spread globally? Medicine laureate Drew Weissman is an advocate for creating research centres around the world to give local researchers the means to have ownership and solve health issues by themselves. As Weissman puts it: ”A lot of people set up a clinic in a city somewhere, collect samples, take them home, and study them. To me, that compounds the problem, because it doesn’t teach people. It doesn’t make scientists better.”  Weissman also tells podcast host Adam Smith about how his interest in science was sparked and how he has maintained that curiosity for the rest of his life.  This conversation was published on 13 June, 2024. Podcast host Smith is joined by Clare Brilliant.  Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.  Drew Weissman: You have to tolerate frustration to be able to work in a lab. But when you do make a finding, even if it’s a little finding, because of all of the frustration and all of the difficulty getting it, it makes it that much more important. It’s really, you know, kind of an inner joy.  Adam Smith: It was a long series of those little findings, which Drew Weissman refers to, which led him and his colleague [Katalin Karikó](https://www.nobelprize.org/prizes/medicine/2023/kariko/facts/), to make the very substantial contribution they made to World Health by helping to develop the mRNA vaccines used during the Covid Pandemic. And it’s interesting to contrast the abundant positivism of Katalin Karikó. With that quiet optimism you hear in Drew Weissman’s voice, whether that optimism is derived from the experiences he went through as a child. I leave you to judge, it’s something we discuss in this conversation. But anyway, I hope you enjoy very much listening to Drew Weissman.  Clare Brilliant: This is Nobel Prize conversations. Our guest is Drew Weissman, who shared the 2023 Nobel Prize in physiology or medicine with Katalin Karikó. He was awarded the prize for discoveries concerning nucleoside based modifications that enable the development of effective mRNA vaccines against COVID-19. Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces. Drew Weissman is the Roberts family professor in vaccine research at the University of Pennsylvania’s Perelman School of Medicine. He speaks to Adam about those aforementioned frustrations in the lab and other hiccups in life, how research is like raising a child and why he’s now involved in 250 different collaborations. But we kick off this conversation with a special introduction.  Smith: That is most definitely the most comfortable looking podcast recording setup I’ve ever seen. You sitting with your cat on your lap. Who are we in the presence of?  Weissman: Yes. This is Zander.  Smith: Zander looks particularly content and particularly beautiful. He’s a big fluffy guy.  Weissman: Yes. When I’m home, he’s in my lap.  Smith: Gosh, that’s lovely. Thank you very much indeed for taking the time to talk to me. I appreciate it very much. I also know that from what you said when you were awarded the Gerdner Award in 2022, you don’t much like attention. I guess these sort of things are not without their pain.  Weissman: I’ve learned how to tolerate them. Nothing personal.  Smith: How have you adapted? Because you have received many awards, you have very much been placed in the public spotlight.  Weissman: Yes, even before the Nobel Prize, Katie and I were traveling around the world giving talks, getting awards. My life was incredibly busy. That started probably seven years ago, when people first got interested in RNA and RNA vaccines. The Nobel has certainly increased that. The number of requests I get for anything has quadrupled. But my life was busy before and it’s still busy after, and I’m afraid it’s always going to be busy.  Smith: Do you have rules you live by that help you control everything?  Weissman: The issue was last year, we were traveling so much. We were at our house maybe four days a month. That was too much. We were getting worn out. Now I limit it to one international trip and one national trip per month. We’re still away half the month, but we’re here half.  Smith: It’s hard on your family.  Weissman: Yes, my wife usually comes with me when it’s interesting. I was just in Houston, Austin and Durham. She didn’t come for those. When it’s Stockholm or Paris or Bangkok, she comes.  Smith: What about just the interference in the daily routine? People like me taking an hour out of your day to talk to you. How do you control all that?  Weissman: The first thing I always schedule are my lab people and lab work. Then any opening is available for non-lab stuff.  Smith: You obviously are very happy in the lab. I suppose you’re very fortunate to have found something that absolutely drives you endlessly.  Weissman: No, and it’s been 40 years. When I was a young kid, my father would tell me, you can do anything you want when you go to work. The most important thing is to enjoy it. I found that.  Smith: Did you know from a young age that science was your thing and that you wanted to be a scientist or did it take time?  Weissman: No, I think I knew from a very young age and my parents knew that they would tell stories that in our house, the doorknobs, the toaster, any appliance never worked because I was constantly taking things apart to see how they worked. I was curious and investigative from a young age.  Smith: How nice to have parents who didn’t mind that you did that.  Weissman: Mostly.  Smith: In the old days, young scientists used to fiddle around with things like chemistry sets and make explosives or build crystal sets? I don’t know what people do as the equivalent now, but what did you do apart from take things apart?  Weissman: No, I had the same thing. I had the sixth grade chemistry sets and physics sets and all of those sort of things. When I got a little older, I got into electronics, and I would put together electronic devices on circuit boards with soldering and make speakers and radios and that sort of thing.  Smith: Were there any hiccups on the route or did science just go smoothly for you?  Weissman: There were hiccups to life. When I was five, I developed type 1 diabetes that severely changed and constrained my life. I had to learn how to deal with that and how to take care of myself and regulate insulin and eating and what was limited and what I could do.  Smith: That’s a terrific blow for your parents at five. I suppose at five one just takes things like that in one stride, because you don’t think about anything too much then.  Weissman: Yes, at five. When you hit 12, then you start to think about it.  Smith: How did it constrain life apart from eating?  Weissman: Back then there wasn’t a good way to control blood sugars. What the doctors would tell my parents is ”he’ll be lucky if he makes 40”. They kept that from me until I was an adult. But, back then diabetics didn’t live full lives. I had to watch what I eat. I couldn’t go out to friends to a pizza place or a hamburger shop and pig out with everybody else. I couldn’t get sundaes for dessert. I had to control my diet, control my eating.  Smith: Did it figure into your thinking about what sort of science you wanted to go into, the fact that you had this genetic disease?  Weissman: When I was in college, I spent a summer at the Jocelyn Diabetes Foundation, which is the main hospital in Massachusetts for child diabetics. I did basic science research there. I didn’t choose to research diabetes. I chose immunology instead probably for a variety of reasons. But I certainly spent time researching diabetes.  Weissman: When I was in high school, my father is an engineer and he was laid off from work and couldn’t find another job. It was back in the 70s where engineers were laid off when they hit 40 and nobody would hire them. He ended up starting his own business and I ended up being his only worker. In addition to going to high school, I used to spend afternoons and weekends working in his company making mirrors.  Smith: That work ethic that you developed then, obviously it stood you in good stead later, did you resent it at the time or was it just part of life and you wanted to help?  Weissman: No, not at all. I wanted to help. I wanted to be part of my father’s company.  Smith: It’s also, I suppose, a rare privilege to get to work so closely with your father as a teenager. Some teenagers and fathers drift apart. It sounds like you would very much together.  Weissman: We had always worked together. When I was younger, we would build furniture together, fix the house together. For a lot of engineering and construction things, we spent a lot of time together.  Smith: I think of this because there’s this lovely video circulating of you telling your parents that you’d been awarded the Nobel Prize just after the announcement, which is an unusual thing to have out there and to share. Talk about that moment for a second as an aside.  Weissman: There’s one part that was left out that I’ll fill you in on, but we got the call at four in the morning and my older daughter had just returned from a honeymoon in Sri Lanka. She had gotten married in August and she had flown back to DC around 1am that night. At 6 a.m. I called her and said, I won. She hopped on a train and came up to Philadelphia. I suspect because she didn’t trust that we could handle it without her. After she got here, it was probably around nine and I thought it was a good time to call my parents. I didn’t realise that the cameraman was filming this. I thought it was just a personal moment and I called them. When I spoke to them I said, ‘Mom and Dad, Rachel’s here, we have something to tell you.’ My mother screams out, ‘Rachel’s pregnant?’ Which we quickly doused and then they cut that part out of the video.  Smith: What a moment for Rachel to have all that on film as well.  Weissman: Yes, she was happy to cut that part out.  Smith: One has to ask, do you think your mother was more pleased with the real news than she would have been with the news she assumed was going to be the reason for the call?  Weissman: That I’m not sure, I suspect so. There’s an old story that they tell. When I was probably around five years old, they did a trip of Europe that included Stockholm, and their tour guide took them into the Nobel Hall. I assume as a joke, but my father turned to the guide and said, reserve these two seats.  Smith: Prescience or what? I am fascinated by the pleasure that the lab gives you, because obviously to sustain you for 40 years, and for it’s still to be, as I gather it is, just as fulfilling as ever, it’s a magical thing. Can you describe the pleasure of being in the lab and finding things out?  Weissman: Yes, so in general, people don’t understand what lab work is. It, of course, varies by your age and experience. In general, I characterise it as four steps back, one step forward. It isn’t a place where if you seek pleasure, you go. You have to tolerate frustration to be able to work in a lab. When you do make a finding, even if it’s a little finding, because of all of the frustration and all of the difficulty getting it, it makes it that much more important. At least for me, it wasn’t one big finding. It was 25 years of finding after finding, some very small, some moderately big. It was a continuous development. The vaccine, the RNA just didn’t pop off the page one day. It was years and years of work and continued development and optimisation. To see something come along, to see something develop. It’s kind of like a child growing up. It’s 21 years of taking care of something with lots of frustration and potentially setbacks to then see them go off to college or get married or do whatever. It’s really kind of an inner joy.  Smith: The idea of RNA as a therapeutic had been explored and basically abandoned by companies because of the problems they encountered, just didn’t produce the protein levels they wanted to see etc. I can see the attraction of trying to tackle the problem, but it must require a special sort of confidence to think that you can solve a problem that is so big.  Weissman: I don’t think I ever looked at it that way. I think I looked at it that much of science, much of life fails the first few times. I’m sure Henry Ford didn’t drive away in the first car he made and Orville and Wilbur crashed a few times before their plane ever flew. It’s an incremental thing. I think what was important is that both Katie and I saw the potential that RNA had. That if we could solve these problems, it would be useful for hundreds or thousands of different treatments. It’s not so much confidence, but it’s seeing the potential. and the importance of it, that kept me going. I joke to my friends and family, if RNA vaccines didn’t work, I would have been some lonely researcher at Penn investigating something for his entire life that had papers and grants, but that’s it.  Smith: Would you have been happy?  Weissman: I would have been happy because I was doing research. I was investigating. I was learning. I was creating knowledge for other people to learn.  Smith: I suppose that is the key right there. Not to say you’re not happier that it does work and that it has an applied benefit, but you have to be content with the search and the finding.  Weissman: Yes.  Smith: Talking of that, in 2005, you and Katie published the paper that basically said it was possible to use RNA as a therapeutic, and then not much happened immediately.  Weissman: Yes, Katie won’t let me forget that night. It was the evening before the journal was to be published and I said to her, tomorrow our phones are going to ring off the hook. We both went home. We waited years before the phone ever run. It didn’t ring much until, so Derrick Rossi called in 2008 to tell us about his findings. Then Moderna called us in 2010 wanting to start a company based on our technology.  Smith: Then you’ve got to go forward another, what, seven years or so until vaccine trials started with mRNA vaccines, yeah. It says a lot about how long it takes ideas to be received and to filter through and start having application. What do you think all of this has taught us about the way that science needs to be funded and treated?  Weissman: Yes, so I’ve been contacted a lot by people in general, but by funders who ask the question, how do we prevent what happened to you and Katie from happening again? My response is usually, you can’t. You don’t know when you start something whether it’s going to turn into a vaccine for 2 billion people or just another experiment that gets you nowhere. There are thousands and thousands of people, all of whom think they’ve got groundbreaking experiments, ideas, and there isn’t enough money to fund them all. I have no idea how you find that one or two that has potential to be great. I don’t think it’s possible.  Smith: Gosh, that is the absolutely essential question though, isn’t it? Can you not say anything about the type of problem, the type of person that you should back, should have trust in?  Weissman: No, because the way NIH works for grants is they fund things that the answer is already in. You put in your preliminary results the answers to everything you propose to do. They’re actually funding future experiments. The other thing that determines funding is how established and successful you are. Getting NIH to stop doing that would certainly be a step in the right direction. But I don’t think it would solve the problem. After I published my Nature paper showing the modified RNA LNP vaccine worked in macaques and worked fantastically in both species, I submitted three NIH grants to do to make three different vaccines, three different pathogens. None of the three were even read by the study sections. They all came back and said, RNA will never work. You’re wasting your time. Forget it. Even after Nature papers were out showing that it works and companies had been starting trials, the reviewers were still dismissive and uninterested.  Brilliant: Adam, why was there initially so little interest in using mRNA as a therapeutic? What made it so tricky?  Smith: Because there had been a lot of interest, but what people found was that if you made RNA outside the body and put it into the body, it evoked an immune response and people couldn’t find a way around that. It looked like you just couldn’t use it. It’s obviously very desirable to put RNA into a part of the body and have the body make the protein you want it to make. There was another problem, which is that you have to deliver it to the right target. It wasn’t so easy to package RNA in a way that would get it to the right place. But those two things, especially the immune response just put everybody off and they decided this wasn’t gonna work.  Brilliant: How did Weissman not get put off and help to overcome these problems?  Smith: He and Karikó had managed to find a way to circumvent the problem. They identified the problem, which is that in the body, mRNAs are modified in a way that makes them acceptable. So when Weissman and Karikó realised that they needed to make these modifications that would con the body into thinking that this was its own product, then they circumvented the problem and that was what they revealed in their big paper.  Brilliant: This sounds like a really big deal. Why then wasn’t that very quickly picked up by others?  Smith: I think that’s so interesting because you know, there’s a sort of feeling that, okay, problem solved, everybody should jump on it. But of course there’s a sort of received wisdom in the field after so many attempts at not making things work. People basically understand that it doesn’t work and then to change people’s mind and to make them see that this has been got around takes time and that happens again and again in science that uh, you know, some groundbreaking paper comes along. But it takes time for the field to, I suppose, notice it, believe it reproduce it all important. So although the person who solved the problem must expect immediate response, hooray, I suppose it’s not so surprising that people take a little time to come around to it.  Brilliant: What do you think it was about Karikó and Weissman that sort of made them keep on going together in partnership with their work?  Smith: That’s the extraordinary thing, that they didn’t seem to be put off. Um, they seemed to have a fundamental belief that they could get this solved. And I suppose it was that they brought two very different perspectives to the problem. Karikó believed fundamentally that RNA therapeutics could work and she was being, if you like, blocked by the immune system. Weissman was an expert on the immune system and that combination of skills and I suppose deep understanding of their respective fields was just an ideal combination. But they’re obviously both pretty dogged personalities who having got their hands on something just don’t want to drop the bone <laugh> <laugh>. And uh, it’s lucky for them both that they found each other,  Brilliant: They found each other over a photocopier. Is that right?  Smith: That’s how the story goes. It’s the joy of having shared lab equipment. If you had your own photocopier, you just wouldn’t meet anybody. But because they had to share the photocopier, they found each other waiting for one to finish. They started talking and those talks seemed to be very productive. Many institutions purposefully build their environment so that people are forced to share equipment and therefore they’re forced to meet each other. A famous case is the laboratory of Molecular biology in Cambridge which has always been so productive. There they have centralised lab facilities in each floor and it’s very purposefully designed to get people to intermingle in the middle of the floor.  Brilliant: There’s sort of informal encounters that can then lead to interesting conversations and potentially good discoveries.  Smith: Yes. As long as you are not so cross about not being able to get your hands on the equipment when you need it, keep just not in the mood to talk to anybody.  Brilliant: In this case it clearly worked for Karikó and Weissman.  Smith: It did indeed. Actually it’s very interesting to listen to Drew Weissman talk about what made them such a good team..  Weissman: The central thing was we cared about the science. We cared about investigating, learning, trying to find people to work with as collaborators, there’s a lot of things that are important. Certainly, personalities matter. But with Katie and I, the central thing was that we both were interested in the research. We didn’t let hiccups or bad data stop us. Instead of giving up, we said, well, let’s figure out why we got results we didn’t expect. We both had that same approach. I think that’s why we worked together so well.  Smith: It’s very interesting that a question shared can be even better, because often I suppose when you get a good question there might be a tendency to keep it to yourself and to try and crack this nut on your own.  Weissman: Yes, but I think what was important with Katie and I was also our previous training. It was completely different. Katie was a molecular biologist who worked on RNA. I was an immunologist who had never worked with RNA or made RNA before. Putting those two knowledge sets together is what solved the problem.  Smith: Yes, it’s recognising where the partnership can be very fruitful. Let me ask you about what it’s like to be, they call you the father of the mRNA vaccine. I guess it’s a title you don’t much care for given what we’ve talked about so far. What’s it like to have contact with all these people who either do or do not love the vaccine and who I know write to you?  Weissman: Yes, so most of my calls, Zooms, whatever, that aren’t lab-related or aren’t outside people-related involve people wanting to collaborate. I almost never say no to a collaboration. I at least listen to what people are proposing. I don’t always say yes. If it’s something we’ve been working on for years already, or it’s something that didn’t work or won’t work, then I don’t. But many of them, we end up collaborating. We end up helping. My lab works with about 250 labs right now on a variety of projects.  Smith: That’s a bewildering number of collaborations.  Weissman: We want to make this work and we want to help the world understand. The other side, the people who send me death threats and those sort of things, those are annoying. The problem is they’re not only directed at me, they’re directed at my lab, they’re directed at my family. That’s when I get very upset when people threaten lab members and threaten my family.  Smith: You have been very engaged though in this question of vaccine hesitancy and how to change people’s mindset. What has that engagement so far taught you?  Weissman: We’ve put together a new institute at Penn that will address hesitancy and misinformation. The main goal is to figure out the messages for each group of people that will help them be convinced to take the vaccine. There’s many parts of hesitancy that others are addressing. We’re looking at the message. How do you convince people? What I’ve learned so far is that there are some people, no matter what we do or say, we’re never going to convince them to take the vaccine. We give up on those people. It’s a waste of time trying to convince them. There’s a lot of people who surround them, who interact with them, who aren’t sure, who haven’t made up their minds yet. They’ve got this very vocal minority who’s telling them vaccines give you cancer, vaccines make you magnetic, Bill Gates puts chips in them, all of these crazy things. Those are the groups that we’re working with to give them the message of what vaccines actually are, how they’ll help them. We work with a Philadelphia pediatric surgeon named Ala Stanford. When the pandemic hit and vaccines first were released, she’s African American. She went back to where she grew up and talked to the people and asked them why they weren’t getting the vaccines. Her assumption was that they would say, we don’t trust the government, they experimented on us. We don’t want them putting their new drugs in us. But that’s not what they said. What they said is, I can’t take a day off from work to drive into the city to get the shot over and over. On her own, she stopped being a surgeon. She set up a clinic in a local church, got vaccine, and started vaccinating people on weekends, on evenings. She vaccinated hundreds of thousands of people who otherwise wouldn’t have received a vaccine. She found the message that worked for this group of people. We know it’s possible. Now we have to address other groups of people who don’t want the vaccine. We’ve got a big group of experts at Penn and elsewhere who are working on this.  Smith: That is so fascinating and it is so much about understanding people and meeting people on their own terms, if you like. There is a sort of, not just with vaccine hesitancy, but with all sorts of ongoing problems, the challenges to democracy that are so much a feature of conversations this year in particular. There is a sort of feeling that people just ought to understand and be able to react in the way that you think is the right way. Often it’s that people seem not to be hearing, not to be able to hear what’s being said because nobody’s actually talking to them.  Weissman: Yes, but the problem is the leaders of these groups are close-minded. If you look at their motivation, it’s not always pure. RFK Jr., who’s a politician who is anti-vax, he works for a law firm who handles vaccine injury cases. All of his screaming and yelling about how vaccines aren’t safe are how he makes his money. They did a study and they identified 13 physicians in the United States who were responsible for 70 percent of the misinformation on social media. When they investigated them, many of them were selling made-up homeopathic treatments. What they were saying was, don’t take the vaccine, it’ll kill you, take my medicine. You can buy it on my website. I don’t know if they were anti-vaccine, but they were pro-capitalist, and their way of selling their drug was to say the vaccines were bad, take theirs.  Smith: Yes, it’s really a meeting of two different cultures, isn’t it? It’s the reasonable arguments of scientists and policymakers against the often very unreasonable behavior of others. This idea that lies spread whatever it is five or six times faster than truth and all the rest of it. Perhaps to combat this you need to play by different rules.  Weissman: Yes, and we have to figure out the rules that will work.  Smith: You also get emails from just individuals, don’t you, who are just immensely grateful to you and Katie and the entire establishment for producing the vaccines.  Weissman: Quite a few. Those emails I respond to. I don’t respond to the hate mail. But often it ranges from people asking for a picture or an autograph to just thanking me saying, I was able to see my grandmother, or grandmother says, I was able to see my grandkids again. Thank you.  Smith: Alongside the idea of combating vaccine hesitancy, there’s also of course the question of distribution of vaccine and the whole idea of equity in access to health resources. You’re active there as well.  Weissman: Yes, that’s something that I actually started working on when I first started in science. When I was at the NIH during my fellowship, I set up a lab in Chiang Mai, Thailand to study HIV transmission. The way the lab was set up is that it was run by Thai scientists. who did the research, did the work, did the analyses. Nothing was sent back to the United States. Everything was done there. A lot of people set up a clinic in a city somewhere, collect samples, take them home, and study them. To me, that compounds the problem, because it doesn’t teach people. It doesn’t make scientists better. It doesn’t give people ownership of the data and the ideas that come out of it. We’ve built or we’re building 15 GMP centers, mostly in South America, sub-Saharan Africa, Southeast Asia, and Eastern Europe. We’re also setting up research consortia in all of those places. My ultimate hope is that the researchers who are investigating local diseases of the local population will come up with new vaccines and new therapeutics to treat what’s in their area. Pharmaceutical companies have little interest in treating malaria or dengue or things that they don’t make their money back on. Local regions do because they’re serious diseases for them. Now the local researchers will make the vaccines, make the therapeutics. They’ll have the GMP production site so they can do the clinical trials and then distribute the drug. I started this with Bangkok, Thailand, 10 years ago. They’ve got one drug finishing phase three trials, another one in phase two, and another one entering phase one, which are all things that were developed in Thailand for Thai diseases.  Smith: That’s fantastic. Thank you very much. I’m delighted to see that Xander stayed with this, fell asleep, but…  Weissman: He’ll sleep all day if I let him.  Smith: I doubt he often gets the chance. I can’t imagine that you spend days sitting on the sofa, not doing anything.  Weissman: No, rarely.  Brilliant: You just heard Nobel Prize Conversations. If you’d like to learn more about Drew Weissman, you can go to nobelprize.org where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Claire Brilliant. Music by Epidemic sound. If you would like to explore the journey of another laureate whose work has significant implications for medicine listen to our earlier episode with chemistry laureate [Emmanuelle Charpentier](https://www.nobelprize.org/prizes/chemistry/2020/charpentier/podcast/). You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| **Telephone**  **interview** | 0504=DW  Drew Weissman: Hello?  Adam Smith: Hello, may I speak to Drew Weissman please?  DW: Speaking.  AS: Hello, this is Adam Smith calling from nobelprize.org, the website of the Nobel Prize.  DW: Hi, how are you?  AS: Very well thank you, many, many congratulations on the news.  DW: Thank you.  AS: It must be very early there, how did you receive the call?  DW: Yes, I got the call a little while ago, I got a call from Kati a little bit earlier.  AS: OK, so she actually broke the news to you that you’d been awarded together?  DW: Yes.  AS: Gosh.  DW: But we weren’t sure it was true, we thought that maybe somebody was playing a joke on us.  AS: Apart from slight disbelief, what was your first reaction?  DW: You know, it’s a lifetime dream. And this is coming from somebody who doesn’t work for or look forward to awards. But you know, the Nobel is the ultimate recognition of work, so it is a wonderful experience.  AS: Have you ever imagined yourself in this moment before?  DW: You know, starting as a basic scientist doing work in high school it was always a dream but I never imagined it would happen  AS: When I spoke to Kati earlier, she described your scientific conversations, you’re two very different personalities, but your scientific conversations as being very much ‘alive’, which I thought was a lovely word to use about the way you interact.  DW: For the 20 years that we’ve worked together before anybody knew what RNA is, or cared, it was the two of us literally side by side at a bench working together. And talking and discussing new data. We both have sleep disturbances so usually around three to five a.m. we would be emailing each other with new ideas. It was always stimulating; we were always talking about science.  AS: Sounds a perfect partnership, and it also sounds like with your sleep disturbance you’re well prepared for what today will bring.  DW: Yes, no, I’m sure!  AS: I know you are very focused on bringing RNA therapeutics to the world, and there are so many things you want to do with mRNA vaccines still to come. I guess the Nobel Prize might be a bit of a distraction. Alfred Nobel I think wanted to make things free from distraction for laureates by giving them some money to sort of get on and concentrate on their work, but how do you feel about the prize?  DW: To me, nothing distracts me from my work. With the new notoriety that Kati and I have, we’ve been traveling around the world for awards or discussions. I got back from Dubai on Sunday, I was in Boston over the last weekend, headed to Thailand in two weeks. But none of it gets in the way of the science and I still meet with everybody in my lab weekly whether it’s on Zoom or in person. So, this just energizes us more!  AS: That’s wonderful. It must be extraordinary to reflect on the fact that all that work led to, in the case of the pandemic, being part of this extraordinary effort to save millions of lives through the vaccines.  DW: No, I mean that’s incredible. We’ve actually started a new group that includes people like Paul Offit and Ala Stanford and many others to combat vaccine hesitancy and misinformation and disinformation. Because as important as the vaccine is, if you don’t take it, it doesn’t work.  AS: Do you think the Nobel Prize will help in that fight?  DW: It’s an interesting point. There’s a large group of people who aren’t sure, who hear these, you know, crazy people spouting nutsy things about the vaccine, but they’re not sure, and those are the people that still believe in science, and I think for those people it will help.  AS: Such an important point. For now, may I ask, could you do me one favour, which is, and Kati has already done it, which is to send me a picture capturing this moment. I don’t know if there is somebody close by you that could take a photograph of you, or just take a selfie.  DW: My wife’s got her camera going, so I’ll have her take a picture.  Mary Ellen Weissman: Hello!  AS: Thank you very much! Hello! How very nice! Well, what a happy day. It’s a real delight to speak to you, thank you!  DW: Thank you very much.  AS: Best of luck the deluge of interest that’s about to …  DW: Yes I know, I’m trying to find a disguise to wear!  AS: I don’t think it will work! Anyway, many, many thanks and congratulations again!  DW: Great. Thank you!  AS: Bye |
| **Interview** |  |
| Q1 | What brought you to science? |
|  | It’s a great question. I’m 64 years old, so there might’ve been when I was five and I just don’t remember anymore. Probably one of the big things. When I was five years old, I was diagnosed with type one diabetes, and back then the life expectancy of kids wasn’t a full life. My parents knew that, I learned about that later. I’m not sure that being a diabetic influenced me into science. I was always interested in engineering and science growing up. So maybe. |
| Q18 | How important were your parents to your scientific career? |
|  | We’ve always been a close family. And they sparked education, and they wanted us to get education and to get as much education as we wanted. I don’t think they cared if it was in science, math, physics, engineering, I think they cared about just getting a good education. |
| Q2 | What do you enjoy most about science? |
|  | I think it’s really searching the unknown, trying to understand things that we don’t understand, and trying to be able to figure out how things work. My family tells jokes, when I was a little kid, I used to take everything apart to understand how it worked. We never had a toaster that worked, and the doorknobs rarely ever worked because I was always taking everything apart to try and understand how things work. I’m still that way now with science and immunology and RNA, but it’s really just the curiosity to understand how things work, how they really work. |
| Q5 | Have you had mentors who have influenced your career? |
|  | There have been a few and at different stages of my career there were different people who were mentors, who were teachers. Early on it was Jerry Fasman at Brandeis University, who gave me my first research job and taught me how to think about research. After that, it was Ann Marshak, who I did my PhD with, who taught me critical thinking and how to read and understand the literature and how to formulate ideas into practice. After that, it was probably Tony Fauci when I worked in his lab, who gave me the freedom to investigate whatever I wanted. He was interested in HIV, I started on a whole new topic in his lab because I thought it would be interesting, and I thought it was important, and he both gave me that freedom, but helped me think about it to create interesting ideas. |
| Q14 | Do you see any similarities between sports and science? |
|  | I think it was more it prepared me, because I’m told I was a hyperactive kid. Back then, they didn’t treat hyperactive kids, they just let them run around the house and bounce off of walls. But I used sports and martial arts as a way of controlling my thinking and controlling my activity and being able to focus. I think those are really critical to be a good scientist, because if you’re bouncing off of walls, you can’t formulate ideas, you can’t test new hypotheses, and that helped me overcome that, that hyperactivity. |
| Q17 | How did you celebrate the news of your Nobel Prize? |
|  | It was kind of a funny interaction. I got a message from Katie Karikó at four in the morning that said, ‘Did Tom call?’ Katie has a habit of sending cryptic notes that I don’t understand, and I texted her back, ‘Tom, who?’ Then I called her and, and we talked at four in the morning, and she said, Well, you know, Tom from the Nobel Foundation called and said that we won the award, but he also said, could I give him your phone number? Because he had a bad phone number for me. And we said, you know, This sounds like a joke. I think some, some anti-vaxxer is playing around with us, this is all a joke, and we didn’t believe it. Then Tom finally called around 05:15 in the morning, and I started to believe it, but I still wasn’t sure. I waited until the video on the internet around six, and then I believed it.  My older daughter had just returned from her honeymoon Sunday evening, had not been to sleep yet, and I called her at six in the morning and said, I won the Nobel Prize. She hopped on a train and took the train up to Philadelphia to be with us. My younger daughter … We kept trying to locate and leave messages for her and find she wouldn’t answer her phone, she wouldn’t answer anything. We called her friends who told them to go over to wake her up. She finally answered the phone, she goes, Why the hell are you waking me up so early in the morning? and hung up the phone, so we didn’t see her until dinner time. My children had a very different way of celebrating the award. |
| Q11 | Tell us about your co-laureate Katalin Karikó and your collaboration. |
|  | You’ll hear about this when I present my gift to the museum. The lore is that Katie and I met over a Xerox machine. I have to explain to young people what a Xerox machine is, because they don’t exist anymore, but back then, the only way you could read a scientific paper is if you photocopied it. We both read a lot, and we would both fight over the copy machine, and we started talking. Katie, as she says, she likes to brag about what she does, and she talked about making RNA and I said, Well, that’s interesting, I work on dendritic cells and I’m interested in trying RNA on them. So it’s, I joke, it’s like the old Reese’s commercial, the chocolate and peanut butter coming together and making a great candy bar. That’s what our meeting at the Xerox machine was like.  Katie was very outgoing, very aggressive, very forceful in what she believed in. I’m a quiet guy, I’m happy just working in the background, not being in the limelight, not being in front of audiences, and Katie enjoys being in front of the audience and running the show. The other Nobel laureates, we were at the House of Sweden, and Katie and I were sitting down and Katie was directing everything, and they turned to me and they said, Oh, we understand how your relationship goes now. It was kind of humorous. |
| Q20 | How important is collaboration in science? |
|  | To me, that’s really the critical thing in science. Right now my lab collaborates with about 250 labs around the world, in every continent except Antarctica. We haven’t found any scientists in Antarctica to collaborate with, to make it all, but we’re close, just about every country in the world. I spend a lot of time just going and visiting collaborators to work on projects, to help understand model systems and diseases. All of our work is really done through collaboration, it’s incredibly critical. |
| Q21 | How important is equity in science? |
|  | It brings you into my other interest in my career, which is equity, and which is making sure the same science and the same medicines are available across the world. I’ve had a lab in Thailand for about 30 years, and I’ve had a lab in Botswana for about 25 years. The chief purpose of both of those was involving local scientists, teaching them about vaccines, about RNA, about different therapeutics that we develop, and then getting them to set up their own labs and set up their own infrastructure. With Thailand, we built a GMP production site. What that means is anything you give to people, any drug, any vaccine, has to be produced under GMP production capabilities, which is very expensive, very highly monitored situations, so we built a GMP site in Thailand. After that, I’ve built 17 more across the world in South America, Sub-Saharan Africa, Southeast Asia, across Eastern Europe – really across the world. We’ve got one right now, operating in the Ukraine, which I’m amazed about. I can’t wait to visit, to actually see how they’re running a GMP site in the middle of a war, but they are. |
| Q12 | What advice would you like to share with young scientists? |
|  | I think young scientists have to think about a lot of things, and I spend a lot of time talking to junior high school and high school students, because I think by the time they get to college, if they don’t want to be a scientist, it’s too late to convince them. You have to start very early and maybe even elementary school, just stimulating their knowledge of science, but I think that’s when you have to get to kids and you have to present to them what science is, what it involves. I did an experiment with a Nobel group yesterday where we made purified DNA from strawberries. That will be a video for young kids to learn about science, and I think those sort of things – just to stimulate interest – not every kid is going be a scientist, I don’t expect that to happen. But any kid that’s curious, that wants to understand things, that’s interested in biology or chemistry or physics or math, I think those kids should consider science as a field to go into. It’s incredibly rewarding, it’s a ton of work, it’s not like going into your father’s business and taking over and having everything laid out for you. It’s a lot of work to set up to establish yourself to become acclimated and, and successful. But the rewards are enormous. |
| Q13 | How can we encourage diversity in science? |
|  | My usual answer to that is I’m a scientist, I’m not a sociologist. I don’t know how you encourage that. The way I do it is I work with teachers because teachers understand their students and teachers know how to influence, to get messages to their students. I’m working with the experts who know what they’re doing. I’m happy to say what I need to say to get people interested, but I think we really have to go with the teachers. |
| Q22 | How have you managed to cultivate your curiosity? |
|  | I’m sure some of it was genetic because my father is similar. He was an engineer and then decided to start his own business in a completely different field of engineering, and he learned, and he developed and he invented. I think a lot of it is genetic. |
| Q17 | How does it feel to know that your research has saved millions of lives? |
|  | I still … It hasn’t sunk in. My view … I’m a physician researcher. I got an MD and a PhD, and my interest starting when I was young was always … I had hoped to someday develop some treatment that would make people better. I think I’ve accomplished that. The number to me is I guess, less important. It’s fantastic that it has helped millions of people. I think in the future, it’s going help a lot more because there’s so much potential that can be done with RNA therapeutics between gene therapy, between therapeutics, protein deliveries, it’s just enormous what can be done. And to me, that’s what I’m looking forward to. |
| Q34 | What are some future uses of your mRNA research? |
|  | I think gene therapy is probably the most important future use. Right now, there are thousands and thousands of genetic diseases. The main way they’re treated is symptomatic. You try to make people better, you give them drugs that make the disease a little better. Most people still die of their genetic disease at young ages. The hope for the future is going to be gene therapy, where you fix the broken gene. The problem with that is there are a few gene therapies. There’s one for sickle cell that’s being approved right now, it costs 1-4 million dollars per person, and sickle cell – 300,000 people a year born with the disease, mostly in Sub-Saharan Africa – they don’t have facilities to do gene therapy. They don’t have a million dollars a person to afford gene therapy. So, what we’re doing is we’re developing what we call *in vivo* gene therapy.  Instead of taking cells out of a patient, infecting them with viruses, screwing around with them in culture and then giving them back, we’re trying to do everything in the body. The only thing our treatment will be is an injection of RNA LNPs. You give one injection, it goes to the bone marrow, it fixes the broken gene, and it cures the disease. If we can do that for sickle cell, there are thousands of other bone marrow genetic diseases that can be done. It’s already been done once for liver diseases, for an amyloidosis, for a company that I work with that gives a single injection of RNA LNPs, and it fixes the genetic disease. It cures the patient so far. To me, that’s the future of gene therapy, because if you can’t use it around the world, great, you save a few people in the US and Europe. But what about everybody else? |
| Q24 | What makes you most passionate right now with your research? |
|  | It is like asking a parent which of their children they like better. You can’t really answer that. Or I can’t, I’m passionate about everything that I do. We’re working on vaccines for peanut allergies, and if you’ve ever had a child patient, their lives are nightmares. There’s no really good treatment for that. We are working on vaccines for autoimmune diseases, so no longer will we people be on Methotrexate or Anti-TNF Antibodies, they’ll have specific therapies that won’t suppress their immune systems. We’re working on vaccines for cancer, both to prevent cancer and to treat cancer. We’ve got our variety of gene therapies. We’ve got a big program in HIV cure. The problem with HIV is that once HIV infects somebody, it becomes latently infected in their cells, never goes away.  They predicted 70 years it would take for the virus to disappear on retroviral therapy. We’re working on PNA LNP based therapies that will cure the disease. It’ll cut the virus out of the latent reservoirs and clear it away. We’re working on vaccines to prevent HIV, so someday we’ll be able to both prevent it and cure people that have the disease. We’re working on therapeutics. People nowadays develop heart disease, is the number one killer in the world. We really don’t have great therapeutics. You can operate on somebody and fix the coronary vessels. You can put stents in, they help with the symptomatology. They extend people’s lives, but they don’t last forever. There are many other heart diseases that we have almost no therapies for. We figured out how to target cardiomyocytes, the muscle cells in the heart, so now we can deliver gene editing technology, we can deliver therapeutic proteins, we can do the same for the lung, for the brain, for kidneys, for the immune system. The potential is just enormous. |
| Q7 | How do you like to spend your free time? |
|  | Unfortunately, over the past six or seven years, my spare time disappeared, so I really don’t have anymore. When I was younger, and my wife would joke about this, when I would get frustrated at research, I would come home and build something. Build a porch onto the house or renovate a bathroom or renovate a kitchen. I stopped doing that because I just didn’t have time anymore. In the summer, I enjoy the water. I enjoy kayaking and being out on the water. |
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| **Podcast** | **“The first thing I did to see if it at all would have a chance was to buy a piece of liver in the food store close to the institute and just dry it in the laboratory”** In a podcast episode with medicine laureate Svante Pääbo, he tells us about the start of his scientific career. Pääbo speaks about his mum and how she encouraged him to pursue his childhood interest, archeology. What makes us uniquely human is also a topic that is up for discussion. The host of this podcast is nobelprize.org’s Adam Smith, joined by Clare Brilliant. This podcast was released on 25 May, 2023.  Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.  Svante Pääbo clip: “Neanderthals were here say 2,000 generations ago. If they would have made it another 2,000 generations, how would we have dealt with them? Would they live in zoos? Or would they live in suburbia?”  Adam Smith: When Svante Pääbo talks about how close we came to living in a state of coexistence with Neanderthals, it makes you realise that our vision of ourselves as top species and like the end of evolution perhaps, which is obviously wrong, is really something that is a very recent perspective. Pääbo’s work really helps us understand our place in nature and how we ought to consider it more carefully.  In a way it’s funny to contrast the far-reaching implications of such thoughts with the down and dirty experiments that Svante Pääbo started with when he burnt livers and ground them up and saw whether he could extract just a little bit of DNA from them, as he began this process of working out how you could reconstruct the degraded DNA of samples that had lain around for thousands of years.  That contrast is one of the fun things about, I think, this conversation, that as you listen to the specifics of the research, bear in mind the truly ground-breaking nature of the implications of his results.  Clare Brilliant: This is Nobel Prize Conversations. Our guest is Svante Pääbo, recipient of the 2022 Nobel Prize in Physiology or Medicine. He was awarded the prize for his discoveries concerning human evolution. By managing to sequence the genomes of our extinct relatives, the Neanderthal and the Denisovan, he unearthed unknown links between us and them.  Your host is Adam Smith, Chief Scientific Officer at Nobel Prize Outreach. This podcast was produced in cooperation with Fundación Ramón Areces.  Svante Pääbo is the founding director of the department of genetics at the Max Planck Institute for Evolutionary Anthropology in Leipzig. He’s also an adjunct professor at Okinawa Institute of Science and Technology. In this conversation you’ll hear him talk about how his mother set him on his path by encouraging his interest in archaeology, and how he discovered an unknown human species in a tiny piece of bone.  But first, let’s hear from the next generation.  Smith: To bring us back to Nobel Week in December, let’s listen to your daughter Freya, being interviewed during the banquet.  *CLIP: An interview from the Nobel Banquet television broadcast*  Victoria Dyring (reporter): It’s quite intense for your dad right now. What does he think of all this?  Freya: He’s mostly like really happy. But sometimes he’s a tiny bit stressed because like he kind of doesn’t always have free time Like oh, so like he’s always on the computer or something like that but now that he like did his speech and everything, so now most of it is like gone so. Still really cool.  Victoria Dyring: He can sort of relax.  Freya: Yes  Svante Pääbo: She will be so proud.  Smith: Oh, good. She spoke very well. In terms of the load that has been imposed upon you by receiving the prize, how have you found that?  Pääbo: It has eased up since the Nobel week, of course. What is slightly stressful is all the invitations and suggestions for activities I got. And have to say no to almost everything. You feel a little bad when you say no all the time. Also to invitations that a year ago, I would be happy to say yes to. I am becoming rather callous and hard with it. I say no to almost everything.  Smith: That presumably is very important. That is the primary thing you need to learn as you become sought after, however it happens. And the Nobel just adds to that, I guess.  Pääbo: Yes, so to still have the ambition to do some of my real work, still.  Smith: Absolutely. Of course, your work involves very much future facing technologies and the state-of-the-art genetics and genomics. But it all comes out of an interest in the past, which is, I think, rooted in childhood. I wondered if you could talk just a little bit about that interest in archaeology and digging around in the far distant past that developed when you were young.  Pääbo: I think it probably started as a sort of fascination with archaeology that many kids probably have. I was fortunate to live in Stockholm, where there are places where there’s lots of ancient remains and places where people lived during the Stone Age. With time I got a bit sophisticated and found out where there were Stone Age settlements. Then, for example, in falls, when there had been big storms and trees tip over, I would go around and look in the roots where lots of soil that had come up for old pot shards and things like that and collected things.  Smith: What was the best thing you ever found?  Pääbo: It is actually on an island outside Stockholm, there was a site where I found lots of pot shards and could puzzle them together, a rather big piece of pot that was around 3000 or 3200 years old. It was absolutely fascinating to me that you could see these things that someone had done so long ago. You could see sometimes fingerprints in the clay of the pot.  Smith: It’s very tempting to think of that being the seed for piecing together other things such as genetic signatures and whole genomes in the future.  Pääbo: Maybe. I still have that pot and it’s a piece of a pot. It’s amazing to me. Then it was really my mom who took me to Egypt when I was 13 or 14 or so, where it really opened my eyes to how much is preserved there. It wasn’t like you have to look for a pot shard with great effort. There were places where the whole soil more or less was composed of pot shards. That really then took off and it somehow didn’t leave me, that fascination.  Smith: That must have been mind-blowing to encounter such a place so young. What was the most memorable moment on that trip?  Pääbo: I think it was really in southern Egypt on this island Elephantine where there was this realisation that the whole earth was composed of at least 50% pot shards in layers, where the older things were lower down. That there were lots of just human remains too that were found every year in cemeteries, old cemeteries and things in Egypt.  Clare Brilliant, voiceover: Svante Pääbo was born in 1955. He grew up in a suburb of Stockholm with his mother Karin Pääbo, an Estonian-born chemist who came to Sweden as a refugee during the second world war. His father was Swedish biochemist Sune Bergström, who received the Nobel Prize in Physiology or Medicine four decades before his son. But Svante was raised by his mother, who played a significant role in shaping his future career.  Smith: It’s interesting to talk about the influence of parents, always interesting. In your case, of course, there’s been a lot of focus on the fact that your father was a Nobel Prize laureate, but you always talk more about your mother. What did your mother do for you that was special in nurturing your interests?  Pääbo: First of all, I grew up as a single child of a single mum. Our father only visited us on Saturdays for a few hours. I think my mum was a very strong woman who took my interest seriously too. When I got interested in runic stones, we would on Saturdays and Sundays drive around and look at runic stones around Stockholm and I would measure them and copy the runes. She really took time to sort of nurture those interests. That was perhaps an advantage of being a single kid to a single parent that she did have that time. I notice myself now that already when you just have two kids, you can’t devote that much attention to just one of them.  Smith: Absolutely. I’m one of a pair of parents, but of a single kid. I recognise very much, I was thinking how absolutely lovely for your mother to have you to sort of go around and be excited with. If my child says, let’s go do something together, it’s the nicest thing in life. She must have been absolutely thrilled to have you say, we need to go off and study runes today, mum.  Pääbo: Yes. I do think that as a single child of a single parent, you have an even more symbiotic relationship than typical family. Where I can also see that one had almost other roles also for each other. I would discuss things with my mum about how to get a new laundry machine, which type should it be a more expensive or cheaper one? Things that we would never discuss, Linda and I, with our kids. They would not even notice there was a new laundry machine installed. That one sort of was taken seriously rather early as a child, because we had multiple roles for each other almost.  Smith: Makes you grow up quickly as well, I can imagine. Or maybe not. Maybe you consider yourself still very much a child in your mind.  Pääbo: I don’t know. Depends on what aspects of personality, probably.  Smith: Yes, indeed. Your story is that egyptology took hold and you thought that’s where you might go into egyptology. Then you switched away and moved into biology and medicine. What went wrong, if you like, with the idea of being an archaeologist?  Pääbo: I do think that I probably had a far too romantic idea what it would mean to be an archaeologist or Egyptologist. I had this kind of childish fascination with it, imagining more or less that it would be excavating and finding amazing things every year. At least as Egyptology was taught in Uppsala, where I studied, it was very linguistic. A large, large part of it was learning to read hieroglyphs and Coptic and things like that. I worked two summers also at the Egyptological Museum in Stockholm. The first summer was pretty fascinating, cataloguing things and stuff like that. Then I sort of came back a year later and it was sort of the same people doing exactly the same thing, going for lunch at the same place, gossiping about the same stuff. Somehow it seemed too slow moving for me. So, I sort of was a bit disenchanted or I sort of realised I didn’t see this as my future and had a crisis of a sort, didn’t know what to do. Then ended up saying, OK, I study medicine because at least you get a job after that. I think I had an eye towards doing research in medicine also already from the beginning, actually.  Smith: Remarkably mature to see that kind of aspect of academia or rather departmental life, which I suppose plagues many places so young and to recognise it and think, I don’t want to be part of that. Interesting. It’s funny to put it in these terms, because, of course, the result of all of these decisions was that you ended up in a position to do amazing things. Then I suppose the same question about medicine that I asked about Egyptology, what was wrong with medicine that meant that you didn’t go in that direction?  Pääbo: I think it was absolutely nothing wrong with medicine. I think I had imagined I would be fascinated by research. In fact, when I did the clinical courses in internal medicine and surgery and things like that, I discovered that I enjoyed seeing patients much more than I would have expected to. Then had another little crisis of sorts saying, shall I become a doctor or shall I do research? I said, OK, I take a break and do a PhD, I can always come back and finish my medical courses. That’s where we still are today. I haven’t quite come back yet.  Smith: I’m sure they’d welcome you back with open arms. As a PhD student, then, obviously, something took hold and an idea took hold gradually. You never know where ideas come from, I suppose. But how did the idea take hold?  Pääbo: I think in this case, it’s pretty obvious that what I learned as a PhD student was the techniques that at that time were rather novel of how you can extract DNA from an organism, modify it and stick it in bacteria and multiply the bacteria and then determine DNA sequences from lots of different organisms and compare the DNA sequences and make inference about the evolutionary history of how these organisms are related. I knew from my studies of Egyptology that there were thousands and thousands of mummies around, human mummies and animal mummies in Egyptological collections. It seemed a rather obvious idea to say, can we apply these techniques to old tissues and find DNA that survived in them? I think most people at the time thought that DNA was very, very sensitive, that it would be enzymes that very rapidly degraded after death and things like that. But I guess, fortunately, I was rather ignorant of all that and just started trying it. I was able to show that you could see in tissues from ancient Egyptian mummies that are then two or three thousand years old, you could sort of see histologically in the microscope cell nuclei and you could also stain them for DNA. So, it seemed to be some DNA preserved there. Then I tried to extract the DNA, tried to clone it in bacteria to study DNA sequences and got some DNA sequences out and among those were some that were clearly of human origin that I then thought came from the mummy and even published that. In hindsight, then over the next years, it became clear that they were very unlikely or not likely at all to actually come from the mummy because they were rather long. It became clear that DNA is very degraded to short little pieces. Then I started a long process of working out techniques to reliably retrieve DNA from old tissues.  *Discovery Discussion:*  Brilliant: Svante Pääbo’s first attempt at extracting DNA from mummies failed, even if he wasn’t aware of it at the time. Can you explain what happened, Adam?  Smith: Probably the sample was simply contaminated. He was looking to amplify and then sequence DNA from the mummy, but as we know from all those TV series about forensics, the world is littered with DNA from all sorts of different sources and mummies, which have been kicking around for a long time, have been touched by many people. It could have been his own DNA on there as well, or the DNA of anything else that had touched the mummy over the years, and he probably just ended up mistakenly sequencing a bit of stray DNA from elsewhere. Part of his work as he went on was to find ways of making sure that the samples he was working with were super pure.  Brilliant: How did he eventually manage to extract DNA from old tissue?  Smith: He found brilliantly ways of reconstructing extremely degraded DNA. The tissue he’s working on has been around for thousands of years. It’s been dried and frozen and goodness knows what else, and the DNA has become very broken up. Through painstaking efforts over a long period of time, he developed ways of piecing that DNA back together again, and being able to eventually recover the entire genome of the organisms he was studying.  Brilliant: What is a genome?  Smith: A genome is simply the collected DNA of an organism. It’s all the DNA instructions within the organism that tell it what it is going to become.  Brilliant: Svante Pääbo received his Nobel Prize for his discoveries concerning the genomes of extinct hominins and human evolution. What is a hominin?  Smith: A hominin!  Brilliant: How am I supposed to say it?  Smith: Exactly, a hominin. Some kind of concatenation of m’s and n’s that makes it very hard to…  Brilliant: A tongue twister.  Smith: It’s a tongue twister. A hominin is the group of species that include us, homo sapiens, and all our close ancestral relatives. Hominins include species we already knew quite a lot about, like Neanderthals, species we knew nothing about, like the Denisovans, that Svante Pääbo’s researchers discovered. It’s interesting to listen to Svante Pääbo describe how he got from that position of failing to sequence DNA from mummies to being able to produce these entire genomes. Let’s listen to him talk about the start of that work.  *End of Discovery Discussion*  Pääbo: The first thing I did to see if it at all would have a chance was to buy a piece of liver in the food store close to the institute and just dry it in the laboratory to somehow imitate mummification in ancient Egypt. From that artificially mummified piece of liver I could easily extract DNA. It was quite degraded, actually, but it was lots of DNA surviving there. That gave me some confidence in that it’s not that the DNA gets totally degraded within hours after death, that many of us thought would be the case. That was what led me on to then try it also on older tissues. Then as I was working with this, there was another group at Berkeley, Alan Wilson, who was a very famous evolutionary geneticist, that published some DNA sequences from a quagga, from the dried skin of a quagga, which is an extinct form of a zebra. Those tissues were about 100 years old, but that sort of encouraged me also very much.  Smith: It’s interesting that you didn’t take what you were told as absolute written truth, you had to go out and find out for yourself. The liver experiment shows an inquisitiveness, which is special, I think.  Pääbo: Yes, sometimes I say that sort of inherent part of doing research is actually to almost take a delight in showing that what people think is wrong, right? That the received wisdom is not how things are.  Smith: Indeed. What did your PhD supervisor think of this direction of research?  Pääbo: At the time when I started this, I had rather big respect of him, so I would not tell him about this. This was done secretly in the lab, just some of my friends among the students would know about it. Some other people found out about it because that liver started smelling pretty badly after a while. Then only when the results were there and I was writing a manuscript about it, then of course I went and talked to my supervisor about it. He was very supportive then, sort of encouraged me to go on.  Smith: Nice. That’s exactly how it should be, isn’t it?  Pääbo: It may be good not to tell your supervisor from the beginning, get discouraged.  Smith: How do you promote that sort of environment in your own working, in your own lab amongst your own students?  Pääbo: I hope I promote it by sort of showing that it’s not that I have much better insights than anyone else, right? I am as often wrong as other people in the group are wrong about what we think.  Smith: It must be difficult to differentiate people trying out things that really do seem to you bonkers and just not worth pursuing. Those who are going down interesting lines, but nothing’s happening. How do you draw the line?  Pääbo: Ideally you have a sort of open enough atmosphere so people are not afraid to bring up ideas that may be crazy. Then my role or the roles of other people in the group will be sort of more to discourage certain ideas that are really bonkers. Sort of say things that might be right, that one can give it a try, right? Sort of sieve out the sort of good ideas among many, many ideas.  Smith: From those early beginnings, you remarkably managed eventually to produce the genome of the Neanderthal. There’s a lot we’ve skipped over there. Were you immensely surprised that you got to that end point?  Pääbo: It was, of course, a gradual process over 25, 30 years, right? Small advances. I think when we first got the first little pieces of Neanderthal DNA that comes from this mitochondrial genome that exist in many copies, so it’s much easier to retrieve: I was sort of amazed that that worked. I think for a couple of years, one was thinking we would never be able to get to the whole nuclear genome to get to single copy genomes, part of the genome, which are much, much less prevalent. It’s, of course, a step-by-step thing where technology advances, you start thinking this might work, you try things. So, of course, by 2004 or 5, I was convinced that in principle, one should be able to do it if one had enough resources and had sort of technological advances that you could see on the horizon coming. Then I was very fortunate that we sort of did convince the people to then give us money to attempt to do that.  Smith: It must, I suppose, have become quite a competitive field over the course of those years. Obviously, it’s not the same as the Human Genome Project. But towards the end, that became such a race and people had so much vested interest in getting there first. Was there a similar feeling in your project?  Pääbo: There were aspects of it that was competitive. There was one other group that we initially worked together with that then had different ideas about how one would do this, that one would actually clone DNA in bacteria. Rather than doing it all in vitro. We didn’t believe in that. Then we sort of went different ways and it became a bit competitive. But I had never sort of felt that competition is a primary driving force of anything like that. It is, of course, an aspect of this working with ancient remains that an important part is getting access to the good specimens. That can get competitive sometimes. There are now fortunate developments in the field, for example. Where one has now realised that one can even use the sediments from archaeological excavations to retrieve DNA from the people who have lived at the cave site. So not working with bones anymore. Then, of course, the material is not limiting anymore. The sort of unlimited amounts of that material, which is also a relief, right? It’s sort of not that you have to compete for the one bone necessarily that is found at the place.  Smith: I was thinking this because when you discovered the Denisovans from a tiny piece of finger bone from a cave, I was wondering how that piece of finger bone came to you, to your lab. You had the good sense to think that was worth investigating.  Pääbo: Yes, we worked with the Russian groups that excavated that cave since quite some time. They gave it to us, but we initially thought, this is so small, it’s not very interesting. It lay around for at least half a year before we got around to analysing it, actually. That’s sort of one of the things that is still a big mystery in the field, why certain bones can be a very good preservation. That little bone, in terms of DNA, has very much endogenous DNA preserved. Other bones from the same layer, just a meter away at the site, are much less well preserved. They do contain DNA, but much, much less. That’s something we still don’t understand.  Smith: How very interesting.  Pääbo: It probably has to do with how much water percolation of things there have been over tens of thousands of years or so.  Smith: This point you make about being able to retrieve DNA samples from sediment, of course, this must be a huge crossover with forensic science now, just in the modern world in crime fighting. It’s extraordinary, isn’t it? That you can piece together things from what one would have thought was almost nothing.  Pääbo: Yes. I mean, the conditions had to be right. For example, the soil can’t be acidic. They say limestone caves are ideal because it’s sort of basic conditions. When it works, it’s really amazing. You can sort of retrieve from different layers, see what humans have been there. It’s still, of course, true that if you want to determine a high-quality genome from a single individual, you will need a well preserved bone. To reconstruct the population history of a site, it’s sort of sediment DNA is amazing.  Smith: There’s so many avenues to go down when thinking about what these genomes that you’ve revealed tell us. The phrase that I think is used in the press release for the Nobel Prize you received by the committee is, it helps us understand what makes us uniquely human. Does that chime with you? In what sense does it help us understand who we are to know what the genome of the Neanderthal or the Denisovan would be?  Pääbo: Different levels to think about this, I think. Of course, what has happened is that thanks to having the genomes from our closest evolutionary relatives, we can estimate when we had a common ancestor with them in order of half a million years ago or so. We have also discovered the fact that many of us today, those of us who have their genetic roots in Europe or Asia or anywhere outside sub-Saharan Africa, have a component in our genome that comes from Neanderthals, and we live in Asia in addition from Denisovans. That those contributions from them have biological consequences today, the variants that have come from them and some of us carry. The same will surely be true in Africa also, I think, when one is able in the future to retrieve genomes from extinct forms of humans in Africa. There is another level of this where one can say what makes us uniquely modern human are then genetic changes that happened since we separated from Neanderthals half a million years ago and spread to everyone, so that everyone has those changes today or most of us. That’s an area that’s just beginning to be explored. You can sort of make a catalogue of such changes and it’s in the order of 34,000 changes or so and then try to start looking as we and some others do, on the biological consequences of that model of changes. I think the direction it is going is probably going to be a combination of those that may be important for some aspects of being a fully modern human and I hope one will understand more of that in the next few years. It may even be the case that none of such changes is in themselves sort of a key change that is absolutely necessary. It may probably be a combination of those things. But that’s really a challenge for the next five or 10 years to try to find out those things.  Smith: Yes, I suppose so much of biology is about finding out what we have in common with the rest of the living world, all the other animals and plants. It’s a different way of looking at things to say, okay, how do these 30,000 changes make us different? Very interesting.  Pääbo: It’s very challenging because by definition those things vary very little. There are very few people who don’t carry these changes. That’s how we define them. It’s quite challenging to find out what they really cause because we can’t easily compare people with and without those changes. We’ll have to use model organisms or engineer these changes into cells using this CRISPR-Cas 9 technology that was awarded another well-deserved prize a few years ago, etc.  Smith: Is there yet an example though that you can call upon that says this?  Pääbo: Yes, so we’ve begun to study in collaboration with the groups that study brain development in Dresden, some of these changes. It turns out that a combination of changes in two genes affect how accurate chromosomes are pulled apart in early brain development in stem cells that generate neurons. That if we engineer in the ancestral state, Neanderthal, ape-like state, there are more errors in how the chromosomes segregate. That’s very interesting. It probably results in that cells with these errors in segregation actually die. If that then has consequences for the adult brain is another question that one needs to explore. One other change in an enzyme, PKTL1, for example, in the ancestral state results in fewer neurons being born. But again, these are changes that we now can study because they happen very early in brain development that you can model in the laboratory in tissue culture. It’s unclear what consequences those will have in the adult individuals, but one is beginning to sort of find some of these things. There is one other change in an enzyme that takes care of oxidative radicals, a sort of damaging side product of metabolism in all cells in the body. There the modern human version seems to be better in terms that it more efficiently takes care of these oxidative radicals because particularly when we’re very few of them there. Actually some people carry the ancestral state today as a result of gene flow from Neanderthals, but less than one in 10,000 or so in Europe. Then we can see that that associates with an increased, slight increased risk of having diseases that have to do with inflammation that may be caused by this radical. So, arteriosclerosis, inflammatory bowel disease, things. One is beginning to learn some things about these things.  Smith: Fascinating. The coexistence with Neanderthals, people talk about the fact that, or you have spoken about the fact that we, that Homo sapiens and Neanderthals interbred. What form did you think, from your genetic evidence, did interbreeding between the two populations take?  Pääbo: I think something that’s striking to me is that when we now start to look at the genomes of very early modern humans in Europe, where one has most data. From modern humans that lived at a time when they could have met, or their immediate ancestors could have met Neanderthals. Then very many of them, I think we have probably in the order of seven such individuals today, and at least five of them have close Neanderthal relatives in their family histories in the last 10 generations or so. If we look at these very early modern humans that come, they seem to have interbred very often with Neanderthals. Only later does it seem to come modern humans that sort of replace Neanderthals so that they disappear. I think that probably part of the story about why Neanderthals disappeared may have been that they’ve simply been absorbed into larger modern human populations that came. That modern humans were more numerous. How this happened is of course anybody’s guess. I sometimes joke and say it says much more about your views of humanity and how we are as human beings, how you speculate about this, than anything about what happened back then because we truly don’t know. We could speculate about anything, really.  Smith: What’s your individual speculation?  Pääbo: I try to stay away from speculations. But it is striking to me that it seems to have been very frequent. I wouldn’t think that it’s all something very bad and violent or something like that. A large part of why Neanderthals disappeared may simply have been that the populations fused.  Smith: I’m afraid it is entirely in the realm of speculation, but it is interesting to speculate on how the two populations viewed each other. We can’t have any insight into that. But how different did they see each other as being? By extension, what does that tell us about how we view the rest of the world today? It’s not as if the concept of species was sort of uppermost in their minds, perhaps. But in terms of something like tolerance, it seems an interesting thing to ponder.  Pääbo: Yes, you must regard it as rather similar if you frequently sort of have kids together, right? You can’t regard each other as totally alien. Sometimes I say it’s sort of interesting to speculate. Neanderthals were here, say, 2,000 generations ago. It’s not tremendously long ago. If they would have made it another 2,000 generations, how would we have dealt with them? Would they live in zoos? Or would they live in suburbia? Would we see even worse racism against them today? Because they were truly in some ways a bit different. Would it rather have blurred this very clear distinction we so easily make between humans and animals? If we would have other forms of humans that still had sort of using tools and having communication, but being quite different. We may not have had this quite limited view of what it is to be a human. Again, it’s only speculation, right?  Smith: Only speculation, but valuable and fascinating speculation. I may be pushing it too far, because we can’t tell too much. But just the common view of Neanderthals as being a subspecies, not having produced art, for instance, and perhaps not being as brilliant as their cousins. Do you think that holds up?  Pääbo: I think it’s a big debate among palaeontologists and archaeologists, where I think the sort of trend goes to recognising more and more abilities in the Neanderthals. It is still true that somehow it is modern humans in the end that become so numerous, spread over the whole world, and eventually develop technology and things that change so rapidly. In my view, there has to be some difference there. It may not necessarily be that you’re individually on average smarter as a modern human than a Neanderthal or something like that. Could also have something to do with sociality or so. Modern humans seem to form larger communities and larger populations. Maybe it’s something social that distinguishes us and maybe having larger societies make for more innovation and more rapid cultural change, for example. Maybe we will understand something of that one day.  Smith: It’s arguable that the progress of the world isn’t entirely linear, that the most brilliant and accomplished always choose the direction that the countries are going to go in, that societies are going to go in. So, we can’t be sure that that’s what was happening back then, I suppose.  Pääbo: Yes.  Smith: You’ve been running an institute since 1997. To build something that truly reflects your vision of how research should be done. Must not be easy.  Pääbo: Or you rather say it’s a great privilege to be able to implement some of your ideas. I mean, I think it was almost a historically unique situation in Eastern Germany when after reunification, there was the ambition and the resources to build up a research infrastructure to a similar level as in Western Germany in terms of population, so to say. It was really a chance to start several new institutes. This was one of them where we then sort of asked the question, how would we study human history and human evolution if we started from scratch, without looking on any traditional ways of doing it? It was, yes, a unique chance in life to do that.  Smith: To be given a tabula rasa like that. Extraordinary. Yes. Do you think you’ve been successful?  Pääbo: I hope so. I have the feeling that this institute has been slightly copied since then at other places in the world. The idea was to bring together different disciplines, no matter if they are traditionally seen as humanities or sciences, as long as they are empirical, as long as they build on collecting data, testing the data statistically. If you do that, you can talk to each other, no matter if you’re a linguist or archaeologist or geneticist. To some extent, I do think it has been successful.  Smith: That’s very important. Much happens on the interface between disciplines. It’s so important to be able to have common language, common conversation. If people wanted to get a picture of your institute, would you say that that little video that’s gone viral of you being thrown into the pond in the middle of the institute, having been awarded the prize, captures the spirit? Students throwing their leader into the pond?  Pääbo: I hope so.  *CLIP: The sounds of Svante Pääbo being thrown into a pond*  Smith: Good. It’s very kind of you to have taken time to speak to me.  Pääbo: Okay, thanks.  *MUSICAL INTERLUDE*  Clare Brilliant, voiceover: You just heard Nobel Prize Conversations. If you’d like to learn more about Svante Pääbo, you can go to nobelprize.org, where you’ll find a wealth of information about the prizes and the people behind the discoveries.  Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of Filt and Nobel Prize Outreach. The producer for this episode was Karin Svensson. The editorial team also includes Andrew Hart, Olivia Lundqvist, and me, Clare Brilliant. Freya was interviewed by Victoria Dyring. Music by Epidemic Sound.  At the Max Planck Institute, Nobel Prize laureates are plentiful. Listen to our conversations with Benjamin List, Klaus Hasselmann, Emmanuelle Charpentier and Hartmut Michel. You can find previous seasons and conversations on Acast, or wherever you listen to podcasts.  Thanks for listening. |
| **Telephone**  **interview** | 0505=SP  Svante Pääbo: Hello, Svante.  Adam Smith: Hello, this is Adam Smith.  SP: Ah, hi, hi. I was warned that you would call.  AS: Well, many, many congratulations on the news.  SP: Thank you.  AS: You sound remarkably calm and collected.  SP: [Laughs] Oh, well, I’ve discussed it with my wife at length already, I must admit.  AS: It sounds like your wife is a calming influence.  SP: Yes, certainly, she is.  AS: How did you receive the news?  SP: So I was just gulping down the last cup of tea to go and pick up my daughter at her nanny where she has had an overnight stay, and then I got this call from Sweden and I of course thought it had something to do with our little summer house in Sweden. I thought ‘oh the lawn mower’s broken down or something’.  AS: Did you manage to get to collect your daughter?  SP: I am going now actually.  AS: I gather today is a holiday in Germany.  SP: Yes, it’s a day of German unification, so it is very calm here, everything is closed.  AS: That’s… that’s a peculiar day in a way to receive the news because otherwise you would have been at the institute, and you would have been surrounded by masses of people I suppose, popping champagne. But as it is you can perhaps have a quieter introduction to life as a laureate than most.  SP: Yes, yes. And I can go out and buy some champagne when the shops open tomorrow morning, and come well equipped to the institute.  AS: I can’t imagine that celebrations would really be delayed by 24 hours though, I’m sure they’ll be… It’s… I remember when we were together in Stockholm in 2012 for that Nobel Week Dialogue on genetics, and then you were sitting at the Nobel banquet the next day, and I guess maybe you’ve been to the Nobel banquet before. I just wondered whether sitting at the banquet you’d ever imagined yourself being the recipient of the Prize?  SP: No, really not. I sort of… No, I have received a couple of prizes before, but I somehow did not think that this really would be… qualify for a Nobel Prize.  AS: Your work is of course on the sequencing of these early hominins. What does our knowledge, your knowledge of the genetic makeup of those species tell us about our relationship with them.  SP: Well, it does tell us that we are very closely related, first of all, and we’re actually so closely related that they have contributed quite directly, 50, 60 thousand years ago, DNA to the ancestors of most people today, those who have their routes outside Africa. And that variation that, sort of, those variants do have an influence, and influence many things in our physiology today.  AS: Do you think that changes our view of ourselves, knowing that?  SP: In some sense, I do think it does so, the sort of realisation that until quite recently, maybe 14 hundred generations or so ago there were other forms of humans around and they mixed with our ancestors and have contributed to us today. The fact that the last 40 thousand years is quite unique in human history, in that we are the only form of humans around. Until that time, there were almost always other types of humans that existed.  AS: That should change our view of our place in the world, shouldn’t it.  SP: Yes, I think so. I mean sometimes I think it’s interesting to think about if Neanderthals had survived another 40 thousand years, how would that influence us? Would we see even worse racism against Neanderthals, because they were really in some sense different from us? Or would we actually see our place in the living world quite in a different way when we would have other forms of humans there that are very like us but still different. We wouldn’t make this very clear distinction between animals and humans that we do so easily today.  AS: The press release uses the word ‘seemingly-impossible’ for the task you undertook. I was wondering what gave…  SP: Oh really? Okay. [Laughs]  AS: I was wondering what gave you the confidence, the courage to undertake a seemingly-impossible piece of research?  SP: Well, it is of course a step-by-step process that started back in the 80s. I was struggling to retrieve a little bit of DNA from things that were just a few … starting with just dried tissues that, you know, that were just a few months old, going back in time and struggling with the technological issues with that over a decade. And then it became possible to retrieve DNA from things like the mammoths or cave bears that lived at a similar time as the Neanderthals. And then I was very lucky to get a job in Germany, where of course Neanderthals is a big presence in our, in the imagination of people, so it was then very, an obvious next step, in a way, to try to do that.  AS: You make it all sound very logical, but I think there’s an understatement there. You of course have a Nobel laureate lineage, and your father was a Nobel laureate. Does that make a difference to you, in receiving the Prize?  SP: To some extent I’m sure, yes it does. I mean, I think the biggest influence in my life was for sure my mother, with whom I grew up. And in some sense it makes me a bit sad that she can’t experience this day. She sort of was very much into science, and very much stimulated and encouraged me through the years. My father I did have some contact to and he took a big interest in my work, but it was not that close a relationship as with my mother.  AS: I was just wondering whether there’s some sense in which Sune Bergström or maybe other laureates or great scientists had given you, again, that sort of approach, that confidence or had helped you acquire the confidence to undertake such major challenges?  SP: Maybe also the realisation a bit that one have less… or realise that also such people are normal human beings, and it’s not such an amazing thing, that you may have bigger confidence to try, sort of, challenging things yourself.  AS: That is indeed a very important point, a very important lesson, yes. People are inclined to put everybody on pedestals, but of course…  SP: Yes, and you don’t put your parents on a pedestal, at least not when you’re a teenager.  AS: Ah, tell me about it! I should let you go and pick up your daughter and get on and enjoy your, what seems to be looking like a relatively quiet day, but…  SP: Yes, I think it may be quite good that it is a holiday today, so I can collect my wits till tomorrow.  AS: You sound like you have all your wits about you in a quite remarkable way. Anyway, it’s been an absolute joy to speak to you, and congratulations again. Have a splendid day, and thank you.  SP: Thanks, yes, bye bye.  AS: Bye. |
| **Interview** |  |
| Q1 | Where does your passion for science come from? |
|  | I really don’t know where my passion from science comes from. I think my initial passion was much more for ancient history or archaeology here in Sweden where I grew up and for Egyptology after my mom took me to Egypt when I was 13 or 14 years old. Later I came to science and realised that one could fuse aspects of science with this interest for our past, both historical past events and evolutionary past events. |
| Q5 | Was there a particular person who influenced you? |
|  | I think the person that was most important to me when I grew up was clearly my mother since I grew up alone with my mother in a suburb of Stockholm. I think what was very important was that she had a sort of great respect and passion for schoolwork and learning and she took my nerdy interests very seriously when I got interested in ancient Vikings. She took me to the museum, she would take me around to look at runic stones around Stockholm and measure them and write up what was on them and so on. Then she took me to Egypt where I discovered a fascination of ancient Egypt. I think one thing that also my mother gave me was probably taking life as it comes because she had of course been uprooted by the second World War in Estonia and had to flee to Sweden and arrived here in 1944 when she was 18 years old or 19. Many, many of her classmates did not survive the war, so I think a little bit she took, but of every day as a gift, as I think all of us should do. |
| Q25 | How important to teachers and a good learning environment. |
|  | I grew up in Bagarmossen, a part of Stockholm where one at that time at least was not necessarily expected to go to university. I think it were a few teachers, for example, that were quite important to me. I remember a teacher of physics at Bergholmsskolan in Bagarmossen who also noticed my interest in ancient things, he collected antiquities and took some along and showed me at a school for example. This thing of feeling that your interests were taken seriously by your teachers was quite important. It’s important in a more research setting, I think, to try to have an atmosphere where everybody in the team can have ideas that they bring in, that you’re not afraid of saying something stupid or so that you realise that nine of ten ideas that come are probably wrong and stupid. But in order to get that 10th idea that’s really brilliant, you have to have an atmosphere where all the things are brought to the table, all ideas are expressed. |
| Q26 | What qualities do you need to be a successful scientist? |
|  | Of course hard to say what do you need to be a successful scientist because there are many different things that you need to come together perhaps, and there are also very different ways to being a successful scientist. There are some people that are extremely smart, for example, and that is important. There are other people that are very knowledgeable and really learn from what other people have done. There are people that bring together combinations of knowledge that otherwise no one brings together – that can be very fruitful. I think one cool thing with science is that there is not just one way to be a good scientist. |
| Q2 | What do you enjoy about science? |
|  | If you think about science, it’s of course driven, I think, by questions and interests you have, for example to see if we can go back in time and see how our genomes or DNA sequences have changed over time. But then once you endeavour on that, of course science is a collective effort. It’s very much a social thing where you work in a group, try to assemble the people with different competencies and make sure that these people get along with each other and that one can together work towards a goal. That’s in a way what I find probably most stimulating every day is this going together after something. |
| Q11 | How are competition and collaboration related? |
|  | Many people talk about competition in science and in some sense I don’t think that that’s an important factor. It’s a human enterprise. Competition comes into it of course, but it’s not the driving force for us. I thin. It’s really going after a question and competing with yourself in a way trying to do it as well and as quickly, of course, as you can. |
| Q12 | What advice would you give to a student or young researcher? |
|  | It is hard to say. What advice should you give to the younger scientists that enter the field? I think following your passion and your interests is important because it’s generally automatically the case that if you’re really interested in something, you tend to do it well just because you put in a lot of effort because you find it really interesting. You should follow the things that you are interested in, then at least you have a good time while you do it. |
| Q4 | How do you cope with failure? |
|  | Of course there are many challenges and failures and setbacks on the way. I think if you hold your gaze on what you want to achieve, you can overcome that rather rapidly because you only start thinking about the next experiment. What can you do to … You always live in the grand illusion that the next thing will solve everything that you do. |
| Q23 | What are the key implications of your research? |
|  | Our research is then curiosity driven if you like. We want to find out what happened to our ancestors in the past, so we have been able to study the genomes of our closest evolutionary relatives, Neandertals, and we discovered the distant relatives of Neandertals that lived in Asia, the Denisovans, and found that they contributed to the gene pool of people today. That many people today, if your roots are outside Africa, carry genetic variants that come from these earlier forms of humans and that these variants, genetic variants influence our biology today, influence our susceptibility to disease or our sense of pain or many other things. |
| Q27 | What’s the relationship of Neandertals to modern humans? |
|  | Now when we have the genome of our closest evolutionary relative, we can look for genetic changes that are unique to Neandertals and that are unique to fully modern humans that happened in our ancestors during the last half million years and spread to everybody or almost everybody today. We can have this catalogue of the genetic changes that make our genome unique. A research direction that is now becoming very exciting is to try to understand which of these may have functional consequences, which of these changes may influence things such as why modern humans became millions and eventually billions of people spread over the entire planet, spread over open oceans where you don’t see land on the other side, and came to a point today where we influence much of the biosphere. |
| Q28 | What makes us uniquely human? |
|  | One can of course ask what makes modern humans unique. That is these things, I think, that we, and not these other forms of humans, became very numerous, started having technology and culture that changed very rapidly and became so numerous that we probably just absorbed these earlier forms into our population. At least that’s probably a large part of why Neandertals, for example, disappeared, we are beginning to learn. I think the big question is to understand in the future what that may have been. It could have been even something more about sociality, that we have the ability to form big societies and transmit much of our knowledge to the next generation. That in reality humans are quite unique in that we spend almost the first third of our lives absorbing all the knowledge that previous generations have generated, and then we build on that. Some people talk about this ratchet effect that in each generation we develop our culture and technology further. I think somewhere there is probably in the future going to be the key what sets modern humans apart so much. |
| Q19 | How did you celebrate the news of your Nobel Prize? |
|  | There was an announcement of this in the beginning of October, it was a great surprise to me, I must say, and was a surprise, I think, to many people in our institute and to many people in the field. I think it feels so good also because it’s sort of a recognition of this entire research field. Yes, there was a lot of celebrations also in the institute immediately actually taking place. It was amazing how many people wrote to me, people from far back in my life that took this as an occasion to contact me again, and that was a lot of fun. |
| Q6 | How is it returning to Stockholm to receive the prize |
|  | Surprise, what should I say? Emotional to be back in the city that I grew up in. Unfortunately to say my mother is not around anymore to experience this. It’s of course an amazing feeling also to realise that exactly 40 years ago my father received the same prize here. |
| Q10 | Will anything special happen when you return to Germany? |
|  | When I have survived this week here, we will have a party for the institute at the oldest techno club in East Germany, actually, which is not far from our institute, The Distillery in Leipzig. |
| Q29 | What environments help with creativity? |
|  | An amazing thing in my career have been the opportunity that came in the mid-nineties to take part in the founding of this new [Max Planck](https://www.nobelprize.org/prizes/physics/1918/planck/facts/) Institute in Leipzig in East Germany. There was a chance to think about how should one create an institute and how would or should one do anthropology in the future. The question that we united the institute from many, many disciplines that moved there was around what makes humans unique, indifferent, genetically, biologically, behaviourally, and so on. It was also a chance to create a building and an environment to bring people together. Of course, science is very international. Many people come from all over the world to work with us and have much of their life in the institute. I think it’s also seemed very important to have things like a sauna on the roof or a climbing wall or things you can do together – things that are not about the science – that you can do together to bring people to talk to each other, all to people from different disciplines that work in different departments. |
| Q13 | Why is diversity of all kinds important in science? |
|  | Often what is important for the progress of science is to bring different perspectives and opinions together. It can be very useful to bring people with different backgrounds and experiences together. It’s often in a combination of disciplines and knowledges that new things emerge. That said, I think it’s very important that each individual is very rooted in their own area of expertise and then interact with other fields, so to say. You have to be expert in something to appreciate what the other people do. |
| Q30 | Can you tell us about the object that you’re donating to the Nobel Prize Museum? |
|  | They of course want you to donate some object to the Nobel Prize Museum here. After some thought, I decided to give them two books, dictionaries of science that my father gave me in 1971 when I decided to not study science in school and rather go for Latin and ancient things. He was a little disappointed with that and gave me these books, I think to say I should keep at least an eye on science still. They remind me about that. Yes, that happened. I did come back to science and it’s a little link back to my dad also. |
| **ID** | 0506 |
| **Biographical** | By now, I have lived in Northern California for more than half my life, but I remain a native New Yorker in temperament and humor. Born in 1955, I grew up in a seaside Brooklyn neighborhood − immortalized by Neil Simon’s play ‘Brighton Beach Memoirs’ – that’s been a landing pad for Eastern European immigrants like my grandparents, who fled Czarist Russia and antisemitism in pursuit of a better life. Consequently, my parents are first generation Americans. They grew up in this NYC enclave, attended public schools, and earned first-class higher educations at tuition-free Brooklyn College, exemplifying what some of us still cherish as the American credo of open borders and opportunity for all.  My father, an electrical engineer, designed and maintained emergency power systems for the telephone company. My mother was an educator and teacher in the NYC elementary school system. Together with my two brothers, Martin and Arthur, we lived in the bottom flat of a rather small ‘semi-attached’ house in Brighton Beach, with the top floor occupied by my maternal grandmother, aunt, uncle, and two cousins, Hope and Rachel. My paternal grandparents lived a few blocks away, in the same pre-war apartment where my father grew up. Quarters were close, but largely convivial, making for a small, close-knit, and loving family unit in which modest resources were devoted to providing opportunities and experiences for us kids. My brothers and cousins have pursued careers in research, education, engineering, and law. They are fantastic people who, like our parents, are warm, generous, and socially minded.  Brighton Beach was dense and somewhat gritty, but not a bad place to grow up, with easy access to the beach and just a subway ride from the metropolis of Manhattan. And in the days before ‘dynamic pricing’, museums, concerts and Broadway shows were generally affordable, enabling even a middle-class kid to experience transformative cultural moments. At the same time, there was plenty of opportunity for pickup games of basketball or summer frolicking at the beach alongside a million or more New Yorkers who would flock to Brighton or nearby Coney Island to catch a breeze on a hot and muggy summer day.  Like my parents, we all attended public schools. I was pretty much a reluctant student who often turned in my assignments late (or not at all) and generally tried to stay below the teacher’s radar. At some point, around 5th grade, I decided that it was time to put in a little more effort and be less afraid of failure, and then things got easier and more inspiring academically. Junior high school – those amorphous two years (grades 7 and 8) between elementary and high school – coincided with social unrest and upheaval marked by, among other things, the civil rights movement, escalation of the war in Vietnam, and the slide of NYC toward fiscal insolvency. As such, I remember these years as mostly chaotic and subliminally stressful, when kids of my age worried about the possibility of older brothers being drafted and whisked from the streets of Brooklyn to the jungles of Southeast Asia. For those who had any sense of social awareness, it was a time to open one’s eyes and grow up quickly.  Perhaps sensing the precarious financial state of public schools, my father lobbied me to take the admissions test for one of NYC’s famous ‘magnet’ schools, which I didn’t mind doing since it meant a day off from school. Consequently, and unexpectedly, I was accepted to Stuyvesant High School, which attracted students interested in science and math. Thus, I spent my first year of high school commuting from Brighton Beach to the lower East Side of Manhattan, which on a good day involved a three-hour roundtrip experience navigating three rush hour-packed subway lines. Together with incessant testing and homework, this left no time for other important facets of teen life. Although holding my own academically, I was truly miserable and needed to make a change. So, with moral support from my older brother Martin, I reported to Stuyvesant on the first day of my sophomore year and went promptly to the principal’s office to de-enroll myself. My dad was, shall we say, unimpressed with my decision, but I never looked back or regretted this moment of self-determination.  I thus ended up at the local venue, Abraham Lincoln High School, from which my mother and other family members had graduated. While Lincoln may not have enjoyed the special academic status generally afforded Stuyvesant, it does boast an impressive list of alumni that includes notable writers (Arthur Miller, Joseph Heller, Mel Brooks), performers (Beverly Sills, Neil Diamond, Harvey Keitel, John Forsythe), and even distinguished scientists (after [Arthur Kornberg](https://www.nobelprize.org/prizes/medicine/1959/kornberg/facts/), [Paul Berg](https://www.nobelprize.org/prizes/chemistry/1980/berg/facts/), and [Jerome Karle](https://www.nobelprize.org/prizes/chemistry/1985/karle/facts/), I am now Lincoln’s fourth Nobelist). In my own class, I graduated alongside Lee Mazilli, who went on to play and coach major league baseball with the NY Mets and Yankees. Signing my yearbook, he wrote, “Hope you see me in the bigs someday.” Touché Lee!  At Lincoln, I was thrilled to be on an early session that let out around noon, leaving ample time to socialize, play basketball, and explore all corners of NYC. Most of my friends were interested in literature, history, and politics and together we enjoyed the many cultural happenings in Manhattan that I never had time to experience when at Stuyvesant − exploring folk and jazz clubs in Greenwich Village, visiting the city’s grand libraries and museums, and seeing truly transformative performances on and off Broadway that opened my eyes to drama and the power of playwrights like Arthur Miller and Tennessee Williams. Group activities also included canvassing for George McGovern (whose unsuccessful bid for the US Presidency was aimed at unseating Richard Nixon and ending the disastrous war in Vietnam) and waiting on tables at local weddings or bar mitzvahs to earn a few dollars. In summertime, I scrounged around for any available jobs, such as packing and delivering merchandise or cleaning office buildings. These experiences gave me an appreciation for the many hard ways that people make a living, while also compelling me to seek a path that was self-motivating, self-directed, and fulfilling – and in which I did not have to punch a time clock!  One step in that direction was enrolling in a physics class taught by Herb Isaacson As a former minor league baseball player, Mr. Isaacson also coached the Lincoln team and was, as I recall, instrumental in getting Mazilli to the majors, adding to his aura as an exceptionally smart, suave and engaging teacher and mentor. He made physics approachable and fun (e.g., plotting the trajectory of a baseball) by challenging us with ideas, not facts, and insisting on participation by boys and girls, alike. Indeed, numerous alums credit Mr. Isaacson for making them seriously consider science as a career trajectory, and this was certainly true for me.  Like my older brother, Martin, I expected to enroll in a NY State college, but a classmate suggested that I apply to M.I.T., of which I had never heard. Indeed, no one in my family had attended a private college, but I decided to give it a try and was rather surprised when a letter of acceptance showed up in the mailbox. Tuition, even in those days, was a stretch for my parents, but in their usual fashion of devoting hard-earned resources to the kids, they encouraged me to enroll with the proviso that I might have to switch to a state college if things got dicey financially. But I led a rather frugal lifestyle and did my part by finding summer employment, and so things somehow worked out.  M.I.T. wasn’t exactly the freewheeling college scene that some of my friends were enjoying elsewhere, but it was an unusual place that I came to appreciate for its quirkiness and intensity. Academically, I was drawn to biology and chemistry because I initially thought about a career in medicine. However, I soon realized that I had no real desire to be a clinician and was instead captivated by biochemistry and the elegance of bacterial genetics. I was especially inspired by the work of [Monod](https://www.nobelprize.org/prizes/medicine/1965/monod/facts/), [Jacob](https://www.nobelprize.org/prizes/medicine/1965/jacob/facts/) and [Lwoff](https://www.nobelprize.org/prizes/medicine/1965/lwoff/facts/), the legendary French microbiologists who shared a [Nobel Prize in 1965](https://www.nobelprize.org/prizes/medicine/1965/summary/) for elucidating mechanisms of gene regulation. While I did not appreciate all the nuances of their work, I was generally amazed at how these scientists could abstract models of complex molecular pathways from seemingly simple and elegant experiments. I was also fascinated by the ingenious ways in which they leveraged chemistry together with genetics to solve puzzles and construct and test these models. Indeed, one of my best classroom experiences at M.I.T. was sitting in on a graduate-level course in molecular genetics taught by Ethan Signer, who had studied at the Pasteur Institute with these legendary scientists and was able to bring their work and these exciting times to life.  But didactic classes and problem sets were not my forté, and for me the magic path was UROP – the Undergraduate Research Opportunity Program that helped students find laboratories in which they could gain hands-on research experience. In my sophomore year, I worked with Janis Fraser, a graduate student in Joel Huberman’s lab who was determining how Okazaki fragments are incorporated into replicating DNA. When Janis stopped doing bench work to write her thesis, she suggested that I work with her husband Tom in Alex Rich’s lab, where I spent the next two years using modified transfer RNAs to study the kinetics and specificity of aminoacylation and how this might influence the fidelity of ribosomal protein synthesis. Working in Alex’s lab was a great experience and a sanctuary from classes and problem sets. And I came to realize that designing, executing, and interpreting experiments satisfied my intellectual curiosity while also providing an outlet to do something creative at the bench – much like a hobby. I also sensed that science attracted an interesting and eclectic group of people who accepted the uncertainty of discovery for a somewhat more independent and self-determined lifestyle. Indeed, Alex’s lab was a rather messy and freewheeling place inhabited by some very entertaining and colorful personalities, forever dispelling any misconceptions I might have had about laboratories being pristine ivory towers for dispassionate research. But underneath this chaos was an energetic and interactive vibe focused on serious science. And to my everlasting benefit, Tom let me know that he expected as much of me, even though I was just a pipsqueak undergraduate intern. I worked hard, enjoyed thinking about and planning experiments, and even published a modest paper from my efforts, providing evidence that I could be inspired and productive in this line of work.  Another great outcome of working in Alex’s lab was meeting Simon and Laura Litvak, Chilean nucleic acid biochemists who were on sabbatical from the University of Bordeaux, France. I somehow convinced the Litvaks to let me work in their lab during the summer between junior and senior years, which turned out to be one of the most formative and memorable times in my life. In those days, the Litvak lab was situated in the Biochemistry Department on the Talence campus, just across the corridor from the Enology Department, where bottles from the great châteaux of Bordeaux, Saint-Émillion and the Medoc could be found in the hallway awaiting analysis. Of course, there were often a few sips left over for sampling during department pastry and coffee breaks in the late afternoon. And so aside from purifying a couple of enzymes (tRNA nucleotidyl transferases from wheat germ and yeast), I thoroughly enjoyed Bordeaux and its environs, learned something about red wine and French culture, and came to appreciate the fact that scientists are exceedingly privileged to be part of a vibrant international community. Simon and Laura were amazing mentors and we have remained in touch ever since.  Having decided on a career in biomedical research, I applied to several graduate programs but received mostly rejections. However, sometime late in the academic year I got a telegram informing me that I’d been accepted to the Biochemistry Graduate Program at Berkeley, initiating my long-term association with an amazing public institution, the University of California. Owing to some unforeseen events and good luck, I came to carry out my graduate studies under the joint mentorship of two young dynamos, Jeremy Thorner and [Randy Schekman](https://www.nobelprize.org/prizes/medicine/2013/schekman/facts/), who were exploiting Saccharomyces yeast to study pheromone signaling and protein secretion, respectively. I worked on a project at the interface of their two labs that involved understanding how a peptide mating pheromone called alpha-factor is synthesized and secreted by these cells. Like many mammalian peptide hormones, yeast alpha-factor is proteolytically cleaved from a larger polyprotein precursor and thus stood as an excellent model system for identifying enzymes and secretory mechanisms involved in their biosynthesis. Together with Lindley (Buff) Blair and Tony Brake (two postdoctoral fellows in the Thorner lab), we succeeded in this endeavor, with the most exciting discovery emerging in the last few months of my graduate studies when I identified the KEX2 pro-protein convertase as the defining member of a family of furin / subtilisin-like proteases. In mammals, these enzymes cleave polypeptide precursors at paired basic amino acids to liberate bioactive hormones, activate viral surface glycoproteins (including the spike protein of SARS-CoV-2), etc. Such enzymes had been sought for decades, but it was the combined power of genetics and biochemistry that finally brought one to light.  When I was in Alex Rich’s lab, Ned Seeman (a senior fellow who later became a pioneer of DNA nanotechnology) told me that graduate training was a process of gradual maturation leading to a moment of crystallization in which you would suddenly realize that you had reached a state of intellectual clarity and confidence. I think there is some truth to this, which I experienced in my last year or so at Berkeley and have witnessed with many of my own students. But this is really a product of daily cumulative influences from all of one’s lab mates, collaborators, and mentors – and in this regard, I was incredibly fortunate to have come under the tutelage of Jeremy and Randy. They were (and still are) passionate, intense, and rigorous in their multifaceted approach to science, and attracted likeminded students and fellows to their labs. At the same time, they gave us latitude to be creative and make our own mistakes. Both were approachable and have a cutting sense of humor, which helped foster a more informal ‘West Coast’ atmosphere in the lab that appealed to me and likely influenced my decision to eventually settle in the Bay Area.  After an exhilarating and very productive era at Berkeley, it was time to move on. Yeast was such a powerful system with a bright and broad future, but I decided to use my time as a postdoctoral fellow to explore new and different territory. Two streams of thought converged: my focus on pheromone processing made me wonder about the molecular and physiological actions of hormones and neurotransmitters in the brain; and perhaps influenced by Bay Area history, I became fascinated by the pharmacology of hallucinogens, opiates, and other natural products that societies have used over millennia to alter consciousness and sensory experience. I began reading books and articles from cultural figures and writers like Timothy Leary and Tom Wolfe but was mostly influenced by papers from scientists − notably Sol Snyder and George Aghajanian − who had used LSD and related ergots to probe serotonergic and other endogenous neurotransmitter systems. Their studies suggested that monoamines like serotonin and dopamine each interact with pharmacologically distinct sites in the brain, but there was no understanding of how such receptor subtype diversity might be manifest at a molecular level. This seemed like a fantastic problem to explore, with great relevance to neuropsychiatric disease.  Around this time (1983), a paper from [Eric Kandel](https://www.nobelprize.org/prizes/medicine/2000/kandel/facts/) and [Richard Axel](https://www.nobelprize.org/prizes/medicine/2004/axel/facts/)’s labs caught my eye in which they described genes encoding precursors for peptide hormones controlling egg laying and related behaviors in *Aplysia* sea snails. This was relevant to my thesis project, but more importantly enticed me to enter the new frontier of molecular neurobiology. I applied to Richard for a postdoctoral position (not realizing that he was already quite well known for developing methods for gene transfer into animal cells), expressing my interest in cloning a serotonin receptor gene. Richard agreed that this was a worthwhile goal and I returned to NYC in the winter of 1984 to begin my fellowship with him at Columbia University. Richard is a person of intense curiosity and intellect who encouraged his fellows to pursue challenging projects and establish their own scientific persona. Consequently, and especially in the pre-olfaction days of the lab, many of us forged our own trajectories along diverse areas, but often with an immediate goal of cloning genes that define a key cell type or physiological process. Having come to the lab with no experience in neurobiology, vertebrate physiology, or mammalian molecular genetics, I had a lot to learn and spent several years spinning my wheels. But I also had the benefit of advice from great Axel lab friends (Greg Lemke, Moses Chao and Dan Littman) and local collaborators (Amy MacDermott and the late Tom Jessell) and after many false starts, I finally achieved my goal by cloning a serotonin receptor (the 5-HT1c/2c subtype) from rat brain using a function-based screening strategy. Altogether, my postdoctoral stint lasted six years with a burst of productivity in the last two. Those middle years, fraught with competition, tested my endurance and confidence, but Richard supported me throughout and never (at least to my knowledge) lost faith – something that I have always appreciated and bear in mind when encouraging my own trainees to undertake exciting but risky projects. I also learned from Richard how important (and intellectually rejuvenating) it is to have fellows develop an independent scientific trajectory that they can then take with them. Indeed, no one has a more impressive list of protégés, which is an aspect of Richard’s career and legacy that many of us strive to emulate.  As noted above, and like many cloning projects of the time, the goal of identifying a serotonin receptor gene was both elusive and competitive. Our main challenger was a very formidable group at the California Institute of Technology led by the neurophysiologist, Henry Lester, and the legendary molecular biologist, Norman Davidson. Richard and Norman were old friends and thus when we ultimately succeeded, we sent the Caltech group a preprint of our manuscript describing the cloning of the 5HT1c serotonin receptor subtype. Henry and Norman responded by sending us a couple of bottles of champagne accompanied by a card reading,  *“To David Julius and Richard Axel – Here’s an expression of warm congratulations from your friendly competitors. We’re delighted with your success. Let’s hope for lots of interesting further results from both labs.”*  I have saved this note through the years as a memento of these times, and more importantly as an exemplar of what science and scientists can be at their best.  Having at long last accomplished my goal in the Axel lab, it was again time to move on. I accepted a faculty position at UCSF, returning to the Bay Area in late 1989. [Mike Bishop](https://www.nobelprize.org/prizes/medicine/1989/bishop/facts/) and [Harold Varmus](https://www.nobelprize.org/prizes/medicine/1989/varmus/facts/) had just become UCSF’s first Nobelists and the Loma Prieta earthquake had just shaken the city up and so there was both joyful and nervous energy in the air. UCSF seemed like a good choice for me because, in addition to having a stellar reputation in familiar areas (molecular genetics and biochemistry), it was also home to a first-class neuroscience community, which I knew would be essential for my future growth and development. Indeed, the challenge now was to begin thinking more like a physiologist, which can be a tough transition for someone trained as a reductionist biochemist.  To my great fortune, the transition to faculty independence was made smoother and more tolerable when Tony Brake, my friend and collaborator from graduate days in Berkeley, joined the lab. Following his postdoctoral stint in the Thorner lab, Tony started a yeast genetics and protein expression group at Chiron Corp., one of the first local biotechnology ventures. When I moved back to the Bay Area, Tony took what was supposed to be a brief sabbatical leave from Chiron to work in my lab; he never went back and worked with me for almost 10 years before retiring from science. During this time, Tony shared his deep knowledge of biochemistry and molecular genetics with our group and many others at UCSF, and his generous and gracious demeanor helped to ground a fledging new lab in its formative years.  While intending to spend my time immersed in the vast biology of serotonergic systems, I realized that the world of G protein-coupled receptors was getting immensely crowded and I therefore pivoted to ion channels, transitioning with cloning of the 5HT3 receptor (the one ionotropic serotonin receptor subtype), followed by nucleotide-gated (P2X2) channels – projects in which Tony played a key part through his own efforts at the bench or by providing advice and inspiration to others. One important outcome of this work was to bring our attention to primary afferent sensory neurons, where these channels are highly expressed. I became intrigued by the idea of studying somatosensation, which was arguably less well understood at a molecular level compared to other sensory systems – and possibly more mechanistically complex in having to detect both chemical and physical stimuli. Moreover, the goal of linking molecular events to behavior seemed more attainable with sensory systems, with the added benefit of possibly finding new inroads to diagnose and treat an unmet clinical problem, chronic pain. Another major selling point was the possibility of exploiting natural product pharmacology to gain a toehold in this area, bringing me back to what had enticed me into neuroscience in the first place. Jancsó and his team in Hungary had famously shown that capsaicin, the pungent principle in chili peppers, was an excitatory agent for a subset of somatosensory neurons, making capsaicin sensitivity a defining functional hallmark of nociceptors. Thus, identifying a mythical capsaicin receptor became something of a Holy Grail in the pain field, but also a frustratingly elusive goal. Like other groups fascinated by this problem, we tested any relevant and newly cloned channel, such as 5HT3 and P2X receptors, for sensitivity to capsaicin. But this low throughput candidate receptor approach never panned out, necessitating an unbiased, function-based screening strategy.  For us, the Eureka moment came when Michael Caterina joined my group and spearheaded our efforts to identify the capsaicin receptor (now called TRPV1) using an elegant expression cloning scheme. Together with Makoto Tominaga and others, he then showed that TRPV1 is a heat-activated ion channel, providing a cogent molecular explanation for a widely appreciated psychophysical experience – the ‘hotness’ of chili peppers. Taking this approach to its logical ‘flip side’, David McKemy and Werner Neuhausser used menthol to identify a related ion channel (TRPM8) as a cold receptor. These studies revealed a molecular logic of thermosensation while more generally illustrating how somatosensory neurons can detect noxious chemical or physical stimuli. Subsequent discoveries by us and many groups have further highlighted roles for TRP channels (and neurons that express them) in acute and chronic pain and itch, reflecting the ability of these beautifully complex polymodal signal integrators to regulate excitability of the nociceptor in the face of injury or other physiological perturbations. Exploiting these channels to develop non-opioid analgesics remains an important translational goal that has not yet come to fruition, but about which I remain optimistic.  A lot has happened since I started my own lab, but it’s still hard to believe that I’ve been at UCSF for over 30years! No institution is perfect, but I’ve stayed at this one because it is home to so many energetic and creative colleagues who have expanded my scientific horizons, and with whom I have developed wonderful, long-lasting friendships and collaborations. Chief among these is Allan Basbaum, with whom we have worked to connect molecular and biophysical findings to pain behaviors, giving our studies greater intellectual depth, impact, and translational relevance. Roger Nicoll, legendary neurophysiologist and lab neighbor, has been a mentor and role model for me and my trainees – always challenging us to put our hypotheses to the test with the cleanest, most rigorous experiments. Robert Edwards, another neighbor and neurologist and synaptic physiologist, has been a friend and colleague throughout my time at UCSF and a partner for daily banter of crazy ideas, strategies, and frustrations. Allan, Roger, Robert, and I also share a similar brand of humor, which is a mainstay of our interactions.  And then there is Yifan Cheng, with whom we have experienced another Eureka moment by leveraging recent advances in electron cryo-microscopy (cryo-EM) to visualize our favorite TRP channels in atomic detail. Seeing is, indeed, believing and the thrill of capturing these channels in various conformational states and in complex with drugs and toxins has been breathtaking. This work began as a synergistic collaboration between two fellows, Erhu Cao and Maofu Liao, and flourished from there over the past few years to include other channels and trainees. Being part of the cryo-EM ‘resolution revolution’ has been a thrill as we have watched its impact go far beyond ion channels and sensory neuroscience. Importantly, our timely contributions to this area were made possible by transformative innovations from the Cheng and Agard labs here at UCSF, once again validating this institution as a special place to do science.  The other great collaboration in my life has been with my wife, Holly Ingraham, also a scientist and professor at UCSF. Holly is well known for her molecular and biochemical studies of neuroendocrine physiology and development, and any appreciation that I may have for integrative physiology comes from watching her intuitive and creative approach to science. Aside from that, she is a talented, generous and loving partner who makes the world a better place for me, our families, friends, and colleagues. Together, we have raised a boy, Philip, whose interest cleave more to the arts than science, but I think he is the most creative spirit in our household. And both Holly and Philip tolerate my attempt to play trumpet music, which also speaks to their gracious patience and flexibility (and perhaps their discovery of noise-cancelling headphones).  My other family, of course, is the community of superbly talented students and fellows who have honored me by choosing to spend part of their career in the Julius lab doing exceptional, creative, and impactful science. My group has never been large (usually around 8 members at any given time), but an intense, yet collegial and collaborative atmosphere has created synergy that works to the benefit of all. I am proud to say that many Julius lab alums now head their own successful research groups and are leaders in their fields, thus carrying on the legacy of my own mentors.  The other shout-out goes to public support of science. Indeed, the National Institutes of Health has been the great engine driving biomedical research and training here in the US. In addition to funding projects with direct clinical relevance, the NIH had the foresight to support basic curiosity-driven research such as ours, which so often lays the groundwork for important advances in modern medicine. Maintaining this balanced portfolio is the secret sauce for continued success and vigor of biomedical research here in the US and elsewhere, and for our trainees and collaborators who hail from around the globe.  In closing, I would like to thank the Nobel Assembly for selecting somatosensation and pain as a topic worthy of recognition. Chronic pain remains a largely unmet medical need (as highlighted in this country by the opioid epidemic) and it is only through support of both applied and basic, curiosity-driven research that we will find new mechanism-based solutions to this pressing problem. While Nobel Prizes are awarded to specific individuals, their power is in inspiring the world to value and trust fact-based thinking and other intellectual and creative pursuits that make life better, richer, and fairer for all. |
| **Autobiographical** |  |
| **Podcast** | **“I didn’t really have a plan for what I wanted to do when I grew up”** In this podcast episode, conducted in June 2022, David Julius speaks about his childhood and how he loved puzzle solving. His father used to tell him that he was great at taking things apart but not so good at putting them back together.  Julius also talks about his journey from anxious pupil to confident researcher, the importance of diversity in science and how his research is connected to how different species experience the world in different ways.  The host of this podcast is nobelprize.org’s Adam Smith. **Nobel Prize Conversations was produced in cooperation with Fundación Ramón Areces.** |
| **Telephone**  **interview** | 0506=DJ  Adam Smith: Sorry to call so early. My name is Adam Smith, calling from Nobelprize.org in Stockholm, and I wondered whether it’s possible to speak to David Julius?  Holly Ingraham: Yes, yes, yes, you guys have a number that will get a hold of him, okay, here he is. [Laughs]  David Julius: Hello, good morning, or afternoon.  AS: Yes, very much morning for you.  DJ: Yes.  AS: My name is Adam Smith, I’m calling from Nobelprize.org, and we have this tradition of recording just very short interviews with new laureates, would you mind speaking?  DJ: Okay. No, let me just finish pouring some water into my coffee maker, because that’s going to be essential, then I’ll be with you. Okay, alright, I’m good.  AS: [Laughs] That is the tip that’s surely passed from laureate to laureate – you need coffee to survive this day.  DJ: Coffee. [Laughs] Exactly! Oh my goodness.  AS: How did the news actually reach you?  DJ: It was actually quite strange. I was nicely asleep and my phone, which I had by my bed going ‘rrrrrr’, so I look at the you know ‘what’s this all about?’ dinging, and there’s a text in there from my sister-in-law who lives in California, in Santa Cruz, and she says, let’s see, I’ll look at the text, she says, I thought it was some kind of a prank, anyway it said, I don’t know, it’s buried back here now, I get so many texts. But it said something like ‘someone’s been trying to reach you by the name of Thomas Perlmann, and I didn’t want to give him your phone number, so… but here’s his phone number’. And she said, ‘I looked him up on the web, he seems like a reasonable guy’ or something like that. Anyway, so, then I said ‘okay, well then…’ It came on my wife’s phone too so she kind of woke up. And I said ‘what do you think about this’. So she called and he said, ‘I’ve been trying to get a hold of David, so then I spoke to him, and he said ‘I have about three minutes and I’m so happy to talk to you but I now have to go out and do the announcements, so call me back in an hour’. So I have to call him back in, you know, 20 minutes. Anyway, so that’s how it happened.  AS: That’s an absolutely marvellous story, and how wonderful to have two gatekeepers protecting you – your sister and your wife.  DJ: Exactly!  AS: A hard man to reach. But how wonderful. So once the news had got to you, what was the first thing you did?  DJ: Well, you know… Yeah I can’t tell you how… ‘It’s a prank, don’t call Thomas’. Anyway, oh then Thomas said, ‘You should go to the YouTube and watch the announcement’. So that’s the first thing I did, sat here in the kitchen and watched the announcement. Yeah… and then… and then I made a couple of phone calls to some close colleagues, or texts, and by that time, you know, I was… my phone was blowing up as they say, so I haven’t had much time to do much else. I talked to my mom, that’s very important.  AS: Yes, indeed. What did she say?  DJ: She’s like overwhelmed, you know. ‘This is just unbelievable,’ she said, ‘but, you know, you work so hard, you deserve it!’  AS: Good, she’s behaving exactly as a mother should do, fantastic, yes.  DJ: Exactly, right. So she’s very proud, and she’s probably a little bit in shock, as we all are. And then my brother called me, and you know, so it’s been an exciting hour or so.  AS: Sounds wild and lovely. Talking of gatekeepers, it’s just extraordinary that you’ve discovered these gatekeepers for temperature sensing, which everybody, kind of, for eons has taken for granted, we can sense temperature, but we never knew how, until now.  DJ: Yes.  AS: So, the question is, how come you were able to get there? How come you identified the right question?  DJ: First of all, I like what you said. It’s actually true that, you know, and it’s true for many of our senses but maybe more so for touch and pain, we experience it but we take it for granted, you know, in terms of… mechanistically. But the reason that we were able to do it is because we started looking at the natural world, in terms of natural products, and we asked how things that tickle our pain sensors work. You know, chemicals from plants that are used to… presumably for them to defend themselves, and so we sort of, kind of, did an end run around the problem, by turning to some natural product pharmacology, and that’s how we did it.  AS: That’s a nice message in there, really, that turning to nature is always a good thing, especially in these days of kind of recognition of the importance of nurturing the planet.  DJ: That’s right, yes. Keeping our different species going and, you know, when you think about how many… when you think about how many drugs were discovered or derived from natural products, it’s really pretty astounding, so… and that’s certainly true in the pain world, you know, aspirin comes from willow bark, morphine comes from the opium poppy, but this extends to all facets of medicine, and so keeping those sources of natural products around is really critical.  AS: These discoveries open up the possibility of new treatments for pain which are so desperately needed.  DJ: Yes, so that’s the hope. You know, molecules we discovered, but also, you know other people have discovered over the years, since molecular biology’s really made inroads into that problem, will reveal all these new targets for, you know, non-opioid-based mechanisms for dealing with pain.  AS: I just wanted to ask you very quickly, you did your doctorate with [Randy Schekman](https://www.nobelprize.org/prizes/medicine/2013/schekman/facts/), you postdoced with [Richard Axel](https://www.nobelprize.org/prizes/medicine/2004/axel/facts/), you’ve…  DJ: I did, yes. That’s true.  AS: What did hanging out with these Nobel Prize laureates teach you about how to approach research?  DJ: I should also say when I worked with Randy I had a co-mentor who I worked very closely with, Jeremy Thorner, who’s not a Nobel Laureate but a superb scientist.  AS: Indeed.  DJ: What I learnt from all these guys was, well of course I worked with them long before they got their Nobel Prizes but, you know, they’re all unbelievably curious, that’s the main thing. And rigorous, you know, and they’re always… they have so much energy, you know, all those people. They’re always intensely, you know, with their groups, interacting with their groups, encouraging them to ask difficult questions. You know, you just sort of get a sense when you’re with those people where the bar should be in terms of doing science. And really, sort of, you know, investing yourself in it, so I guess that’s kind of what drew me to them in the first place, but, somehow, I figured that out even when I was young. But you know they have an intensity and a curiosity that’s just really special.  AS: Wonderful, thank you very much indeed. Well, I should let you get to the coffee and to the rest of the day which is just going to be mad.  DJ: Thank you.  AS: Thank you, it’s been so lovely speaking to you.  DJ: Thank you Adam, thank you very much. |
| **Interview** |  |
| **ID** | 0507 |
| **Biographical** | For the past two decades, I have studied the molecules that convey our sense of touch. I entered this field pursuing the allure of basic biology research, never anticipating the many directions these findings would take. Indeed, my life has been full of directions I never imagined. As an 18-year-old refugee from Lebanon, I had no idea I would become a scientist, and certainly not the recipient of a Nobel Prize. **From Lebanon to Los Angeles** I am of Armenian descent, born in Beirut, Lebanon, in 1967. My mother, Haigouhy Ajemian, is a retired elementary school teacher and principal, with a degree in biology; my father, Sarkis Patapoutian, is a retired accountant and a writer, under the pen name Sarkis Vahakn. My older brother, Ara, is an electrical engineer; my older sister, Houry, an architect and teacher. My early childhood was typical, at times even idyllic – I recall the beauty of Lebanon, the delicious cuisine, visits to the Mediterranean Sea and the surrounding mountains, and running wild in nature in the summer months.  But in 1975, clashes erupted between religious factions in Beirut. Armenians like my family were mostly thought of as neutral observers to the conflicts between Christians and Muslims, but times were tough for everyone. Beirut’s infrastructure – both physical and cultural – began to deteriorate, and lives were upended by curfews, limited hours of electricity, lack of running water, and bombings of the city. Still, between the blasts, I had many of the trappings of a usual childhood; I quite fondly remember playing basketball and table tennis, reading *Tintin*, and spending a lot of time watching TV.  I attended small private Armenian schools in Beirut, first Demirdjian and then Hovagimian-Manougian, both located not far from the Green Line that separated Muslim West Beirut from Christian East Beirut. Each year, though, my class grew smaller: Armenian families one by one moved away to escape the war. By my freshman year of high school, I only had four peers in my grade. I was ranked third out of the five of us, an average student. The school closed the next year.  I was a late bloomer, and it wasn’t until I enrolled at a new school, the more academically challenging Rawdah High School, that I began to discover how much I loved math and science classes. The bar was set high as I followed in Ara’s footsteps, and I still remember the first day of class in 10th grade when the physics teacher recognized my last name and asked if I was as scholarly as Ara. “I hope so,” I answered. After graduation, I enrolled at the American University of Beirut, a sprawling and lush campus overlooking the Mediterranean Sea. With my newfound interest in science, I declared a pre-med major; I really didn’t know, at the time, that being a scientist was a career option.  One frightening day, however, changed everything. I lived in West Beirut and had spent the night after a party at a friend’s house in East Beirut. The next morning while crossing the border between the halves of the city, I heard sniper shots. Terrified, I started running. As I sprinted into West Beirut, a group of militants motioned me toward them – a young man running across the Green Line seemed suspicious.  The militants held me for a day, at one point threatening to shoot me in the knee to see if I could feel pain. If I couldn’t feel pain, they said, it meant I was a spy. I responded, rather foolishly, “Couldn’t I just pretend to feel pain?” Eventually, the men realized I was harmless and let me go. But that was the final straw for me.  Despite the drawbacks of leaving the only life I knew behind, I began making plans to emigrate. A few months later, I packed my bags and flew to Los Angeles. **Discovering Science** Your body uses a sense called proprioception to help you stay afoot. Sensory cells innervating your muscles inform your brain of your precise posture and place in space. Without this sense, you’d struggle to stay upright and balanced. When you find yourself on rocky ground, proprioception is especially useful. My first months in the United States were, in a metaphorical sense, rocky. It wasn’t until years later, of course, that I learned about proprioception – a sense that, along with touch, my lab would help explain at the molecular level.  My goal was to continue my pre-med trajectory at the University of California, Los Angeles (UCLA). But first there were the common immigrant struggles to face – adapting to a new country, earning some money, and gaining admission to the school. To establish residency in California, I first spent a year working, delivering pizzas and writing horoscopes for an Armenian newspaper. Although I’d grown up watching English language television and taking English classes in school, I initially struggled to understand people speaking around me in Los Angeles. Slowly, as I figured out the pace and language of LA, I found my footing.  A year later, I was accepted to UCLA to study chemistry as a pre-med student, eventually changing my major to biochemistry and then biology. I knew very little about the revolution in molecular biology dominating research in the latter half of the twentieth century. Professor Bob Goldberg taught an introductory molecular biology class called Biology 7, where I first learned the power of DNA and genetics to describe human physiology and disease at a level unimaginable by prior generations. Dr. Goldberg also had us read *The Double Helix* by [James D. Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/), who shared the 1962 Nobel Prize in Physiology or Medicine for co-discovering the structure of DNA. Today I feel Jim’s legacy is compromised, but his book portrayed the fun of basic science and had a huge impression on me.  Hoping to round out my pre-med curriculum and get a letter of recommendation for medical school, I was fortunate to join Professor Judy Lengyel’s research lab focused on the fruit fly *Drosophila*. It was there that I fell in love with research. It was the late 1980s, an exciting and rapidly changing time for fly genetics, and I learned molecular biology from Lengyel’s graduate students Eiríkur Steingrímsson and Richard Baldarelli. Although I was an inexperienced undergraduate, they let me join in their experiments as they hunted for the genes critical for fly development. The lab discovered *tailless*, the gene that establishes anterior and posterior polarity in *Drosophila* embryos. Our results on *tailless* were published in 1990, with me listed as the fifth author, one of my most treasured publications to this day.  Working in a lab felt completely different from anything else that I had done before. I loved the camaraderie, the flexible hours, and the drive to discover. Working as part of a team, with a diverse group of other scientists, was addictive. When I found out that graduate school–but not medical school – paid a monthly living stipend, I made up my mind. I dropped my dream of medical school (or was it my parents’ dream?) and applied to PhD programs in biology.  I was very happy to stay in LA for graduate school at California Institute of Technology (Caltech), where I continued studying transcriptional regulation, this time in the context of muscle differentiation. I joined the lab of Barbara Wold, a big thinker who would go on to co-found Caltech’s Gene Expression Center and direct the Beckman Institute at Caltech. She developed and adopted new technologies and taught us all to look at science broadly, rather than getting slowed down by the small details of a mature field. I embraced lab work and once again learned so much from senior students in the lab, including Jeff Miner and Paul Garrity, as well as from contemporaries such as Kyuson Yun.  I loved my years at Caltech, a small and beautiful campus full of curious folks who are very passionate about research. There was very little bureaucracy, and we had easy access to professors, often worldwide leaders in their fields. I worked long hours in the lab, often late into the night and over the weekend. But always a fan of work/life balance, I also fit in various hobbies: doing photography, running, and cooking at the Prufrock House, where I lived as a graduate student. By 1996, I had defended my thesis and published three papers with Wold that described my graduate work – a look at how cells decide to become muscle cells during development. Most of our work in the Wold lab at the time was focused on a small group of transcription factors, that when expressed in naïve cells, were sufficient to induce myogenesis. This concept that one gene can regulate a whole developmental program was very powerful and got me hooked for life on finding other genes that play a central role in physiology.  Also important during this time, I met my future wife, Nancy Hong, an undergraduate Biology student at Caltech. Over these past 32 years, we have grown up together, discussing science in the car and at the dinner table, tackling the joys and challenges of our science-related careers. I am a far better scientist today thanks to her input on my papers, grants, and talks. **A New Interest in Sensory Neurons** After graduating from Caltech, I joined the lab of Louis Reichardt at the University of California, San Francisco (UCSF), for postdoctoral work from 1996 to 2000. Lou is one of a kind. An accomplished scientist, he was one of the founding editors of the journal *Neuron*, a Howard Hughes Medical Institute (HHMI) Investigator, and head of the neuroscience graduate program at UCSF. However, in some circles, he was more famous for being a world-class mountaineer. He was a member of the first American expedition to climb K2, the second highest peak on Earth. He also climbed Mt. Everest using a route never before attempted. As Isabel Farinas, a senior postdoctoral fellow, said to me when I joined the lab, “Don’t ever tell Lou something can’t be done.” Lou became my role model for how to run a lab, giving his students and fellows a great deal of independence at the same time as being a strong supporter. He almost never stopped by to check on work progress but was always available to chat when you wanted or needed it.  As in previous labs, my fellow researchers also became mentors and good friends. Uli Mueller, a senior postdoc, seemed to spend a good part of his last year in Lou’s lab distracting me and another junior postdoc, Ralph Brandenberger, with endless invitations to coffee. We enjoyed great discussions during these coffee breaks, gossiping about science and scientists and fending off Uli’s challenges to the importance of our projects. I continued to learn how to focus on questions that I could defend as truly impactful if answerable.  In Lou’s lab, I turned to studying the somatosensory neurons that initiate touch and pain. Lou let me start a variety of projects, many of which did not develop into full-fledged efforts. But three eventually grew into related insights on how signaling proteins called neurotrophins drive the survival and specialization of sensory neurons.  After five years in lovely San Francisco, I decided to embark on my independent research career at an unconventional new enterprise led by Pete Schultz. Renowned as one of the top chemists in the world, Pete is also an entrepreneur who has founded many biotech companies. He was leaving his UC Berkeley and HHMI positions to join Scripps Research in San Diego and to create a genomics institute funded by Novartis Research Foundation, a nonprofit associated with the Swiss drug company. I began a joint position with these two institutions in 2000, just as the sequence of the human genome was being completed. The opportunity to use novel genomics technologies to address fundamental questions in biology was extremely exciting.  I established my own lab and continued studying the development of somatosensory neurons: how does a temperature-sensitive neuron decide to become a so-called “thermosensor” while neighboring neurons become specialized in sensing touch? As interesting as this developmental biology question was, I also realized that another fundamental question about the function of these cells remained a huge mystery. Instead of sensing chemicals (e.g., hormones or neurotransmitters), these neurons sense physical stimuli such as temperature and pressure. How they accomplish this at the molecular level was mostly unknown. I felt we could use genomics tools to identify the molecular receptors for temperature and pressure.  Somatosensory neurons like those that I studied with Lou stretch from the tips of a person’s extremities to the spinal cord and all the way to the brain, carrying messages about temperature, touch, itch, and pain. At their ends, ion channels receive the initial messages about these senses. The channels are tiny – a few nanometers in diameter – but vital to cells’ functioning. In response to stimuli, ion channels open and close, changing the flow of ions in and out of cells and thus changing the voltage of the cells’ membranes, the language of the nervous system.  The electrophysiological properties of temperature and mechanically activated ion channels had been studied, but their molecular identities remained unknown. Back at UCSF, David Julius had just demonstrated TRPV1 to be the first ion channel activated by heat. Armed with early sequence data from the human genome, we asked if other TRP ion channels were involved in thermosensation. In a few years, we identified a channel activated by both cold temperatures and menthol, the cooling compound derived from mint leaves. We published our results in 2002, dubbing the channel TRPM8, at the same time David’s lab published very similar independent findings.  Over the next couple years, my young lab further characterized TRPM8 and identified other somatosensory ion channels, including TRPV3 and TRPA1. TRPA1 can be activated by noxious cold and plays a role in sensing reactive chemicals to transduce a painful signal. Indeed, we and others have shown that the burning of mustard oil (wasabi), wintergreen oil (a key ingredient in mouthwashes such as LISTERINE®), and raw garlic all act through TRPA1. This link between TRPA1 and pain led several pharmaceutical companies to research TRPA1 blockers for various types of clinical pain in humans. It was an important lesson that studying the basic biology of sensory ion channels could have further consequences for medicine. **The Sense of Touch** After working for a decade on temperature-activated sensory channels, I felt that the field was maturing. Many scientists were focused on TRP ion channels now, and I thought it was time to ask a new question: Which channels sense mechanical forces, allowing touch and pain? Hearing, sensing blood pressure, and many other critical biological processes depend on mechanically activated ion channels, and yet the molecules responsible for detecting pressure were mainly unknown.  What was the best way to identify these unknown channels? We quickly shelved efforts to identify them directly from the somatosensory neurons responsible for touch. Working with these finicky and heterogenous cells in the lab was difficult enough; trying to isolate channels from them seemed nearly impossible. Instead, postdoctoral fellow Bertrand Coste spearheaded a new assay to determine cell types that would respond to pressure and could be easily and homogeneously grown in culture. We reasoned that this might lead us toward a pressure-sensing channel that, while discovered elsewhere, could turn out to be relevant in sensory cells.  For this purpose, Bertrand screened cell lines, recording the electrical activity of a cell while poking it with a glass probe. If the cell expressed a mechanically activated channel, we expected to see changes to the current when it was pushed. He found that Neuro2A cells were exquisitely mechanosensitive and decided to focus on these cells.  Next, Bertrand worked through a list of 300 genes expressed in Neuro2A cells that might possibly encode an ion channel. He knocked each gene down using RNA interference (RNAi) molecules, and then once again recorded the effect of poking the cell on its electrical current. For a year, no gene seemed to have an effect on the ability of the Neuro2A cells to sense pressure. But on the 72nd candidate that Bertrand tested, removing the gene wiped out the currents. I recall that – despite the “Eureka!” potential for the moment – Bertrand came to my office very calmly and told me, “I found it.” He knew the importance of what he had discovered.  We named the new protein PIEZO1, after the Greek word for pressure, *piezi.* In 2010, we reported the results: not only did removing PIEZO1 from Neuro2A cells inhibit their ability to sense pressure, but adding PIEZO1 to embryonic kidney cells gave them the new ability to respond to mechanical force. PIEZO1 is necessary and sufficient for producing mechanically activated currents, a double condition cherished by biologists. Our reductionist approach to finding a molecule responsible for mechanically activated currents in Neuro2A cells and hoping to extend that to touch sensation was quite a leap. I am glad that Bertrand took that leap with me! **Uncovering Piezo Biology** When we searched the genome for other genes related to PIEZO1, we quickly turned up another protein, which we named PIEZO2. In the years after our discoveries of PIEZO1 and PIEZO2, we undertook a range of projects to more fully characterize the biology of these two ion channels – determining their structures, which cells they were expressed in, and what biological functions they play roles in.  An important milestone was showing PIEZO2 is robustly expressed in sensory neurons. This was followed by experiments demonstrating that PIEZO2 is the principal *in vivo* sensor of light touch, as mice without PIEZO2 are not able to sense vibrations or detect a piece of tape attached to their back. Importantly, we also showed that tactile allodynia (a condition in which touch becomes painful, such as after a sunburn), is also dependent on PIEZO2, raising the possibility that PIEZO2 could be a relevant target for neuropathic pain. But as my colleagues and I continued analyzing the effects of PIEZO mutations, we found that the channels go far beyond allowing us to sense a gentle breeze or a pinch on the arm. PIEZO2 also helps control other important functions by giving the body feedback on the pressure and stretch experienced by internal organs. PIEZOs sense how much a person’s lungs stretch with each breath – information that’s used to control breathing rate. They sense the pressure exerted by blood moving through the aortic arch, which then mediates blood pressure changes. They also tell us when the bladder is stretched out and full.  I also became especially interested in the concept of proprioception – that sense of where your body is in space. I think in many ways it is the most important of our senses, even though most people have never heard of it. We found that, indeed, mice without the PIEZO2 ion channel lack coordination. In a fascinating turn of events, Alex Chesler and his collaborators at the NIH, identified and characterized human subjects who are born without PIEZO2. Remarkably, many of the deficits described for mutant PIEZO2 mice are also experienced by humans without PIEZO2. For example, PIEZO2-deficient individuals don’t sense touch, struggle to learn to walk due to lack of proprioception, and don’t have a sense of their bladder being full. All this work on somatosensation and interoception was carried out by a dedicated group of graduate students and postdocs in my lab as well as collaborators across the globe. While there are too many important contributors to be mentioned here by name, I am forever indebted to them. **Pressure Sensing Beyond the Nervous System** One of the most rewarding features of science is the unanticipated direction it may lead you. Most recently, my team has launched projects looking at the role of PIEZO1 in non-neuronal cells. Scientists know that many different cell types experience, sense, and respond to mechanical forces. But exactly how they sense forces – and in many cases, why – is unknown. My lab and others have in recent years found important roles of PIEZO1 in the development of the cardiovascular system, bone formation, and in red blood cells, where it seems to have an interesting connection to malaria. Distant relatives of PIEZO can be found in plants and unicellular organisms. Indeed, we recently showed that PIEZO is expressed in the tips of plant roots, and without it, the roots can’t penetrate hard surfaces or soil. From proprioception to malaria to plant roots, research that began with a simple, fundamental question in sensory neurobiology has already taken me on a remarkable journey, and I intend to keep at it for years to come. **Looking Back** When the Nobel Prize call was made – at two in the morning California time – my phone was set to “do not disturb.” But the committee was able to reach my 94-year-old father, who was then the one to give me the news.  Amidst the celebrations with my family, friends, colleagues and collaborators, the Nobel Prize also helped me reconnect with my roots. I am the first Nobel laureate of Armenian origin as well as the first from Lebanon, so both communities celebrated from afar.  When I reflect on my career, I credit my mentors, collaborators, and trainees for much of my success. My time in the Wold and Reichardt labs imparted on me not only my love of science, but examples of how to run collegial, high-achieving, fun lab groups, and I have strived to do the same ever since. I have emphasized the importance to collaborate. Bringing researchers together who have different expertise and backgrounds creates a rich, fun environment and is a more effective way to do science.  I also learned during my years as a trainee that science is very hard, and that if your projects are ambitious, many if not most will fail. As Lou told me a while back, batting 1 out of 3 in baseball is considered a great feat. Good ideas can come from well-researched experimental plans, but they can also come from something as vague as an informed intuition. So it is crucial at times to trust your training and knowledge, and to take a leap as Bertrand did. In addition, although it is important to have bold ideas, it is equally imperative to know when to let go of the ones that aren’t working out.  Lastly, securing funding and publishing results are two of the biggest frustrations researchers face. For example, our first grant application proposing to find out whether PIEZO2 was the touch/pain sensor was rated in the bottom half of applications and rejected. And the manuscript showing definitive evidence that PIEZO2 is the touch sensor was declined by two journals before finding its home. I mention this to remind young investigators that they are not alone facing such difficulties and to persevere in the face of negative feedback. In my experience, well-supported science will eventually prevail.  Having learned all these lessons, I have advised my trainees to initiate multiple projects early on, and I work with them to monitor progress through a reiterative process of prioritizing and editing. To watch my students and postdocs go on to establish themselves as independent scientists in academia and industry is one of my great pleasures.  Individual laboratories do not function by themselves. The institutions I have belonged to have also been critical, allowing me to explore my interests and let my results take me in new directions. Indeed, I so enjoy my wonderful faculty colleagues at Scripps Research who not only enrich my science but also join me for swims in the Pacific Ocean and backpacking in the Sierra Nevada mountains. Biomedical research is expensive, and I am thankful for funding from the National Institutes of Health and the Howard Hughes Medical Institute.  As mentioned, I am a big proponent of work/life balance, and I have always prioritized my family over work. Nancy has been my full partner in this journey, and our son, Luca, has been such a wonder to watch grow. Through my uncertain times as a youth, my parents and siblings always prioritized education and unwavering love.  Finally, I am immensely privileged to be a scientist. I feel such joy to be on this incredible intellectual journey, to be working with diverse and dedicated colleagues, and to be experiencing amazing opportunities that science has given me, all while unraveling the mysteries of biology. Prizes are brilliant tools to recognize science that impacts humanity and to hopefully inspire the next generation; however, they work less well as the goal of a scientist, at least in my opinion. The Nobel Prize, in particular, brings a great deal of attention to scientists. This can be dizzying. As I adjust to this new recognition, I remind myself that the Nobel Prize can be granted to ordinary people who have been lucky enough to discover extraordinary results. |
| **Autobiographical** |  |
| **Podcast** | **“The best thing was to come up with the experiment itself”** In this podcast episode, conducted in May 2022, Ardem Patapoutian tells us about his shock and happiness after receiving the Nobel Prize, or as he puts it: “All of us in science know that the Nobel Prize is a big deal but I really didn’t anticipate it to be this big of a deal.”  Patapoutian also shares his life story immigrating to the US from war-wrecked Lebanon as a young boy. He speaks about his beautiful home country and its excellent food and warm people and the new life in the US and his university experience at UCLA. Patapoutian tells us that he quickly fell in love with the idea of doing science: “The best thing was not to see if the experiment worked, the best thing was to come up with the experiment itself.”  He also shares a strong and valuable message: “We all take things for granted, whether it is our jobs, our schools, our parents, our family and the best thing to not take anything for granted is to let go off it a little and then you realise how much something means to you.”  The host of this podcast is nobelprize.org’s Adam Smith. |
| **Telephone**  **interview** | 0507=AP  Adam Smith: Oh hello, am I speaking with Ardem Patapoutian?  Ardem Patapoutian: Yes, speaking.  AS: Hello, my name’s Adam Smith. I’m calling from Nobelprize.org, the website of the Nobel Prize.  AP: Hello there.  AS: Hi. First of all, many, many congratulations on the award of the Nobel Prize.  AP: Thank you so much.  AS: What was it like getting the call from Thomas Perlmann?  AP: It was… I had ‘do not disturb’ on my phone actually, so I didn’t get his phone calls, and then he somehow found my father’s, who’s 92 years old, lives in Los Angeles, and he called me. And so I heard it from him, which was very special.  AS: [Laughs] It’s nice that your 92-year-old father knows how to bypass your do not disturb.  AP: [Laughs] Yes, it is, indeed. I’m watching the video feed right now of the announcement.  AS: Would you like to watch it or is it okay to talk for a couple of minutes?  AP: We can talk for… quickly.  AS: The pressure receptors that you’ve discovered. We’ve taken our ability to sense pressure for granted for all of humanity’s existence. It’s quite amazing that you’ve actually located the gatekeepers for this. What was it, do you think, that led you to ask the right question to get to the answer?  AP: As you said, in science many times it’s the things that we take for granted that are of high interest. And us being in the field of sensing touch and pain, this was kind of the big elephant in the room where we knew they existed, we knew they did something very different than how most other cells communicate with each other, which is through chemicals, and it was a difficult question to answer, because technically it was… it was difficult. But you’re right in the sense that just identifying that this was a big unknown and ignored, you know, things like sense of proprioception, your sense of where your limbs are compared to your body, most people don’t even think about that’s an important sense. Without it you cannot walk, you cannot… you cannot stand up, and so it’s a very important part of physiology.  AS: Yes, because the focus will be on touch very much, and that’s what we’ve all missed during lockdown I suppose, but of course these pressure receptors control many things – blood pressure, as you say, proprioception.  AP: Absolutely, and one of the exciting things about it is that it’s taking us into directions and places where we didn’t know that pressure sensing was important, and that’s one of the exciting things in the future.  AS: What’s an example of one of those things?  AP: So, for example, we have found that red blood cells can sense pressure and adjust their volume. And in clinical settings when you have too much of this sense you can actually have dehydrated red blood cells that is protective against malaria. We also have found that in immune cells this protein regulates things like how much iron there is in your blood. Nobody ever could have thought that pressure sensing is related to these… to these processes.  AS: How wonderful. Last question – what’s… what do you think the secret of your successful research environment is?  AP: It’s two in the morning, it’s difficult to say very intelligent things right now, but I think it’s the environment, the people around you, and just to, kind of, focus on big questions that can be answered. In science, many times we focus on the big questions, but you have to ask it at the right place, and the right time, where the tools are present to answer those questions.  AS: Thank you. I think that was a very intelligent answer for any time of the day, let alone 2am, so… [Laughs] Thank you very, very much indeed for talking to me.  AP: Thank you. Nice talking to you.  AS: Lovely talking to you, thank you, congratulations.  AP: Bye, bye.  AS: Bye, bye. |
| Interview |  |
| Q1 | First of all, I want to hear a bit about your childhood. What did you want to be when you were a kid? Did you always want to be a scientist? |
|  | No, I didn’t know I wanted to be a scientist until much later in my life. I’m Armenian in origin. I grew up in Lebanon and I lived there the first 18 years of my life. There weren’t any scientists around, science as a career was not something I envisioned. My whole childhood I thought I was going to become a medical doctor. The reason, honestly, it was mainly because my parents wanted a doctor in the family. Funny enough, my brother and sister who were older than me didn’t want to do that because they were very queasy. They couldn’t stand looking at a cockroach for example. I was very brave in the sense that I used to kill cockroaches. So that’s what started me in the medical field, a very uninspiring story. But after immigrating to the United States and going to college to undergraduate at UCLA, I really fell in love with this, at that time decades-old, revolution in molecular biology. I took a molecular biology course, really got inspired, worked in a lab mainly to get a letter of recommendation for medical school, but I really fell in love with doing basic biology research. That’s when I kind of shifted and decided to go into the sciences and get my PhD. |
| Q8 | You spoke about the fact that when you were 18, you moved to the US as an immigrant. That must have been a challenging journey. Can you tell me a bit about that experience? |
|  | Yes, it was a very eventful time in my life. I was 18 years old, left all my friends and my parents in Lebanon and I came to the United States. It was indeed very difficult. I thought I was proficient in English, but coming to Los Angeles, I realised I couldn’t understand anybody. That was a big challenge. The culture of course was so different. It was a very big adjustment, but I had to also stop going to college for a year and have odd jobs like delivering pizzas and working in an Armenian newspaper for a year mainly to gain residency so I could go back to college. I came in with $2,000 in my account. It was a very tough year, but I think that experience has really made me tougher and appreciate what I have now. I keep talking about how it’s a privilege to do science. I think those experiences of both growing up in war-torn Lebanon as well as the difficulty of leaving everything and coming has not just toughened me up, but I’ve appreciated everything I have more because I remember those days and that kind of gives me some inspiration to realise how privileged we are. |
| Q5 | Could you tell me if there was like a particular person, a role model, parent or teacher that influenced you a lot when you decided on your field? |
|  | There’s a few people. As I said, one of the big inspirations was taking this basic molecular biology class. It was called molecular biology seven at UCLA and the teacher was Bob Goldberg. It’s funny to say someone has inspired you because while I was his student I never got to talk to him because the class was very large. It was 200-300 people taking the class and yet he had these amazing ways to make this large class seem like an intimate affair. He had discussions with people, he grouped people into small groups to talk to them, gave us books to read about molecular biology and it felt very intimate. That’s when I really fell in love with the material. I also have to mention, most of education for biology happens in a laboratory. When I was working in Judy Lengyel’s lab at UCLA and there were these two graduate students, Eirikur Steingrimsson and Richard Baldarelli, and they really took me under their wings and showed me how to think about science and how to appreciate it. I really loved it and owe those guys a lot early on to help with my journey. |
| Q2 | What would you say is the best thing about being a scientist? |
|  | I think this has been said by many before, but when you do an experiment and you find this result that is unexpected, or you realise that you saw something about nature that no one had seen before. You’re the first one observing this, you’re the first one understanding a concept that no one else has. It’s hard to explain that feeling, but I feel like that’s one of the most special things scientists experience. My favourite words are someone from the laboratory coming in and saying, “You got to come to the microscope and take a look at this”, that gets your excitement going like no other sentence. |
| Q26 | What qualities would you say are needed to become a successful scientist? |
|  | I’ve been thinking about this a lot and it’s a very unusual combination of traits, I would say. First of all, you have to be dedicated to your science and think and read a lot. I find that people who know the literature very well, who know what’s going on, what’s known in the past is very important to have ideas of what one should do in the future. Strong knowledge is very important. But it’s also important to know what kind of questions to ask. It’s an interesting overlap between being a dreamer where you’re thinking big, you’re imagining answering questions that no one else has, but you have to inject that with a little bit of practicality. What I mean by that is that anyone can dream, but if you dream something unimaginable or something that is not practical to do in the next few years, you might not be successful. People talk about the dreaming part a lot, which is necessary. It’s important, it’s wonderful, but a little bit of practical injection into that is also important. You have to look at where science and the field is and figure out what is really attainable in the next five years or not. That intersection of big thinking and practical approach I think is where success lies. |
| Q12 | Would you say that you have any advice that you would give to young up-and-coming researchers today? What kind of advice do you usually give to your students? |
|  | I think in science many times we get discouraged by these practical setbacks that we all experience, a paper doesn’t get accepted, a grant you write does not get funded. Sometimes these difficulties take center stage and you kind of become very upset about them. What I try to remind myself and everyone else is to remember why you got into science to begin with. I used the word privilege before, it’s a privilege to do what we do. We come into the lab every day, ask questions about nature, how things work, and you design to address them. What a great luxury that is, what a privilege it is. I think if you focused on the pleasure we get from the discovery process, the joy we get from doing experiments, I think that takes care of all the other setbacks. Not to minimise the setbacks because they are very important and it’s very difficult to do science. We need lots of support from the government, from funding agencies, etc. But it’s very important also to keep in mind why you got into science to begin with – for the love of science – and keep reminding yourself of that and not taking it for granted is the best advice I can give. |
| Q13 | How do you think that we can encourage more women or minorities to enter the field of science? |
|  | I think the good news is that all scientists that I know are talking about this, I think we realise that there is a problem of not being inclusive for people from underrepresented backgrounds and everyone’s working at this and it’s important to work at it from two perspectives. One is to educate the young and get them interested in science from communities, whether it’s male or female or it’s immigrants, like I was, or people who are not represented in science early on to get them involved, which is very important. But we also want to make sure that the people we already have in science are taken care of and are not discriminated against. I actually hadn’t thought about this too much but I remember that when I first came here, I am kind of a bit ashamed to admit this, but I was trying to hide the fact that I came from Lebanon. I thought my name was very long, difficult to pronounce and people associated Lebanon with war and in my CV where I went one year to American University of Beirut and then graduated from UCLA, early on in my days I didn’t put AUB in there. I just had the bachelor’s degree of science from UCLA, I did not really want to deal with potential negative perceptions of being from the middle east. Honestly after the Nobel Prize, the great positive feedback I’ve received for not just winning the Nobel Prize, but being an immigrant who’s won a Nobel Prize, made me realise that I was thinking about this completely wrong. I’m trying to correct that now by highlighting it more than I normally would. It’s back on my CV. I’m very proud to have this background and if I can help a young kid who sees this and says, “Well, maybe I can do that as well”, then that would be my pleasure. |
| Q31 | Would you say that you see yourself as American or Armenian or would you say that you are an international citizen? |
|  | I’ve often said that I found my tribe among scientists. It’s a particular tribe and I am really proud because I witnessed this from every lab I’ve been in. It’s such an international community that work and collaborate together. I definitely identify with that the most, but I have a very interesting mix, of course I’m an American but I grew up mainly speaking Armenian in an Armenian family but was born in Lebanon. I have a very mixed past and I am reconnecting to some of this past as well as realising that most and foremost we’re humans. Human rights and human equality should be at the forefront. Not to diminish the importance of cultural contributions of different countries, which is also very nice and important to celebrate. It’s a very interesting mix. |
| Q7 | How do you like to spend your spare time? I’ve seen pictures of you with the trumpet, are you a musician in your spare time? |
|  | I’m a big believer of work and life balance. I feel like one of the great things about science is a lot of it is about thinking, you’re thinking about questions. You can do this any time, any place. I’m not in the lab all the time. I do lots of things outside, but honestly, most times I’m thinking about the science and I don’t think of this as a burden. I think of it as a great thing, because I really enjoy it. Having said that, I love physical activities. I’ve also said before that many of my great science ideas have come to me while I’m running or doing any kind of exercise outdoors because it kind of frees the brain to think in a new way. I love that feeling. I love to hike. I used to love to run. I have a knee injury now, so mostly walking and hiking. We, a bunch of faculty here at Scripps, go swimming in the ocean. I love lots of outdoors things.  I also love music. I like to go to concerts and I play a little bit of trumpet and it’s interesting. I’m really, really bad at it. I’ve played for many years and I have not mastered this instrument. It’s not an easy instrument. But I enjoy being bad at trumpet. Let’s put it that way, but I cannot say the same thing about my wife, son and our two cats who immediately leave the room when I start playing. |
| Q32 | On another note: we love your Twitter activity! How do you see Twitter and social media and the responsibilities that we have on social media? |
|  | Science Twitter is a very interesting subcategory of Twitter. I like it a lot because it’s a very interesting mix of science, science gossip, and fun as well as science-related issues such as representation and all these things we talked about. It’s not utterly professional. There’s lots of fun in it, but actually it has come to a point where I hear about new scientific studies from PubMed, but also from Twitter, it’s become one of the sources of getting science stories. Beyond that, it’s a platform where you can reach many people. In my case, I went from, for example, having 3000 followers before the Nobel Prize to now approaching 30,000. It’s a pretty big jump. I guess I’m a nano influencer now because science is still a smaller market than the general public. I overall like it. I think there’s lots of positivity there. If someone is having a tough time in science, they talk about it. They seem to get amazing positive support. It’s also important to highlight that science has to be and can be fun, we do things outside of science that we enjoy and it’s just total representation of what a scientist is and does these days. It’s not to be taken too seriously. It’s just meant to be my state of mind, whether it’s talking about science or any of the other things I’m interested in. |
| Q10 | Besides having more Twitter followers, has your life changed in any other ways since you became a laureate. Have you noticed anything that has changed since that happened? |
|  | There’s a lot more attention paid, on Twitter I have to be more careful. But I think I’m trying to make the best out of it. One of the things that my wife Nancy and I have talked about is that we really liked our lives before the Nobel Prize. Part of me doesn’t want to change that too much because I want to still come to lab every day, interact with the young scientists in my lab and mostly do science. At the same time, this attention makes you realise, I don’t want to say responsibility, but the opportunity to do more than that. Again, I don’t tweet to do this for example, but when I do, and I see people be inspired that they can do this as well that gives me amazing satisfaction to try to do that.  I’m dealing with lots of more invitations to visit amazing places in the world, which is a good thing. I am also trying to keep my old rule of only 12 visits a year to places so that I can still focus on science. Honestly, it’s a work in progress. I’m still trying to think of how I want to use this new opportunity. I think immigration and science is an important aspect to me. My Armenian origin is important to me, and this will be some of the aspects that I will talk more about and get involved in and try to get science blossoming in countries that haven’t had the opportunity is one of the long-term goals. |
| Q19 | I can’t leave you without asking a question about this touching moment that you shared on Twitter, the picture depicting you and your son when you got the announcement call. Can you tell us a bit about that moment? |
|  | Yeah, it was a touching moment, as you say. I had my phone on do not disturb so I didn’t receive the three or four phone calls from Stockholm at two in the morning. They reached my 94-year-old father who then was able to call me and tell me that I should pay attention to this. As soon as this happened, we had literally one minute before the public announcement. My wife Nancy woke up my son Luca who came in and we wouldn’t even have thought about it but someone from the Nobel Foundation said we would love to have an image as soon as possible of a reaction. This was a genuine moment where I had just opened the laptop to see the live announcement and Luca was sitting next to me. When he saw my name, that’s exactly when the photo was snapped by Nancy, my wife. He was kind of excited and touching my shoulder. It was an in-the-moment shot that turned out great. As I said in my Nobel lecture, traditionally when you win the Nobel all these cameras come to your home and because of COVID, we didn’t have any of that. This picture kind of became the main way I shared this with the rest of the world. I am very fond of that moment. I’m glad it’s captured. |
| ID | 0508 |
| Biographical | **I never had no Nobel dreams** I was born in 1935, a pivotal year in American history, although it is possible that my birth had nothing to do with these historical events. In 1935, the US was emerging from the Great Depression and the election of Franklin Roosevelt in 1932 instilled hope for a new deal. Hope was on the rise and a newborn such as myself had the opportunity to live in a freer, more progressive and more prosperous world. But for those with foresight, 1935’s optimism was tempered by a growing fear of the rising tide of fascism in Europe. The Big Lie was to counter The Big Hope and by the time I was six, the US was at war with a Nazi regime that had already overrun most of continental Europe. Only England and Winston Churchill stood between my childhood and a direct attack on US soil.  I do not have many direct memories of my birth year since my brain cells were as immature as the rest of me. Indeed, I could not talk for that entire first year nor could I play a competitive game of Scrabble. However, at some subliminal level, it is possible that these opposing forces of hope and despair were imprinted on my developing psyche. In retrospect, I see 1935 as a harbinger of the future vicissitudes of my existence, the yin and yang of Harvey Alter.  Most of my conscious early memories were strongly influenced by World War II. After the Japanese surprise attack on Pearl Harbor, our isolationist, conservative Congress declared war on Germany and Japan barely in time to support an embattled Britain and its courageous people. However, we did not enter in time to prevent the annihilation of 6 million Jews. My people were decimated by a monstrous force beyond imagination in the 20th century. Not until I later saw films of piled skeletons did I realize the ravages that occurred as I grew up in pristine and protected Ridgewood Queens.  What I do remember of the war years was that my life was barely affected by it. I played ball in the streets and went to school just as before. I was reminded of the war only by newsreels in the movie theaters and a rash of exciting war films where the Americans always won the critical battles. There was no TV or social media in those days so the news came only from radio and from newspapers that I did not read. Because of my young age and because there was some censorship of bad news, I didn’t realize the truth and horror of war and was always certain America and the allies would ultimately win. This certainty abated fear. To me, the hardship of war was that I had to wait on line for bubble gum and was restricted to only two pieces, that we had to use black-out shades, that my favorite pink Spalding balls were in short supply because the rubber was being used by the military, that my father would leave the house at night to roam the streets as an air-raid warden and that we were encouraged to plant victory gardens which was difficult because the closest earth to our apartment was a mile away. One of the most exciting events of my war experience was that the FBI captured a German spy who was living in the apartment house next to ours, the FBI had picked up signals from his radio-transmitter. Who knows what the spy relayed to Germany about myself and my gang of friends? A second war memory was that I returned home from grammar school one day to find my mother crying. President Roosevelt had died and for my family, it was a time of profound mourning. In contrast, when I returned to the street in my predominantly German neighborhood, there were people cheering because Roosevelt was perceived as anti-German and most critically, a “Jew lover.” My neighborhood was not a paean for democracy or emblem of liberalism, but the latent anti-semitism was not generally manifest.  As alluded to, I measured out my youth in pink Spalding balls, thrown on traffic laden city streets, hurled against walls, stoops and curbstones, hit with bats, racquets and shortened broomsticks, and constantly lost to gaping sewer drains or thrust on commercial rooftops lined in jagged glass to thwart retrieval. These balls were my lifeblood and I was seldom without one. A lost ball required immediate replacement which was done at Olsen’s candy store where I would get a free chocolate egg-cream using Frequent Spalding Mile credits and where I would also buy a comic book. The ecstasy of buying a new ball and a new comic book was the equivalent of buying a new Lexus today. Harold Olsen was one of my two best friends and after school he had to run his father’s candy store until it closed at 10:00 pm. I spent a lot of time there and was always amazed at his business skill even as a teenager, and his hard work and sacrifices bore fruit because 30 years later he was made president of the mid-west division of Macy’s; a true Horatio Alger story.  I spent my first 17 years on one street of apartment houses and stoopfronted duplexes. These were modest edifices in a lower middle-class neighborhood. My family, though not wealthy, were better off financially than most of our neighbors and sufficiently solvent to escape the sweltering city in the summer when I was young and then to send me to summer camp in my early teens. I was privileged in a modest way. Our apartment was on the second floor of a 5-story building. Directly below our apartment was a muscle building studio and a barbershop. Given the proximity of these establishments one would have thought that I would have grown up stronger and with more hair. Putnam Avenue, the street I lived on for 17 years, was nestled between two commercial avenues. Within 3 blocks of my house were 3 movie theaters one or the other of which I attended twice a week, a German delicatessen where I would get delicious ham sandwiches unbeknownst to my kosher mother, a kosher delicatessen where I loved hot pastrami sandwiches even better than ham, innumerable candy and magazine stores like Olsen’s, a very good Chinese restaurant, a hobby shop where I spent endless hours selecting the next wood model to put together, my pediatrician, a synagogue and the rabbi who lived in the next apartment house and whom we had to assiduously avoid when driving on the sabbath. There were all manner of clothing stores, small food markets, butcher shops and even a live chicken market. When going to the butcher shop with my mother, I was intrigued by the butcher knives and the way they methodically sliced the fat off the choice cuts that my mother ordered from Abe the Butcher. For a brief period in my childhood I wanted to be a butcher, and I am now surprised that I was not drawn to being a surgeon. In any case, Ridgewood Queens was a thriving and bustling neighborhood of which I knew every inch. Hence, the family did not move for 25 years because there was nothing we were missing, unless, of course, you count luxury. I might still be there, if college did not intervene.  My parents were first generation Americans, their parents emigrating from Western Russia and Poland. Recently, when I had a gene profile, I was found to be 99.5% Ashkenazy Jew. We are still looking for the other 0.5% who disrupted the purity of my family tree. My parents were both good and kind people who showered me with love. My sister, Jackie, who was 5 years older, also treated me well though she often joked that she was an only child. Although my parents tried to be evenhanded, I think that I got favored treatment because my sister challenged them more, but Jackie never seemed resentful of me. She died about 3 years ago with dementia and smoking-induced obstructive lung disease. By the time she reached age 75, our parents, her husband and her two children had all died and I became her sole caretaker, albeit with the substantial help of an excellent nursing home. She died in hospice at age 85, my mother died at age 79 and my father at 81. I somehow always expected to die at the same age as my father, but here I am writing this autobiography at age 86 so I am, as they say in the gambling world, living on house money. I am intrigued by Woody Allen’s idea of achieving immortality, not by great accomplishments, but by not dying. For me, so far so good.  Despite their good natures, my parents had one major flaw… they didn’t get along. Their personalities were diametrically opposed. My father, one of 9 children from the lower east side of Manhattan, was college educated, active in the business world, president of every organization he belonged to, expansive in his thinking, handsome, a fashion plate, interested in the arts, particularly opera, adventurous and flamboyant. My mother came from meager beginnings. Her father died early in her life and she was raised by my favorite grandmother who earned a living by working a push-cart in the Bronx and in old age was supported by my father. Whether because of this hard beginning or other psychological factors, my mother grew up as a fearful person, afraid to take risks, to try new things, to drive, to spend money, to fully engage in life. Hence, my parents often argued, one wanting to move forward, the other holding back. The arguments affected me deeply because to my young mind they portended divorce. I often wondered which parent I would be left with and how I would bear the shame because I had no other friends whose parents had separated, divorce being rare in those days. My fears were not justified, as they remained married for 60 years and between arguments had a reasonably good life together. Nonetheless, I was stuck in their polarization, trying not to take sides while admiring my father more but sympathizing with my mother because she played the role of the eternally injured party. Their dichotomy influenced my personality because I too became dichotomous, on the one side fearful and holding back and on the other trying to break out and be more expansive. While my parents did not separate, their dipole exists in me.  Because my parents were overly protective of me, they allowed my elementary school to place me in a specialized health class, the concept of which was that an extra carton of milk and a rest period after lunch would instill vigor and growth. This decision, over which I had no control, separated me from my usual classmates and curriculum and labelled me as different when all I wanted to be was the same. The Health class was for kids who were too thin, too fat, too lazy, too active or too anything but the school’s definition of “normal.” I was ashamed to be segregated in this way, but nonetheless adapted, as is my tendency. I made some nice friends among the more normal of the “abnormal” and developed a crush on Roxanne who became perhaps my first sort-of girlfriend and bestowed my first real kiss. Ms. Gunther, the only teacher in the class, deemed me the brightest in the class and had me skip an entire year of elementary school. This magnanimous gesture, however, had its downside as I graduated at age 13 and entered high-school as the smallest in the class. I could have used another year of extra milk.  Although I was likeable and had a “good personality” and was even funny, because I was small and shy and socially inept, despite Roxanne, high school was not a great time for me. I did pretty well scholastically, but was not an outstanding student, wrote for the school paper and magazine, won some minor honors and a national essay contest and most importantly, grew to a reasonable size. They were able to take my face off the milk cartons and send a good progress report to Ms. Gunther. Overall, my high school days were nothing like one sees in the movies; Ferris Bueller or Tom Cruise, I was not. So, I will give short shrift to my highschool years as they were less than memorable.  After visiting six small coed colleges in the Northeast, I selected the University of Rochester because it had a renowned medical school that I ultimately attended. I did not apply to Harvard or Yale, but thought they would call me anyway. Somehow, they did not. If you are listening, Harvard, it is still not too late to call. I got off to a rough start academically getting a D on my first essay, despite the fact that writing was my strong point. My first mid-term GPA was C+ and I saw my medical career careening into an abyss of uncertainty. High school had been too easy and my study habits were poorly founded. I then taught myself to study hard and my grades responded accordingly. I graduated cum laude, but not magna or summa. I was sort of a “cum plus laude.” My subsequent achievements may have surpassed my innate intelligence through extra effort and perseverance. I remember a meeting with my college advisor at the end of my junior year where he told me that I had done much better than they had expected. Exceeding expectations may be the keynote of my life.  College represented my social transformation. I grew up fast emotionally in that first year at the University of Rochester. I did not join a fraternity as most freshmen did. Being an independent proved to be a great advantage, giving me some stature among those who were not accepted into or declined to join the fraternity system. I became a small big-man on campus, was managing editor of the school paper, was elected into the junior and senior honorary societies, made great friends and generally thrived. My social life burgeoned, my social skills accelerated and my shyness with women dissipated. I loved those four years, possibly the best in my life, and if I had one wish, it would be to relive them.  Toward the end of my senior year I received a letter that was the fulfillment of my life’s dream, an acceptance letter to Rochester Medical School. Only at the birth of my children did I ever experience equal elation. My path was set, though it was yet to take several twists and turns. If there was one week in my life that stands out, it would be the week after finals of my senior year when I awaited graduation, had absolutely no responsibilities and had my medical school acceptance letter in my back pocket. I have been trying to recreate that pressure-less feeling for the past 60 years and fear I am running out of time.  Medical school was everything I had hoped for. I found almost every course interesting, even anatomy, and each succeeding year more interesting as the program became more clinical. We had only 70 students in a class and grades were not given out to decrease competitiveness. Only if you were doing poorly were grades revealed to you. Fortunately, I never knew. The medical curriculum was highly integrated with the psychiatric service headed by John Romano and George Engel, two giants in the field. Great emphasis was given to medical history-taking and to understanding the patient as a person as well as a disease. This approach has stayed with me and has enhanced my patient interactions. I have found that what patients want most from their doctor, in addition to competence, is his or her time and empathy. NIH has allowed me to spend quality time with patients and that has greatly enriched my clinical experience. I found it incredibly rewarding to see patients in the context of a study that had a beginning and an end that could be summarized in a publication. That was the path I ultimately chose but it was a very circuitous path.  In med school I was fascinated by many subjects, the first being pathology which I learned from Lowell Orbison, who wrote a classic text and later became Dean. I wanted to take a year out studying under Orbison but he told me that I would also have to do autopsies and that put a cadaverous chill on the deal. In my clinical rotations, I was intrigued by ophthalmology and how many medical conditions had diagnostic ocular manifestations. By my next rotation, I was on to something else, but I am now back to the eye as I have developed dry macular degeneration, but so far without visual consequences. I am now also fascinated by studies that are restoring vision through stem cell implants. Pediatrics was another attraction, but I realized that my forte was verbal communication and pediatrics required other skills; also, I could not emotionally handle the death of infants and children. Thus, I navigated to internal medicine and particularly hematology. I liked the process of differential diagnosis that internal medicine demanded and still love to read diagnostic dilemmas in the *New England Journal* and the Health Sections of the *New York Times* and *Washington Post*. My big diagnostic breakthrough came as an intern when I had a patient with unexplained acute renal failure. No one could discern the cause until an eavesdropping patient in the same room showed me an article from *Readers Digest* that described a case of renal failure due to carbon tetrachloride (CCL4) toxicity. It was well known that CCL4 caused hepatotoxicity when ingested, but this lay article noted that it caused renal disease when inhaled. On further questioning of the patient, who was a long-haul truck driver, I found that he slept in the cab of his truck which housed a fire extinguisher in close proximity to his bed. I obtained the keys to his truck that was parked about a mile from the hospital. I then embarked on my first epidemiologic investigation. I found the truck and the sleeping cabin and the extinguisher just above the bed. Reading the metal tag, I was excited to find that the fire extinguisher was fueled by CCL4 and importantly that it was empty, the fumes already residing in my patient. Case closed! I was a medical hero for a brief time and was asked to give Grand Rounds where I was both the case presenter and the discussant, a rare event at the intern level. I have subsequently given Grand Rounds many times in my life, but this one was the most scary, most exciting and most memorable. The patient recovered fully and was prescribed a new fire extinguisher. The patient who clued me in to the Reader’s Digest article shared in my fleeting glory.  I seemed to have segued into my internship year at Strong Memorial Hospital in Rochester, NY. This was another pivotal year in my medical growth curve. I learned very rapidly how little I knew of real medicine coming out of medical school. Learning the Henderson-Hasselbalch Equation in physiology was quite different than managing a patient with renal failure and electrolyte imbalance. Memorizing the Krebs cycle in biochemistry was quite remote from managing diabetic ketoacidosis. Internship engendered a steep learning curve. It was a sink or swim environment. Once I caught on, I felt empowered and enjoyed that year more than any other in my training despite the long hours and intense pressure. Fortunately, Strong Memorial had a humane night-float system so that after 10:00 pm one could pass on new admissions to the night float. This did not mean that my day ended at 10 pm, because one still had to clean up the day residue and then write up cases admitted before 10. Generally, I would be writing notes to 2 or 3:00 am, often cat-napping as I did so. Many years later I returned to these wards and while flipping charts, by chance, found one of my old notes which was characterized by a descending line on the paper where I had fallen asleep mid-note. Unmarried interns lived in the staff house, which was a cross between a dormitory and a bordello, as various nurses slipped in and out of the rooms of the interns they were dating. Some things were even more important than sleep. Having free room and board at that time was essential because the annual intern’s salary was $600. This amount seemed to suffice because there was no time to spend it on entertainment or fine meals and no need for clothes beyond the white pants and white jacket that were provided. Only those who smoked were short on cash. My main source of entertainment, beyond that alluded to above, was to watch Robert Stack in the Untouchables, a weekly episode that I prioritized above all else. I hope that no patients were lost as a consequence of my addiction to this FBI drama. My internship year was lightened by a wonderful relationship with a woman whom I will call Sue, because that was her name. Sue was beautiful, sweet and uncomplicated and a person I might have married, if I had not been brainwashed since childhood that the worst thing I could do to my parents was to marry out of my religion. It was a Hebraic curse placed on Jewish children and it was powerful. As you will see, I later broke through this guilt-driven curse, but that was too late for Sue and myself. It is a chapter in my life whose end I will never know.  I continued my tenure at Strong Memorial by entering their Internal Medicine residency. It was easier to be a resident because the program was intern-centric, but I enjoyed being the hands-on intern more than the advisory resident. Near the beginning of my residency, I received a letter that was to dictate the future course of my life … my career path, my wife-to-be and consequently the children I would have. It was 1961 and the letter, which I still have, was from my draft board and began with the infamous word, “Greetings.” I had been drafted into the army and was to report to Fort Dix, New Jersey by Nov. 30 of that year. They even attached a subway token to help me get there, though the subway from upstate New York to New Jersey, encompassing about 400 miles, had not yet been built. I’m still holding that token should it ever come to pass. I can’t overstate the pivotal nature of that invitation from the government. Had I gone into the army, I probably would have been sent to Germany for the Berlin crisis that was the basis for calling up previously deferred physicians at that time. After 2 years in the army, I would definitely have gone into clinical practice since that had been my long-term goal and since I would have had no research experience to direct me toward academia. The alternative was that I could spend my military time at NIH where I had already been accepted, but not yet commissioned in the Public Health Service (PHS). This critical fork in the road had my future teetering on divergent paths. Either might have been fine, but in retrospect, the path I ultimately took to NIH had amazing outcomes I could never have anticipated. Through multiple conversations with the PHS, I learned that if I could secure a position at NIH and report there before my draft date, the PHS had authority over the draft. With the help of Scott Swisher, the head of Rochester hematology, I found a position at the Division of Biologic Standards (DBS), the forerunner of the FDA and the division responsible for the Clinical Center Blood Bank. I reported to DBS on Nov. 27, 1961, 3 days before my scheduled visit to Fort Dix. Fortunately, DBS did not require that I do push-ups every morning. DBS had an active research program as well as regulatory responsibilities and there I learned about plasma fractionation and how to do column separations. Within 6 months, the blood bank was transferred to the Clinical Center Pathology Department and I was transferred with it. The blood bank was a miniaturization of the one that now exists and had a staff of only about 10. I, as a first-year fellow, was a de facto assistant Chief and the second year fellow was Chief. When it was my turn to become Chief, they realized the weakness of this hierarchy and hired Paul Schmidt as permanent Chief. Paul began to grow the department and to gain its independence from the Pathology Department. In my long tenure in the blood bank, I have had only three bosses, Paul Schmidt, Paul Holland and Harvey Klein. Each was instrumental in advancing my career and each expanded the Department of Transfusion Medicine to its current stature as perhaps the best and most innovative in the world with a current staff of about 150.  As a first-year blood bank fellow, I had to come up with a research project. I had no research mentor and for reasons I cannot now remember, I decided to study whether blood recipients might have transfusion reactions because they harbored an antibody against a serum protein distinct from their own. I had read about polymorphisms in human albumin and haptoglobin, and this gave the study some scientific underpinnings. To test for these immune reactions, I cut circular wells into agar plates by the double immunodiffusion method of Ouchterlony and allowed serum from a multiply transfused patient to diffuse into the agar toward normal donor serum in surrounding wells. An immune reaction would be indicated by a curved precipitin line. Although agar plates continued to pile up, publications did not. One day, Richard Aster, a soon-to-be famous platelet immunologist, told me that he heard an interesting lecture by a geneticist named [Baruch Blumberg](https://www.nobelprize.org/prizes/medicine/1976/blumberg/facts/) who was doing experiments very similar to my own. I went to see Blumberg soon thereafter and found him to be interesting, quite chatty and very collegial. We immediately established a collaboration to, so to speak, join wells. Blumberg had already discovered polymorphisms in human beta-lipoproteins and these precipitin lines characteristically stained blue for their lipid content. One day, I observed a precipitin line that did not stain blue, but stained red when counterstained with azocarmine for protein. The antigen detected became known as the Australia antigen and was later shown by Blumberg to be the surface coating of the hepatitis B virus as described in my current [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2020/alter/lecture/) and in the 1976 [Nobel Lecture by Blumberg](https://www.nobelprize.org/prizes/medicine/1976/blumberg/lecture/). This serendipitous finding of the Australia antigen was my first introduction to the hepatitis field and served as my conduit to non-A, non-B hepatitis, now known as hepatitis C. As yet another example of the serendipity of my life, had Richard Aster not heard the Blumberg lecture and told me about it, I probably would not have found and published about the Australia antigen and perhaps not wended my way back to NIH to complete my scientific history. The rest of my long NIH career is chronicled in my accompanying lecture. I can summarize briefly to say that none of what has brought me to this Nobel Prize would have happened had I not been at NIH and its nurturing, supportive, intellectually stimulating and highly collaborative environment. It was, and is, a research Valhalla and I owe everything I have achieved to this tower of hope and innovation.  Full bent on entering clinical practice, after completing my NIH fellowship, I did a second-year medical residency at the University of Washington Hospitals in Seattle and then did a hematology fellowship at Georgetown University under a wonderful mentor and life-long friend, Charlie Rath. Rath taught me as much about life as medicine and both have been invaluable. Charlie died with his mind and humor intact at age 93. I was honored to give his eulogy. At the end of my heme fellowship, I applied for a coveted group practice position in Washington DC. I was not offered the position, ostensibly because they needed a cardiologist, and was quite disheartened. Rath said “Why not stay here at Georgetown, you can always go into practice later” and indeed he doubled my salary from $6,000 to $12,000 a year. It sounded good at the time. This was my introduction to academia, where I seemed to fit well and where I soon lost my interest in entering clinical practice. My career path had changed for the better as the result of failure to be selected. Another yin and yang of my trajectory.  Although, I liked my time in academia, I was becoming overwhelmed by it because I was heavily involved in teaching, had a high case load of hematology consults and private patients and was nominally head of hematology research. I found these three academic hats difficult to manage so that when I got a call from Paul Holland in 1969 to come back to NIH and resume my research on the Australia antigen and transfusion-associated hepatitis, I jumped on it. Hence, that serendipitous precipitin line, a Blumberg lecture that I heard only second-hand, and a failed job opportunity forged the rest of my working life and brought me to this Nobel Prize. Not even my mother could have predicted this and I’m so sad that she and my father were not alive to see me accept this award, albeit by Covid-dictated zoom.  I have been remiss not to write about my immediate family. I met my first wife, Barbara, at NIH. We had a seemingly happy marriage, but after 12 years it dissolved, in part because of the demands of my work and my compulsive response to those demands. After a period of deep remorse, I recovered my equilibrium and as a born-again bachelor I emerged into a phase of professional productivity and social awakening. During the early 80s, my career was expanding and I was being invited to speak at wonderful locations around the world that I never thought I would see. Those were heady times as HCV and Har-V were both coming into full blossom. From that point forward, I measured out my life in Power Point slides. In 1984, I met Diane Dowling and after an interminably long courtship, which will go unexplained, we married in 1995. It has been a wonderful relationship and seems to get better with time. As a psychotherapist, Diane had a lot to work on within her marriage, namely me, and she has made me a better husband, a better parent and a better person. I am very grateful for her love, support and guidance. I had two children with Barbara, Mark and Stacey, of whom I am incredibly proud and who continue to give me joy into old age. Diane brought me two step-daughters, Lydia and Erinn, whom I consider daughters without the step. Wonderful and accomplished ladies. Each of these children married and have brought me 9 grandchildren that now age 11–21. My family cup runneth over.  My essay also runneth over, but I have one more topic to cover. Now, in old age, I measure out my life in losses. It is the curse of a long and healthy life that those closest to you disappear, one by one. First parents, aunts and uncles, then siblings and now first cousins. I have watched near two generations of the Alter clan depart; near 50 persons linked by blood, but no longer able to bleed, lying in scattered cemetery plots in Queens and remembered only sporadically by placing a small stone upon their grave; multiple lifetimes reduced to chemicals and molecules that no longer have cohesive function. And as I age, still in good health, my friends also begin to leave me one by one. I recite or listen to their eulogies, I learn new things about them that I wish I had known before, I console their survivors, but I find no consolation in their loss. I miss these friends deeply and wonder what friendship or what love I might lose next. The siphoning of other lives from my small residual well of being is hard to endure, but I do because this is the inexorable cycle of life. I am consoled by the fact that when my time comes, I can say these were my family and my friends and I was so lucky to have had them enrich my life. My last hope is that if there is a heaven, it will be filled with a limitless supply of pink Spalding balls. **I never had no Nobel dreams** When I grew up in Ridgewood Queens I never had no Nobel dreams My goal was to hit the ball between the seams To perhaps be a hero on one of my teams To not have mom detect my schemes  High-school was unauspicious I mixed with the mob, did nothing suspicious I was small for my age and basically shy Could have been the model for Catcher in the Rye I was not voted most likely to succeed But there was already a hint, my hair would recede When I graduated high school, I gave no speeches  There was no sign that one day my deeds would exceed that of my teachers Nothing about me was the fodder for memes And certainly, I never had no Nobel dreams  In my 20’s, it was medical school Reading textbooks by the reams Studying cadavers splayed at the seams From massive texts, I was sucking the nectars Studying all night and sleeping through lectures At Rochester Med great teachers abounded Everything was interesting, my career choices compounded But of Nobel thoughts I had naughts  Then came marriage and baby screams My first house secure in its beams I was ready to take on whatever life deems Children growing My career flowing Lots of patients, lots of teaching Deep research seemed beyond my reaching Nobel aspirations, no one was preaching  Then an aboriginal antigen I had observed in my youth Was linked to hepatitis B by Blumberg the sleuth Of hepatitis viruses we were discerning the truth For me a chance to return to my NIH roots Non-A, non-B arose from long prospective studies I tracked this agent along with bright NIH buddies And with Chiron’s cloning of C, there came the safest of bloodies With this my career advanced But Nobel dreams I never chanced  And now my non-Nobel dream has unfolded With new credentials I’m suddenly embolded A thousand congratulatory emails my computer uploaded But for Nobel aspirations, I was not truly molded I expect any day, Karolinska will have annulled it And I will be the first Laureate to have his medal ungolded To have the King of Sweden say, “from Alter we best hold it; Get the medal back before he has sold it.”  This award has given my life a massive shake-up My heart and my mind are having a break-up Strange forces are scrambling my genetic make-up Though the leaves of my life, age will soon rake-up I’m happy to be where I am because in life there’s no make-up From this Nobel dream, I’m afraid to wake up! |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0508=HA  Harvey J. Alter: Hello?  Adam Smith: Hello, am I speaking with Professor Alter?  HA: Yes, yes you are. Just woken up.  AS: My name is Adam Smith. I’m calling from Nobelprize.org, the website of the Nobel Prize in Stockholm.  HA: Yes, I’m not shocked because I got a morning phone call, which put me into shock. You’re the aftershock.  AS: I’m proud to be the aftershock, that’s a nice idea. So, were you asleep when the call came?  HA: Yes, I was, yeah, it was 4:45 I think on the east coast here. The phone rang… and who the heck is calling? And I didn’t answer it. And then about 5 minutes later it rang again and still, still didn’t answer it, and the third time I got up angrily to answer it. It was Stockholm. It was a weird, weird experience.  AS: I imagine your anger subsided fairly fast.  HA: [Laughs]. It did, yes, it went away in about a second. It was replaced by the shock.  AS: What was the first thing you did after hearing the news?  HA: I told my wife. I woke her up. It’s just… you know, it’s so kind of other-worldly. It’s something that you don’t think will ever happen, and sometimes don’t think you deserve it to happen. And then it happens in this crazy COVID year, just where everything is turned upside down. This is another, nice upside down for me.  AS: It’s a very hopeful story of science, the discovery and then virtual eradication, at least in many countries, of Hepatitis C. I mean, it was decades of work wasn’t it?  HA: Yeah, you know, it’s a good story for kind of non-directed research, where we have a hypothesis, but you have no idea where it’s going to go, just looking to see what caused post-transfusion Hepatitis, and initiated, you know, a very, very, very long study, that involved many people. And that was all done at NIH, and probably could not have been done anywhere else because it took so long to come up with something you didn’t really expect to find. But it was decades, and a lot of people, Bob Purcell and particularly Paul Holland and Paul Schmidt who were in the blood bank with me. But Bob Purcell was a very basic scientist. It’s really a 50-year story.  AS: It’s a real detective story as well. I mean, it’s thrilling stuff. And these stories in a way need to be told to the next generation so that they too become virus hunters.  HA: Yeah, yeah, the message that I think is important is that you don’t always know where you’re going. Nowadays research is so directed, and so has to come up with a drug fast, but at NIH they allowed me to just… go my way. And, so, paid off, way beyond… You know, to have a cure, to see the first case, what was officially called ‘non-A, non-B’, the first case, and then see these curative drugs, and see so many people getting cured, and nobody getting post-transfusion Hepatitis, that’s like astounding.  AS: It must be amazing, to see the direct effect of your work and the work of many others, yes.  HA: Yeah, you know, nothing I thought would happen really.  AS: How wonderful.  HA: Thank you. Thank you for calling.  AS: Thank you. Many congratulations.  HA: It’s the best alarm clock I’ve ever had!  AS: Well you should record it, you should have recorded the call and then you could use it every day thereafter.  HA: [Laughs]. Okay!  AS: Thank you.  HA: Thank you.  AS: Look forward to speaking again. Thank you.  HA: Bye bye, thank you. |
| Interview |  |
| Q33 | What does it mean for you to receive the Nobel Prize? |
|  | It’s such an unimagined honour. It’s not something I strove for, or thought would be possible in a clinical type of research. So it was nice that they recognised that this clinical piece was important. But I think any prize, and this one the most, is an acknowledgement that your peers respect what you did and think it was good. I always wondered how good it really was. |
| Q6 | Has it impacted your life already? |
|  | Yes, it’s turned it over. I decided to just enjoy it but there’s a huge burden that comes with it. Nice things but the number of emails and cards and things like that are enormous and I want to answer every one of them. I’ve answered hundreds already. But my, like my speeches, my answers are lot. Somebody says congratulations, I write back a paragraph. So I still have piles of people to answer. So that’s been a burden, but nice! |
| Q5 | As a Nobel Laureate you will be a great source of inspiration for many people. Who inspired you when you were younger? |
|  | I learned something from everybody. I think my father in retrospect was a big inspiration because of his love of science, and he was a smart guy who to me could do anything. I’m kind of a gadget person, I can fix things and he was like that whatever it was he could fix it.  From [Dr. Blumberg](https://www.nobelprize.org/prizes/medicine/1976/blumberg/facts/), I learnt persistence because he could have dropped this thing at any point. It was kind of bizarre finding this antigen. But he kept at it – he made a lot of wrong hypotheses and when they failed, he’d go to another one. And he kept at it and it proved to be the hepatitis B virus, and he got the Nobel Prize. So persistence was something I learned from him.  But every one of my mentors, every one of my collaborators taught me. And I had great bosses. I had bosses who were not into my research but who were so supportive to allow me to do it and to go to their higher ups to get funding to keep it going.  So for young people, I say, fine go to the best institution that you can get into. Find a mentor who wants more than just your hands. Somebody who wants to foster your career. It’s not easy to find that person, it’s not easy to start out. You know you can’t just start out de novo and have a great experiment. But if you go into somebody else’s lab and you find your own niche. I think that’s a good way to start out. |
| Q1 | Did you have an early passion for science and research? |
|  | The short answer is no. I think I leant towards science for a couple of reasons … My father was very interested in science. He was not a doctor or scientist, but he was always reading science. He liked that, he didn’t like TV. So I had that influence.  And as a Jewish boy in New York it is kind of in your genes that you’re going to be a doctor. So that was in the background. But then I found in high school I really liked biology better than other things. I wasn’t good in math, I wasn’t going to be an engineer. So medicine was the natural place to go. And then when I got into med school, I loved it. |
| Q2 | What is the most stimulating part of your work? |
|  | It’s always fun. I’m a pretty collegial person. I worked with really brilliant people and so we had fun, I enjoyed coming to work every day. And I liked seeing patients, I could see patients and do research at the same time. It was always enjoyable, and there weren’t too many setbacks. You know the only setback was we couldn’t actually find the [Hepatitis C] virus per se. |
| Q11 | So a lot of the enjoyment is collaborations and interactions with other people? |
|  | Yes, the NIH is such a unique place. Not only does it allow you time for things to play out, but it’s not competitive, everybody does their own thing. But if you have a question, there’s always somebody there who has some expertise that will help you. |
| Q12 | Looking back at your life, what advice would you give the young Harvey? Would you tell him to take the same path as you have done – going into medical research rather than practice? |
|  | Yeah, definitely. And that wasn’t a path I planned to take. But once it happened, I couldn’t have had a better path, I don’t think I would have been happy in practice. I think I’m a good doctor, but the way you practice now you have to see patients so fast and there is also paperwork. At NIH, because I didn’t have a huge number of patients, I could see them, spend time with them, that’s what I enjoyed. And, you know, patients really appreciate when you give them time, they prefer that to good medicine. |
| Q17 | Is it rewarding to see the direct results of your research by working with patients? |
|  | For me that was yes. I wanted to work in clinical practice, but didn’t go that way. But to still see patients but see them in the context of research and to bring something to conclusion in a paper and then go on to the next. You can’t have a better life. |
| Q35 | It must be nice to say there is nothing you would change in your career path. |
|  | I had to be lucky too you know. The first person I worked with we happened to find the Australia antigen [Hepatitis B] while looking for something else. So serendipity and luck – finding that antigen is what got me back to pursue it further. If that hadn’t happened, I would have still been in practice.  So you know I can’t say to a young person, well, you go and you work hard, you’re going to get a Nobel Prize – you can’t predict that. But you won’t get it if you don’t work hard – I can say that. And you won’t get it if you don’t observe things well and you don’t collaborate well. |
| Q12 | What advice would you give to a young researcher who is thinking of pursuing a career in science? Is it worth it? |
|  | Oh, yeah, I’d say it’s worth it. I think you have to try to find a balance between family and work. I didn’t find a very good balance for a long, long time. And then there are a lot of perks in academic medicine, you get invited to talk and go to wonderful places, you get treated well. So if you are lucky enough to find something or become an expert in some field, then there’s a lot of perks to it as well. But I would, if I could do it over again, spend more time with my family. |
| Q7 | You read a poem about frustration in your Nobel Lecture. Can you tell us a little more about your interest in poetry? |
|  | I use humour in my talks, and much more than I used in the Nobel talk. I found poetry goes over very well. I started writing poems when people left the blood bank, they retired, they went to another job. And I would write a poem based around their name. And they were always very popular.  Actually I was at a meeting once in Rochester, New York, this is way, way back. About three speeches ahead of me guy gave a brilliant poem about cleaning the red blood cells. So I quickly scribbled down a four line poem so when my turn, I had a poem in response to his poem. And that went over well. Then I started writing poems for my talks, and I was a poet laureate of the transfusion world. And I became a poet laureate of hepatitis. |
| Q15 | So humour has been important to you in your work? |
|  | For me it has been. Humour has been a way to get along with people, to teach, to collaborate. I’m not a stand up comic but funny things come into my head.  I have a good way with people and humour helps that. If you have a good way with people it’s more fun to work with them so it all ties up. Not only in work but in relationships … [my wife and I] both got woken up by the Nobel call and when I finally got back to bed she’d fallen back to sleep and I said: ‘That was Stockholm calling and I won the Nobel Prize.’ And she said, ‘Stop joking!’ |
| Q3 | That’s a problem when you tell a lot of jokes! Do you also cope well with failure and mistakes? |
|  | No! I don’t like to fail. I felt very secure at NIH so I never sought going into a new environment or starting over or becoming a Chief of Medicine. Position didn’t mean anything to me. Comfort meant a lot to me. I always thought if you’re happy where you are, why move, why change? Part of that was the fear of going somewhere and failing. I was already doing ok and I didn’t want to jeopardise that. |
| Q23 | The Nobel Prize is given to a person who has achieved the greatest benefit of humankind. What would you say that the greatest benefit to humankind has been with your work? |
|  | Well my work, as a piece of a lot of people’s work, has eradicated post-transfusion hepatitis. And it looks like there’s no other agent out there of a hepatitis variety. And then, by leading to treatments of which I had nothing to do with, that are now 100% effective virtually and have no side effects – they’re amazing. So almost every patient I had has been treated now. We’ve got about 10 or 12 more to treat. And to see them so happy … it’s had a huge impact. And there’s still millions and millions of people that are silent carriers of hepatitis C that need to get treated. |
| Q36 | Is there a discovery that you wish you had made? |
|  | I would have liked to do the cloning of Hepatitis C! I would have liked to write a really good book, not a science book, a good novel. |
| Q37 | What would the title of your book be? |
|  | I haven’t thought about that. I can give you my epitaph – I’ve written that! It will be: ‘As in life, he ran out of time.’ |
| ID | 0509 |
| Biographical | Born in London, England in 1951 to Leonard George and Elsie Cressy Houghton, he was raised in a working-class family along with elder brother Graham. Educated at an excellent government primary school (Lyndhurst Grove) until the age of 11, he then won a scholarship to Alleyn’s School in Dulwich, London, founded by Edward Alleyn, a lead actor and producer of William Shakespeare’s plays in the 16th and 17th centuries. Graduating with college entry examinations in physics, chemistry and math, he decided to study biology at college, having been heavily influenced by reading at age 17 about the life and works of Louis Pasteur and also watching BBC TV coverage of the discovery of the DNA double helix early on Sunday mornings. In 1969, he entered the school of Biological Sciences at the new University of East Anglia, where he was highly motivated by the teachings of Professors Balls, Wilden and Thane as well as by full extracurricular activities including playing for the college cricket and squash teams. Offered attractive PhD positions at a London cancer research center, Oxford University, and Glasgow University, he failed to secure a stipend so entered the research laboratories of GD Searle & Co. in High Wycombe, UK, which was engaged in basic molecular biology research. Registering for a PhD in Biochemistry at King’s College, University of London in 1973 and co-supervised by Dr. Norman Carey (Searle) and Dr. James Chesterton (King’s), he graduated with a PhD in 1977 in a ceremony at the Alberta Hall with his wife, Han Fong Ida, who received her B. Pharm degree at the same ceremony from the London School of Pharmacy.  He then continued as a Research Investigator at Searle, benefiting from the excellent mentorship of Dr. Norman Carey and Dr. Richard Palmiter, where he characterized the human fibroblast interferon gene using newly emerging recombinant DNA technology. Offered many positions at burgeoning genetic engineering companies in the UK and US, in 1982 he chose to join the Chiron Corporation in California, founded by University of California Professors Bill Rutter and Ed Penhoet. Intending originally to work on chimeric type 1 interferons and to identify what became known later as type 3 interferons, he was introduced to the problem of Non-A, Non-B hepatitis by Dr. Dino Dina, then Director of Virology at Chiron. As a result, he decided to devote his laboratory to the pursuit of the causative agent(s) of this infectious disease, using a molecular biological approach, which was known not to be caused by the already charac- terized hepatitis A & B viruses. After pursuing numerous avenues unsuccessfully for many years, along with Dr. Qui-Lim Choo in his own laboratory, Chiron collaborator Dr. George Kuo, and CDC collaborator Dr. Dan Bradley, he published on the discovery of the hepatitis C virus (HCV) genome in 1989 with his collaborators, having published on the novel structure of the HDV genome in 1986. Following the HCV discovery, he and collaborators developed a series of patient diagnostics and blood screening tests that prevented post-transfusion hepatitis globally, as well as contributing to the identification of key enzymes crucial to the virus life cycle, which then became drug development targets for the field.  HCV infection represents a serious pandemic and so again with Dr. Choo and Dr. Kuo along with Dr. Ralston and others, he published the first evidence for an efficacious HCV vaccine in 1994 and subsequently performed 4 clinical trials in 3 different countries. His work has indicated the feasibility of developing an HCV vaccine, which he hopes to roll out to high-risk groups by the mid-2020s using both adjuvanted recombinant protein approaches as well as by applying the new RNA vaccine technologies at the Li Ka Shing Applied Virology Institute at the University of Alberta in Edmonton, Canada. He is also working with and supporting other leaders at the University of Alberta to develop a vaccine for Group A Streptococcus, and better drugs to treat Alzheimer’s disease and CMV infections. Now that HCV is a curable disease, he and others in the hepatology field are also turning their attention to the problem of non-alcoholic liver disease. **Education** 1969–1972 BSc (Honors) Biological Sciences, University of East Anglia, Norwich, England  1973–1977 PhD Biochemistry, King’s College, University of London England  2019/7 Honorary Doctorate of Science University of East Anglia. Norwich, England **Positions** 1977–1982 Research Investigator, Human Interferon Genetics, Searle Research Laboratories, Buckinghamshire, England  1982–1988 Project Leader, Non-A, Non-B Hepatitis Discovery Research, Chiron Corporation, Emeryville, CA  1988–2000 Director, Hepatitis C Research, Chiron Corporation, Emeryville, CA  2000–2003 Vice-President, Hepatitis C Research, Chiron Corporation, Emeryville, CA  2003–2006 Vice-President, Hepatitis C & Virology Research, Chiron Corporation, Emeryville, CA  2006–2007 Vice-President, Hepatitis C & Virology Research, Novartis Vaccines & Diagnostics, Inc., Emeryville, CA  2007–2009 Chief Scientific Officer, Epiphany Biosciences Inc., San Francisco, CA  2010–2018 Canada Excellence Research Chair in Virology and Li Ka Shing Professor, Department of Medical Microbiology and Immunology, University of Alberta Edmonton, AB, Canada  2013 – present Director of the Li Ka Shing Applied Virology Institute, University of Alberta, Edmonton, AB, Canada **Awards/Honors** The following honors were awarded for research on hepatitis C:  1992 Co-recipient of the [Karl Landsteiner](https://www.nobelprize.org/prizes/medicine/1930/landsteiner/facts/) Award from the American Association of Blood Banks  1993 Co-recipient of the [Robert Koch](https://www.nobelprize.org/prizes/medicine/1905/koch/facts/) Medal from Germany  1993 Honoree of the Japanese Medical Congress  1993 Honoree of the Triennial International Hepatitis Meeting  1994 Co-recipient of the William Beaumont Prize from the American Gastroenterology Association  1994 Recipient of Beatrice Bitiello Award from Italian Association for Prevention of Viral Hepatitis  1994 Awardee of the Princess Takamatsu Cancer Research Fund from Japan  1998 Co-recipient of the International Hepatitis Foundation Award  1999 Co-recipient of the Hans Popper Award (Falk Foundation, Germany)  2000 Co-recipient of the Clinical Lasker Award (USA)  2005 Co-recipient of the Dale Smith Memorial Award of the American Association of Blood Banks  2009 Recipient of the Hepdart Lifetime Achievement Award (USA)  2011 Gold Medal from the Canadian Association for the Study of the Liver (CASL)  2011 The Australian Society for Microbiology Annual Scientific Meeting Bazeley Oration  2013 International Gairdner Award (Canada; declined)  2018 American Liver Foundation Distinguished Scientific Achievement Award (USA)  2020 The Nobel Prize in Medicine (The Nobel Foundation)  2021 Knighthood awarded by Queen Elizabeth II **Publications (by subject area and chronological order)** *Transcriptional and Translational Control in Eukaryotes*  Houghton M, Cox RF. (1974) The purification and properties of hen oviduct Form B DNA-dependent RNA polymerase. *Nucl. Acids Res*. 1:299–308.  Doel MT, Houghton M, Cook EA, Carey NH. (1977) The presence of ovalbumin mRNA coding sequences in multiple restriction fragments of chicken DNA. *Nucl. Acids. Res*. 4:3701–13.  Lilley DMJ, Houghton M. (1979) The interaction and RNA polymerase II from wheat with supercoiled and linear plasmid templates. *Nucl. Acids. Res.* 6:507–23.  Lilley DMJ, Jacobs MF, Houghton M. (1979) The nature of the interaction of nucleosomes with eukaryotic RNA polymerase II. *Nucl. Acids Res*. 7:377–99.  Lane CD, Colman A, Mohun T, Morser J, Champion J, Kourides I, Craig R, Higgins S, James TC, Applebaum SW, Ohlsson RI, Pauchas E, Houghton M, Matthews J, Miflin BJ. (1980) The Xenopus oocyte as a surrogate secretory system. *Eur. J. Biochem*. 111:225–35.  Sumikawa K, Houghton M, Emtage JS, Richards BM, Barnard EA. (1981) Active multi-subunit ACh receptor assembled by translation of heterologous mRNA in Xenopus oocytes. *Nature*. 292:862–4.  Sumikawa K, Houghton M, Smith JC, Bell L, Richards BM, Barnard EA. (1982) The molecular cloning and characterization of cDNA coding for the alpha subunit of the acetylcholine receptor. *Nucl. Acids Res*. 10:5809–22.  Kenten JH, Molgaard HV, Houghton M, Derbyshire RB, Viney J, Bell LO, Gould HJ. (1982) Cloning and sequence determination of the gene for the human immunoglobulin epsilon chain expressed in a myeloma cell line. *Proc. Natl. Acad. Sci. USA*. 79:6661–5.  Sumikawa K, Houghton M, Miledi R, Barnard EA. (1983) “A study of the mRNA and genes coding for the nicotinic acetylcholine receptor” *in* Cell Surface Receptors (Strange PG. ed.) pp. 249–69. Ellis Horwood Ltd., U.K.  Barnard EA, Houghton M, Miledi R, Richards BM, Sumikawa K. (1982) Molecular genetics of the acetyl choline receptor and its insertion and organization in the membrane. *Biol. Cell.* 45:383.  *Molecular Genetics of Human Fibroblast Interferon*  Houghton M, Stewart AG, Doel SM, Emtage JS, Eaton MAW, Smith JC, Patel TP, Lewis HM, Porter AG, Birch JR, Cartwright T, Carey NH. (1980) The amino– terminal sequence of human fibroblast interferon as deduced primers. *Nucl. Acids Res.* 8:1913–31.  Houghton M. (1980) Human interferon gene sequences. *Nature*. 285:536.  Houghton M, Eaton MAW, Stewart AG, Smith JC, Doel SM, Catlin GH, Lewis HM, Patel TP, Emtage JS, Carey NH, Porter AG. (1980) The complete amino acid sequence of human fibroblast interferon as deduced using synthetic oligodeoxyribonucleotide primers of reverse transcriptase. *Nucl. Acids Res.* 8:2885–94.  Houghton M, Jackson IJ, Porter AG, Doel SM, Catlin GH, Barber C, Carey NH. (1981) The absence of introns within a human fibroblast interferon gene. *Nucl. Acids Res.* 9:247–66.  Houghton M, Doel SM, Catlin GH, Stewart AG, Porter AG, Tacon WCA, Eaton MAW, Emtage JS, Carey NH. (1981) “The cloning and expression of a human fibroblast interferon gene in bacteria” *in* Proceedings of the Battelle International Genetic Engineering Conference (Keenberg M. ed.). Battelle Seminars and Studies Program.  McCullagh KG, Davies JA, Sim IS, Dawson KM, O’Neill GJ, Doel SM, Catlin GH, Houghton M. (1983) Biological properties of human interferon beta 1 synthesized in recombinant bacteria. *J. Interf. Res*. 3:97–111.  Porter AG, Bell LD, Adai JR, Catlin GH, Clarke JM, Davies JA, Dawson KM, Derbyshire RB, Doel SM, Dunthorne L, Finlay ME, Hall J, Houghton M, Hynes C, Lindley IJ, Nugent ME, O’Neill GJ, Smith JC, Stewart AG, Tacon WC, Viney JH, Warburton N, Boseley PG, McCullagh KG. (1985) “Active hybrids formed between human beta and alpha interferons” *in* The Biology of the Interferon System (Schellekers and Stewart eds.).  Porter AG, Bell LD, Adai JR, Catlin GH, Clarke JM, Davies JA, Dawson KM, Derbyshire RB, Doel SM, Dunthorne L, Finlay ME, Hall J, Houghton M, Hynes C, Lindley IJ, Nugent ME, O’Neill GJ, Smith JC, Stewart AG, Tacon WC, Viney JH, Warburton N, Boseley PG, McCullagh KG (1986) Novel modified beta interferons: gene cloning, expression and biological activity in bacterial extracts. *DNA*. 5:137–48.  *Hepatitis Delta Virus*  Wang KS, Choo QL, Weiner AJ, Ou JH, Najarian RC, Thayer RM, Mullenbach GT, Denniston KJ, Gerin JL, Houghton M. (1986) The structure, sequence and expression of the hepatitis delta (δ) viral genome. *Nature*. 323:508–14. Erratum in Nature. (1987) 328: 456.  Wang K-S, Choo Q-L, Weiner AJ, Ou J-H, Denniston KJ, Gerin JL, Houghton M (1987) “The Viroid-like structure of the hepatitis delta genome: synthesis of a viral antigen in recombinant bacteria” *in* The Hepatitis Delta Virus and its Infection (Rizzetto M, Gerin JL, Purcell RH. eds.) pp. 71–82. Alan Liss Inc., New York.  Weiner AJ, Wang K-S, Choo Q-L, Gerin JL, Bradley DW, Houghton M. (1987) Hepatitis delta (δ) cDNA clones: Undetectable hybridization to nucleic acids from infectious Non-A, Non-B hepatitis materials and hepatitis B DNA. *J. Med. Virol.* 21: 239–47.  Weiner AJ, Choo Q-L, Wang K-S, Govindarajan S, Redeker AG, Gerin JL, Houghton M. (1988) A single antigenomic open reading frame of the hepatitis delta virus encodes the epitope(s) of both hepatitis delta antigen polypeptides p24 delta and p27 delta. *J. Virol.* 62:594–9.  Weiner AJ, Choo Q-L, Wang K-S, Govindarajan S, Redeker AG, Gerin JL, Houghton M. (1988) A single antigenomic open reading frame of the hepatitis delta virus encodes the epitope(s) of both hepatitis delta antigen polypeptides p24 delta and p27 delta. *J. Virol*. 62:594–9.  Ponzetto A, Eckart M, D’Urso N, Negro F, Silvestro M, Bonino F, Wang KS, Chien D, Choo Q-L, Houghton M. (1993) Towards a vaccine for the prevention of hepatitis delta virus superinfection in HBV carriers. *Prog. Clin. Biol. Res.* 382:207–10.  Eckart MR, Dong C, Houghton M, D’Urso N, Ponzetto A. (1993) The effects of using recombinant vaccinia viruses expressing either large or small HDAg to protect woodchuck hepadnavirus carriers from HDV superinfection. *Prog. Clin. Biol. Res.* 382:201–05.  Nisini R, Paroli M, Accapezzato D, Bonino F, Rosina F, Santantonio T, Sallusto F, Amoroso A, Houghton M, Barnaba V. (1997) Human CD4+ T-cell response to hepatitis delta virus: identification of multiple epitopes and characterization of T-helper cytokine profiles. *J. Virol.* 71:2241–51.  *Non-A, Non-B Hepatitis / Hepatitis C Virus*  Choo Q-L, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. (1989) Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*. 244:359–62.  Kuo G, Choo Q-L, Alter HJ, Gitnick GI, Redeker AG, Purcell RH, Miyamura T, Dienstag JL, Alter MJ, Stevens CE, Tegtmeier GE, Bonino F, Colombo M, Lee W-S, Kuo C, Berger K, Shuster JR, Overby LR, Bradley DW, Houghton M. (1989) An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science*. 244:362–64.  Esteban JI, Viladomiu L, Bonzalez A, Roget M, Genesca J, Guardia J, Esteban R, Lopez-Talavera JC, Hernandez JM, Vargas V, Buti M, Kuo G, Choo Q-L, Houghton M. (1989) Hepatitis C virus antibodies among risk groups in Spain. *Lancet*. 334:294–7.  Van Der Poel CL, Ressink HW, Lelie PN, Leentvaar-Kuypers A, Choo Q-L, Kuo G, Houghton M. (1989) Anti-hepatitis C antibodies and non-A, non-B post-transfusion hepatitis in the Netherlands. *Lancet*. 334:297–8.  Parker T, de Medina M, Jeffers L, Reddy R, Bradley D, Schiff E, Houghton M, Choo Q-L, Kuo G. (1989) Hepatitis C virus HCV: A causative agent of cryptogenic cirrhosis CC among Cubans. *Hepatology*. 10:685.  Saracco G, Houghton M, Kuo G, Choo Q-L, Rosina F, Lattore V, Torrani Cerenzia MR, Chiandussi L, Bonino F, Rizzetto M. (1989) Anti-hepatitis C virus in non-A non-B patients responding and non-responding to alpha 2A interferon. *J. Hepatol.* 9:S219. Supplement 1.  Colombo M, Kuo G, Choo QL, Donato MF, Del Ninno E, Tommasini MA, Dioguardi N, Houghton M. (1989) Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. *Lancet*. 334:1006–8.  Alter HJ, Purcell RH, Shih JW, Melpolder JC, Houghton M, Choo Q-L, Kuo G. (1989) Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. *N. Engl.* *J. Med*. 321:1494–1500.  Takeuchi K, Boonmar S, Katayama T, Choo QL, Kuo G, Weiner AJ, Bradley DW, Houghton M, Saito I, Miyamura T. A cDNA fragment of hepatitis C virus isolated from an implicated donor of post-transfusion non-A, non-B hepatitis in Japan. *Nucl. Acids Res*. 17:10367–72.  Miyamura T, Saito I, Kubo Y, Takeuchi K, Boonmar S, Katayama T, Kuo G, Choo Q-L, Houghton M. (1989) “Hepatitis C virus complementary DNA clones isolated from a single healthy carrier who was shown to be an implicated donor of post-transfusion non-A, non-B hepatitis” *in* Proceedings of the International Meeting on Non-A, Non-B Hepatitis, Tokyo (Shikata T, Purcell RH, Uchida T. eds.) Elsevier Science Publishers, Amsterdam.  McHutchison JG, Kuo G, Houghton M, Choo Q-L, Redeker AG. (1989) Autoimmune hepatitis is not associated with antibodies to hepatitis C virus (HCV). *Hepatology*. 10:701.  Kamitsukasa H, Harada H, Yakura M, Fukuda A, Ohbayashi A, Saito I, Miyamura T, Choo Q-L, Houghton M, Kuo G. (1989) Intrafamilial transmission of hepatitis C virus. *Lancet*. 2:987. Letter.  Colombo M, Kuo G, Choo Q-L, Houghton M, Donato MF, Tommasini MA, Bargiggia S, Piva A, Del Ninno E, Dioguardi N. (1989) High prevalence of antibody to hepatitis C virus in patients with primary liver carcinoma. *Hepatology*. 10:700.  Colombo M, Kuo G, Choo Q-L, Houghton M, Tommasini MA, Rumi MG, Dioguardi ML, Donato MF, Del Ninno E. (1989) High prevalence of antibody to hepatitis C virus in patients with hepatocellular carcinoma HCC. *J. Hepatol.* 9:S20. Supplement 1.  Katkov WN, Cody H, Evans AA, Kuo G, Choo Q-L, Houghton M, Dienstag JL. (1989) The role of hepatitis C virus HCV in chronic liver disease. *Hepatology*. 10:644.  Katkov WN, Friedman LS, Cody H, Evans AA, Kuo G, Choo Q-L, Houghton M, Huggins CE, Dienstag JL. (1989) Elevated serum alanine aminotransferase ALT in blood donors: The contribution of hepatitis C virus HCV. *Hepatology*. 10:581.  McHutchison JG, Kuo G, Houghton M, Choo Q-L, Redeker AG. (1989) Circulating antibodies to hepatitis C virus HCV: A study of 160 cases of acute and chronic NANB hepatitis. *Hepatology*. 10:645.  Jeffers L, de Medina M, Hasan F, Reddy R, Parker T, Silva M, Mendez L, Schiff E, Houghton M, Choo Q-L, Kuo G. (1989) Hepatitis C HCV associated idiopathic chronic hepatitis and cryptogenic cirrhosis. *Hepatology*. 10:644.  Hasan F, Jeffers L, de Medina M, Reddy R, Parker T, Schiff E, Houghton M, Choo Q-L, Kuo G. (1989) Hepatitis C HCV associated hepatocellular carcinoma. *Hepatology*. 10:608.  Evans AA, Cody H, Kuo G, Choo Q-L, Houghton M, Katkov WN, Dienstag JL. (1989) Seroepidemiology of hepatitis C virus HCV in selected population. *Hepatology*. 10:644.  Krawczynski K, Kuo G, Dibisceglie A, Houghton M, Bradley DW. (1989) Bloodborne non-A, non-B hepatitis PT-NANB immunohistochemical identification of disease and hepatitis C virus-associated antigens. *Hepatology*. 10:580.  De Bisceglie AM, Alter H, Kuo G, Houghton M, Hoofnagle JH (1989) Detection of antibody to hepatitis C virus in patients with various chronic liver diseases.  *Hepatology*. 10:581.  Prince AM, Brotman B, Huima T, Krauledat P, Houghton M, Kuo G, Kuo Q-L. (1989) “Distinction between chronic and self-limited forms of hepatitis C virus infection” *in* International Meeting on Non-A, Non-B Hepatitis, Tokyo, Japan (Shikata T, Purcell RH, Uchida T. eds.) pp.7–16. Elsevier Science Publishers, Amsterdam.  Houghton M. (1990) Discovery of hepatitis C virus and assay of non-A, non-B hepatitis virus. *Jikken Igaku.* 8:203–6.  Mosley JW, Aach RD, Hollinger FB, Stevens CE, Barbosa LH, Nemo GJ, Holland PV, Bancroft WH, Zimmerman HJ, Kuo G, Choo Q-L, Houghton M. (1990) Non-A, non-B hepatitis and antibody to hepatitis C virus. *JAMA*. 263:77–8.  Weiner AJ, Kuo G, Bradley DW, Bonino F, Saracco G, Lee C, Rosenblatt J, Choo Q-L, Houghton M. (1990) Detection of hepatitis C viral sequences in non-A, non-B hepatitis. *Lancet*. 335:1–3.  Choo Q-L, Weiner AJ, Overby LR, Kuo G, Houghton M. (1990) Hepatitis C virus: The major causative agent of viral non-A, non-B hepatitis. *Br. Med. Bull.* 46:423–41.  Miyamura T, Saito I, Katayama T, Kikuchi S, Tateda A, Houghton M, Choo Q-L, Kuo G. (1990) Detection of antibody against antigen expressed by molecularly cloned hepatitis C virus cDNA: Application to diagnosis and blood screening for posttransfusion hepatitis. *Proc*. *Natl. Acad. Sci.* USA. 87:983–7.  Kew MC, Houghton M, Choo Q-L, Kuo G. (1990) Hepatitis C virus antibodies in southern African blacks with hepatocellular carcinoma. *Lancet*. 335:873–4.  Chien D-S, Kuo GC, Sung J-L, Lai M-Y, Sheu J-C, Chen P-J, Yang P-M, Hsu H-M, Chang M-H, Chen C-J, Hahn L-C, Choo Q-L, Wang T-H, Houghton M. (1990) Hepatitis C virus infection in an area hyperendemic for hepatitis B and chronic liver disease: The Taiwan experience. *J. Infect. Dis.* 162:817–22.  Makris M, Preston FE, Triger DR, Underwood JCE, Choo Q-L, Kuo G, Houghton M. (1909) Hepatitis C antibody and chronic liver disease in haemophilia. *Lancet*. 335:1117–9.  Stevens CE, Taylor PE, Pindyck J, Choo Q-L, Bradley DW, Kuo G, Houghton M. (1990) Epidemiology of hepatitis C virus. A preliminary study in volunteer blood donors. *JAMA*. 263:49–53.  Jeffers L, Perez G, de Medina M, Schiff E, Ortiz-Interian C, Bourgoignie J, Vaamonde CA, Houghton M, Choo Q-L, Kuo G. (1990) Hepatitis C HCV infection in hemodialysis units. *Kidney Int*. 37:303.  Oliveri F, Baldi M, Brunetto MR, Saracco G, Rosina F, Cerenzia MT, Rizzetto M, Soranzo ML, Colla L, Vallauri P, Verme G, Kuo G, Houghton M, Bonino F. (1990) Antibody to hepatitis C virus in the serum of patients with chronic hepatitis. Eur. J. Gastroenterol. *Hepatol*. 2:347–50.  Houghton M, Richman K, Han J, Berger K, Lee C, Dong C, Overby L, Weiner A, Bradley D, Kuo G, Choo Q-L. (1990) “Hepatitis C virus (HCV): A relative of the pestiviruses and flaviviruses” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 328–33. Williams & Wilkins, Baltimore, MD.  Choo Q-L, Berger K, Kuo G, Houghton M. (1990) “Detection and mapping of immunologic epitopes expressed by bacterial cDNA clones of the hepatitis C virus” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 345–6. Williams & Wilkins, Baltimore, MD.  Kuo G, Choo Q-L, Shuster J, Kuo C, Berger K, Lee WS, Medina-Selby A, Houghton M. (1990) “Serodiagnosis of hepatitis C viral infection using recombinant-based assays for circulating antibodies to different viral proteins” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 347–9. Williams & Wilkins, Baltimore, MD.  Weiner AJ, Truett MA, Rosenblatt J, Han J, Quan S, Polito AJ, Kuo G, Choo Q-L, Houghton M. (1990) “HCV: Immunologic and hybridization-based diagnostics” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 360–3. Williams & Wilkins, Baltimore, MD.  Boonmar S., Takeuchi K, Kubo Y, Katayama T, Harada H, Ohbayashi A, Choo Q-L, Kuo G, Houghton M, Saito I, Miyamura T. (1990) “Molecular cloning of hepatitis C virus cDNA from plasma of an implicated donor or post-transfusion non-A, non-B hepatitis” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 371–4. Williams & Wilkins, Baltimore, MD.  Shimizu YK, Weiner AJ, Rosenblatt J, Wong DC, Shapiro M, Popkin T, Houghton M, Alter HJ, Purcell RH. (1990) Early events in hepatitis C virus infection of chimpanzees. *Proc. Natl. Acad. Sci. USA*. 87:6441–4.  Van der Poel CL, Reesink HW, Lelie PN, Cuijpers MT, Leentvaar,-Kuypers A, Bakker E, Exel-Oehlers PJ, Polito A, Houghton M, Schaasberg W. (1990) “Impact of blood-donor screening for anti-HCV versus ALT, and cofactors for infectivity of anti-HCV-positive blood” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 427–30. Williams & Wilkins, Baltimore, MD.  Esteban JI, González A, Hernández JM, Madoz P, Muniz E, Torras J, Enriquez J, Buenestado J, Martin-Vega C, Sánchez C, Esteban R, Guardia J, Houghton M, Alter HJ. (1990) “Open prospective efficacy trial of anti-HCV screening of blood donors to prevent posttransfusion hepatitis: Interim report of the Barcelona PTH study” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 431–3. Williams & Wilkins, Baltimore, MD. Krawczynski K, Kuo G, Dibisceglie A, Bradley D, Houghton M, Alter M, Ebert J. (1990) “Blood-borne non-A, non-B hepatitis: Detection and identification of hepatitis C virus and disease-associated antigen HCV Ag in hepatocytes” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 434–5. Williams & Wilkins, Baltimore, MD.  Prince AM, Brotman B, Huima T, Krauledat P, Houghton M, Kuo G, Choo Q-L, Polito A, Di Nello R, Nelles MJ. (1990) Use of anti-HCV determinations for diagnosis of chronic HCV infection” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 450–5. Williams & Wilkins, Baltimore, MD.  Miyamura T, Saito I, Yoneyama T, Takeuchi K, Ohbayashi A, Watanabe Y, Choo Q-L, Houghton M, Kuo G. (1990) ‘Role of hepatitis C virus in hepatocellular carcinoma” *in* Viral Hepatitis and Liver Disease (Hollinger FB, Lemon SM, Margolis HS. eds.) pp. 559–62. Williams & Wilkins, Baltimore, MD.  Takeuchi K, Boonmar S, Kubo Y, Katayama T, Harada H, Ohbayashi A, Choo Q-L, Kuo G, Houghton M, Saito I, Miyamura T. (1990) Hepatitis C viral cDNA clones isolated from a healthy carrier donor implicated in post-transfusion non-A, non-B hepatitis. *Gene*. 91:287–91.  Watanabe J, Minegishi K, Mitsumori T, Ishifuji M, Oguchi T, Ueda M, Tokunaga E, Tanaka E, Kiyosawa K, Furuta S, Katayama T, Kuo G, Choo Q-L, Houghton M, Nishioka K. (1990) Prevalence of anti-HCV antibody in blood donors in the Tokyo area. *Vox Sang.* 59:86–8.  Katayama T, Kikuchi S, Tanaka Y, Saito I, Miyamura T, Choo Q-L, Houghton M, Kuo G. (1990) Blood screening for non-A, non-B hepatitis by hepatitis C virus antibody assay. *Transfusion*. 30:374–6.  Takeuchi K, Kubo Y, Boonmar S, Watanabe Y, Katayama T, Choo Q-L, Kuo G, Houghton M, Saito I, Miyamura T. (1990) The putative nucleocapsid and envelope protein genes of hepatitis C virus determined by comparison of the nucleotide sequences of two isolates derived from an experimentally infected chimpanzee and healthy human carriers. J. Gen. *Virol*. 71:3027–33.  Kremsdorf D, Thiers V, Garreau F, Duclos H, Porchon C, Houghton M, Tiollais P, Brechot C. (1990) Cloning and sequence analysis of hepatitis B virus variants in non-A and non-B infections. *J. Hepatol.* 11:S36. Supplement 2.  Saito I, Miyamura T, Ohbayashi A, Harada H, Katayama T, Kikuchi S, Watanabe Y, Koi S, Onji M, Ohta Y, Choo Q-L, Houghton M, Kuo G. (1990) Hepatitis C virus infection is associated with the development of hepatocellular carcinoma. *Proc. Natl. Acad. Sci. USA*. 87:6547–9.  Hasan F, Jeffers LJ, De Medina M, Reddy KR, Parker T, Schiff ER, Houghton M, Choo Q-L, Kuo G. (1990) Hepatitis C-associated hepatocellular carcinoma. Hepatology. 12:589–91.  Takeuchi K, Kubo Y, Boonmar S, Watanabe Y, Katayama T, Choo Q-L, Kuo G, Houghton M, Saito I, Miyamura T. (1990) Nucleotide sequence of core and envelope genes of the hepatitis C virus genome derived directly from human healthy carriers. *Nuc. Acids Res.* 18:4626.  Weiner AJ, Truett MA, Han J, Polito AJ, Choo, Q-L, Rosenblatt J, Quan S, Kuo G, Houghton M, Page E, Agius C, Nelles MJ. (1990) HCV testing in low-risk population. *Lancet*. 336:695. Letter.  Makris M, Dewar MS, Preston FE, Choo Q-L, Kuo G, Houghton M. (1990) The relation of hepatitis C antibodies to acute non-A, non-B hepatitis NANBH in previously untreated hemophilic patients. *Br. J. Haematol.* 74:44. Supplement 1.  Magrin S, Craxi A, Almasio P, Fabiano C, Fiorentino G, Palazzo U, Pinzello GB, Provenzano G, Pagliaro L, Houghton M, Han JH. (1990) HCV infection in autoimmune chronic active hepatitis. *J. Hepatol.* 11:S99. Supplement 2.  Thaler MM, Landers DW, Wara DW, Houghton M, Veereman-Wauters G, Sweet RL, Brauer M, Han JH. (1990) Vertical transmission of hepatitis C virus detected by the polymerase chain reaction. *Hepatology*. 12:849.  McHutchison JG, Kuo G, Houghton M, Choo Q-L, Redeker AG. (1990) Patients with acute and chronic NANB hepatitis. *Hepatology*. 12:966.  Leal RJ, McHutchison JG, Houghton M, Choo Q-L, Kuo G, Redeker AG. (1990) Antibodies to hepatitis C virus anti-HCV in alcoholic liver disease: An analysis of risk factors. *Hepatology*. 12:881.  Makris M, Preston FE, Triger DR, Underwood JCE, Kuo G, Choo Q-L, Houghton M. (1990) The role of hepatitis C virus in chronic liver disease in hemophilia. Br. J. *Haematol*. 74:6. Supplement 1.  Nishioka K, Watanabe J, Furuta S, Tanaka E, Suzuki H, Iino S, Tsuji T, Yano M, Kuo G, Choo Q-L, Houghton M, Oda T. (1991) Antibody to the hepatitis C virus in acute hepatitis and chronic liver diseases in Japan. *Liver*. 11:65–70.  Nishioka K, Watanabe J, Furuta S, Tanaka E, Iino S, Suzuki H, Tsuji T, Yano M, Kuo G, Choo Q-L, Houghton M, Oda T. (1991) A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. *Cancer*. 67:429–33.  Katkov WN, Dienstag JL, Cody H, Evans AA, Choo QL, Houghton M, Kuo G. (1991) Role of hepatitis C virus in non-B chronic liver disease. *Arch. Int. Med*. 151:1548–52.  Choo Q-L, Han J, Weiner AJ, Overby LR, Bradley DW, Kuo G, Houghton M. (1991) “Hepatitis C virus is a distant relative of the flaviviruses and pestiviruses” *in* Proceedings of the International Meeting on Non-A, Non-B Hepatitis, Tokyo, Japan (Shikata T, Purcell RH, Uchida T. eds.) pp. 47–52. Elsevier Science Publishers, Amsterdam.  Di Bisceglie AM, Order SE, Klein JL, Wagoner JG, Sjogren MH, Kuo G, Houghton M, Choo Q-L, Hoofnagle JH. (1991) The role of chronic viral hepatitis in hepatocellular carcinoma in the United States. *Am. J. Gastroenterol*. 86:335–8.  Choo Q-L, Richman KH, Han JH, Berger K, Lee C, Dong C, Gallegos C, Coit D, Medina-Selby A, Barr PJ, Weiner AJ, Bradley DW, Kuo G, Houghton M. (1991) Genetic organization and diversity of the hepatitis C virus. *Proc. Natl. Acad. Sci. USA.* 88:2451–5.  Weiner AJ, Brauer MJ, Rosenblatt J, Richman KH, Tung J, Crawford K, Bonino F, Saracco G, Choo Q-L, Houghton M, Han JH. (1991) Variable and hypervariable domains are found in the regions of HCV corresponding to the flavivirus envelope and NS1 proteins and the pestivirus envelope glycoproteins. *Virology*. 180:842–8.  van der Poel CL, Cuypers HTM, Reesink HW, Weiner AJ, Quan S, DiNello R, van Boven JJP, Winkel I, Mulder-Folkerts D, Exel-Oehlers PJ, Schaasberg W, Leentvaar-Kuypers A, Polito A, Houghton M, Lelie PN. (1991) Confirmation of hepatitis C virus infection by new four-antigen recombinant immunoblot assay. *Lancet*. 337:317–9.  Reesink HW, Van der Poel CL, Plaisier ADD, Verstraten JW, Cuypers M. (1991) Comparison of first and second generation anti-HCV recombinant immunoblot assay with 5’ UTR PCR. *Transfusion*. 31:57S.  Han JH, Shyamala V, Richman KH, Brauer MJ, Irvine B, Urdea MS, Tekamp-Olson P, Kuo G, Choo Q-L, Houghton M. (1991) Characterization of the terminal regions of hepatitis C viral RNA: Identification of conserved sequences in the 5’ untranslated region and poly(A) tails at the 3’end. *Proc. Natl. Acad. Sci. USA.* 88:1711–5.  Magrin S, Craxi A, Fabiano C, Fiorentino G, Almasio P, Palazzo U, Pinzello G, Provenzano G, Pagliaro L, Choo Q-L, Kuo G, Polito A, Han J, Houghton M. (1991) Hepatitis C virus replication in ‘autoimmune’ chronic hepatitis. J*. Hepatol.* 13:364–7.  Cha T-A, Kolberg J, Irvine B, Stempien M, Beall E, Yano M, Choo Q-L, Houghton M, Kuo G, Han JH, Urdea MS. (1991) Use of a signature nucleotide sequence of Hepatitis C virus for detection of viral RNA in human serum and plasma. *J. Clin. Microbiol.* 29:2528–34.  Houghton M. (1991) “Molecular virology of HCV” *in* Report on the Proceedings, Second International Symposium on HCV, Los Angeles (Bradley DW. ed.) pp.2–3. Advanced Therapeutics Communications, Secaucus, New Jersey.  Krawczynski K, Beach M, Mimms L, Meeks E, Vallari D, Taskar S, Kuo G, Houghton M, Bradley D. (1991) Replication and antigenic expression of HCV antiviral antibody response and liver pathology in acute and chronic HCV infection. *Hepatology*. 14:78A.  Houghton M, Weiner A, Han J, Kuo G, Choo Q-L. (1991) Molecular biology of the hepatitis C viruses: Implications for diagnosis, development and control of viral disease. *Hepatology*. 14:381–8.  Colombo M, Rumi MG, Donato MF, Tommasini MA, Del Ninno E, Ronchi G, Kuo G, Houghton M. (1991) Hepatitis C antibody in patients with chronic liver disease and hepatocellular carcinoma. *Dig. Dis. Sci.* 36:1130–3.  Thudium K, Spaete R, Berger K, Choo Q-L, Houghton M, Ralston R. (1991) Expression and characterization of HCV structural proteins using in-vitro translation and recombinant vaccinia viruses. *J. Cell. Biochem.* 47:92. Supplement 15E.  McHutchison JG, Kuo G, Houghton M, Choo Q-L, Redeker AG. (1991) Hepatitis C virus antibodies in acute icteric and chronic non-A, non-B hepatitis. *Gastroenterology*. 101:1117–9.  Saracco G, Baldi M, Calvo PL, Manzini P, Abate M, Chiaberge E, Brunetto MR, Rizzetto M, Chien D, Kuo G, Houghton M, Bonino F. (1991) Hepatitis C virus markers for monitoring interferon therapy in chronic hepatitis C. *Hepatology.* 14:75A.  Cuypers HT, Winkel IN, van der Poel CL, Reesink HW, Lelie PN, Houghton M, Weiner A. (1991) Analysis of genomic variability of hepatitis C virus. *J. Hepatol.* 13:S15–9.  Rosina F, Fabiano A, Garripoli A, Smedile A, Mattalia A, Eckart MR, Houghton M, Bonino F. (1991) Rabbit-derived anti-HD antibodies for HDAg immunoblotting. *J. Hepatol.* 13:130–3.  Weiner AJ, Christopherson C, Hall JE, Bonino F, Saracco G, Crawford K, Marion CD, Crawford KA, Venkatakrishna S, Miyamura T, McHutchinson J, Cuypers T, Houghton M. (1991) Sequence variation in hepatitis C viral isolates. *Hepatology*. 13:S6–14.  Krawczynski K, Beach MJ, Bradley DW, Kuo G, di Bisceglie AM, Houghton M, Reyes GR, Kim JP, Choo Q-L, Alter MJ (1992) Hepatitis C virus antigen in hepatocytes: Immunomorphologic detection and identification. *Gastroenterology*. 103:622–9.  Bresters D, Mauser-Bunschoten EP, Cuypers HT, Lelie PN, Han JH, Jansen PL, Houghton M, Reesink HW (1992) Disappearance of hepatitis C virus RNA in plasma during interferon alpha-2B treatment in hemophilia patients. *Scand. J. Gastroenterol.* 27:166–8.  Bresters D, Cuypers HT, Reesink HW, Schaasberg WP, van der Poel CL, Mauser-Bunschoten EP, Houghton M, Choo Q-L, Kuo G, Lesniewski R, Troonen H, Lelie PN. (1992) Enhanced sensitivity of a second generation ELISA for antibody to hepatitis C virus. *Vox Sang*. 62:213–7.  Overby LR, Houghton M. (1992) “Hepatitis viruses” *in* Laboratory Diagnosis of Viral Infections (Lennette EH. ed.) pp. 403–44. Marcel Dekker, New York.  Spaete RR, Alexander DA, Rugroden ME, Choo Q-L, Berger K, Crawford K, Kuo C, Leng S, Lee C, Ralston R, Thudium K, Tung JW, Kuo G, Houghton M. (1992) Characterization of the hepatitis C virus E2/NS1 gene product expressed in mam-malian cells. *Virology*. 188:819–30.  Weiner AJ, Geysen HM, Christopherson C, Hall JE, Mason TJ, Saracco G, Bonino F, Crawford K, Marion CD, Crawford KA, Brunetto M, Barr PJ, Miyamura T, McHutchinson J, Houghton M. (1992) Evidence for immune selection of hepatitis C virus (HCV) putative envelope glycoprotein variants: Potential role in chronic HCV infections. *Proc. Natl. Acad. Sci. USA.* 89:3468–72.  Houghton M. (1992) “Heterogeneity of the HCV genome: Importance for control of the disease” *in* Hepatitis C Virus: Scientific and Clinical Status (Deinhardt F, Bradley DW, Houghton M. eds.) pp. 8–9. Advanced Therapeutics Communications, Secaucus, New Jersey.  Jeffers LJ, Hasan F, De Medina M, Reddy R, Parker T, Silva M, Mendez L, Schiff ER, Manns M, Houghton M. (1992) Prevalence of antibodies to hepatitis C virus among patients with cryptogenic chronic hepatitis and cirrhosis. *Hepatology*. 15:187–90.  Weiner AJ, Christopherson C, Hall JE, Crawford K, Marion CD, Crawford KA, Barr PJ, Richman K, Kuo G, Houghton M. (1992) “The hypervariable amino terminus of the hepatitis C virus E2/NS1 protein appears to be under immune selection” *in* Vaccines 92 (Brown F, Chanock RM, Ginsberg HS, Lerner RA. eds.) pp. 303–8. Cold Spring Harbor Laboratory Press, New York.  Chien DY, Choo Q-L, Tabrizi A, Kuo C, McFarland J, Berger K, Lee C, Shuster R, Nguyen T, Moyer DL, Tong M, Furuta S, Omata M, Alter H, Schiff E, Jeffers L, Houghton M, Kuo G. (1992) Diagnosis of hepatitis C virus (HCV) infection using an immunodominant chimeric polyprotein to capture circulating antibodies: Re-evaluation of the role of HCV in liver disease. *Proc. Natl. Acad. Sci. USA*. 89:10011–5.  Choo Q-L, Kuo G, Weiner A, Wang K-S, Overby L, Bradley D, Houghton M. (1992) Identification of the major, parenteral non-A, non-B hepatitis agent (hepatitis C virus) using a recombinant cDNA approach. *Sem. Liver Dis.* 12:279–88.  Cuypers HT, Bresters D, Winkel IN, Reesink HW Weiner AJ, Houghton M, van der Poel CL, Lelie PN. (1992) Storage conditions of blood samples and primer selection affect the yield of cDNA polymerase chain reaction products of hepatitis C virus. *J. Clin. Microbiol.* 30:3220–4.  Weiner AJ, Venkatakrishna S, Hall JE, Houghton M, Han J. (1992) “PCR: Application to hepatitis C virus (HCV) research and diagnostics” *in* Frontiers in Virology (Becker Y, Darai G. eds.) pp. 86–100. Springer Verlag, New York.  Van der Poel CL, Bresters D, Reesink HW, Plaisier AAD, Schaasberg W, Leentvaar-Kuypers A, Choo Q-L, Quan S, Polito A, Houghton M, Kuo G, Lelie PN, Cuypers HTM. (1992) Early antihepatitis-C virus response with second generation C200/C22 ELISA. *Vox Sang*. 62:208–12.  Han JH, Houghton M. (1992) Group specific sequences and conserved secondary structures at the 3’ end of HCV genome and its implication for viral replication. *Nucl. Acids Res*. 20:3520.  Koziel MJ, Dudley D, Wong JT, Dienstag J, Houghton M, Ralston R, Walker B. (1992) Intrahepatic cytotoxic T lymphocytes specific for hepatitis C virus in persons with chronic hepatitis. *J. Immunol.* 149:3339–44.  Yoo BJ, Spaete RR, Geballe AP, Selby M, Houghton M, Han JH. (1992) 5’ end-dependent translation initiation of hepatitis C viral RNA and the presence of putative positive and negative translational control elements within the 5’ untranslated region. *Virology*. 191:889–99.  Botarelli P, Brunetto MR, Weiner AJ, Minutello MA, Unutmaz D, Calvo P, Bonino F, Houghton M, Abrignani S. (1993) T cell response to recombinant proteins of hepatitis C virus in blood and liver of patients with different clinical courses of infection. *Gastroenterology*. 104:580–7.  Chien DY, Choo Q-L, Tabrizi A, Kuo C, McFarland J, Berger K, Lee C, Shuster JR, Nguyen T, Moyer DL, Tong M, Furuta S, Omata M, Fong CT, Tegtmeier G, Alter H, Schiff E, Jeffers L, Houghton M, Kuo G. (1993) Use of recombinant HCV antigen in the serodiagnosis of hepatitis C virus infection: Significant improvement in HCV antibody detection as compared with the first generation HCV C100-3 ELISA and the synthetic peptide EIA tests. *J. Gastroenterol. Hepatol.* 8:S33–9.  Eckart MR, Selby M, Masiarz F, Lee C, Berger K, Crawford K, Kuo C, Kuo G, Houghton M. (1993) The hepatitis C virus encodes a serine protease involved in processing of the putative nonstructural proteins from the viral polyprotein precursor. *Biochem. Biophys. Res. Comm*. 192:399–406.  Saracco G, Rosina F, Abate ML, Chiandussi L, Gallo V, Cerutti E, Di Napoli A, Solinas A, DePlano A, Tocco A, Cossu P, Chien D, Kuo G, Polito A, Weiner AJ, Houghton M, Verme G, Bonino F, Rizzetto M (1993) Long-term follow-up of patients with chronic hepatitis C treated with different doses of interferon-α2b. *Hepatology*. 18:1300–5.  Koziel MJ, Dudley D, Afdhal N, Choo Q-L, Houghton M, Ralston R, Walker BD. (1993) Hepatitis C virus (HCV)-specific cytotoxic T lymphocytes recognized epitopes in the core and envelope proteins of HCV. *J. Virol*. 67:7522–32.  Bresters D, Mauser-Bunschoten EP, Cuypers HT, Han JH, Jansen PL, Chamuleau RA, Houghton M, Reesink HW. (1993) Long term treatment of chronic hepatitis C with interferon alfa-2b: disappearance of HCV-RNA in a pilot study of eight haemophilia patients. *Gut (England).* 34:S124–5.  Rosina F, Fabiano A, Maran E, Cozzolongo R, Smedile A, Mazzucco G, Garripoli A, Costa C, Eckart MR, Houghton M. (1993) Rabbit-derived anti-HD antibodies for HDAg immunoblotting. *Proc. Clin. Biol. Res.* 382:189–91.  Selby MJ, Choo Q-L, Berger K, Kuo G, Glazer E, Eckart M, Lee C, Chien D, Kuo C, Houghton M. (1993) Expression, identification and subcellular localization of the proteinsencoded by the hepatitis C viral genome. *J. Gen. Virol.* 4:1103–13.  Weiner AJ, Thaler MM, Crawford K, Ching K, Kansopon J, Chien DY, Hall JE, Hu F, Houghton M. (1993) A unique, predominant hepatitis C virus variant found in an infant born to a mother with multiple variants. *J. Virol.* 67:4365–8.  Minutello MA, Pileri P, Unutmaz D, Censini S, Kuo G, Houghton M, Brunetto MR, Bonino F, Abrignani S. (1993) Compartmentalization of T lymphocytes to the site of disease: Intrahepatic CD4+ T cells specific for the protein NS4 of hepatitis C virus in patients with chronic hepatitis C. *J. Exp. Med.* 178:17–25.  Lok ASF, Chien D, Choo Q-L, Chan T-M, Chiu EKW, Cheng IKP, Houghton M, Kuo G. (1993) Antibody response to core, envelope and nonstructural hepatitis C virus antigens: Comparison of Immunocompetent and immunosuppressed patients. *Hepatology*. 18:497–502.  Chien DY, Choo Q-L, Ralston R, Spaete R, Tong M, Houghton M, Kuo G. (1993) Persistence of HCV despite antibodies to both putative envelope glycoprotein. *Lancet*. 342:933. Letter.  Erickson AL, Houghton M, Choo Q-L, Weiner AJ, Ralston R, Muchmore E, Walker CM. (1993) Hepatitis C virus-specific CTL responses in the liver of chimpanzees with acute and chronic hepatitis C. J. *Immunol*. 151:4189–99.  Ralston R, Thudium K, Berger K, Kuo C, Gervase B, Hall J, Selby M, Kuo G, Houghton M, Choo Q-L. (1993) Characterization of hepatitis C virus envelope glycoprotein complexes expressed by recombinant vaccinia viruses. *J. Virol.* 67:6753–61.  Botarelli P, Brunetto MR, Minutello MA, Calvo P, Unutmaz D, Weiner AJ, Choo Q-L, Shuster JR, Kuo G, Bonino F, Houghton M, Abrignani S. (1993) T-lymphocyte response to hepatitis C virus in different clinical courses of infection. *Gastroenterology*. 104:580–7.  Choo Q-L, Kuo G, Ralston R, Weiner A, Chien D, Van Nest G, Han J, Berger K, Thudium K, Kuo C, Kansopon J, McFarland J, Tabrizi A, Ching K, Moss B, Cummins LB, Houghton M, Muchmore E. (1994) Vaccination of chimpanzees against infection by the hepatitis C virus. *Proc. Natl. Acad. Sci. USA*. 91:1294–8.  Simmonds P, Alfredo A, Alter HJ, Bonino F, Bradley DW, Brechot C, Brouwer JT, Chan S-W, Chayama K, Chen D-S, Choo Q-L, Colombo M, Cuypers HTM, Date T, Dusheiko GM, Esteban JI, Fay O, Hadziyannis SJ, Han J, Hatzakis A, Holmes EC, Hotta H, Houghton M, Irvine B, Kohara M, Kolberg JA, Kuo G, Lau JYN, Lelie PN, Maertens G, McOmish F, Miyamura T, Mizokami M, Nomoto A, Prince AM, Reesink HW, Rice C, Roggendorf M, Schalm SW, Shimotohno K, Stuyver L, Trépo C, Weiner A, Yap PL, Urdea MS. (1994) A proposed system for the nomenclature of hepatitis C viral genotypes. *Hepatology*. 19:1321–4.  Houghton M, Selby M, Weiner A, Choo Q-L. (1994) Hepatitis C virus: Structure, protein products and processing of the polyprotein precursor. *Curr. Stud.* *Hematol. Blood Trans*. 61:1–11.  Houghton M, Choo Q-L, Kuo G, Ralston R, Selby M, Weiner A, Chien D, Han J, Walker C, Abrignani S, Koziel M, Walker B, Cummins L, Muchmore E. (1994) “The hepatitis C virus: Genetic organization, persistence, and vaccine strategies” *in* Viral Hepatitis and Liver Disease (Nishioka K, Suzuki H, Mishiro S, Oda T. eds.) pp. 33–7. Springer-Verlag, Tokyo.  Weiner AJ, Thaler MM, Crawford K, Kansopon J, Ching K, Hall JE, Hu F, Chien D, Houghton M. (1994) “HCV-positive, HIV-1-negative mothers transmit HCV” *in* Viral Hepatitis and Liver Disease (Nishioka K, Suzuki H, Mishiro S, Oda T. eds.) pp. 463–7. Springer-Verlag, Tokyo.  Ray R, Khanna A, Lagging LM, Meyer K, Choo Q-L, Ralston R, Houghton M, Becherer PR. (1994) Peptide immunogen mimicry of putative E1 glycoprotein-specific epitopes in hepatitis C virus. *J. Virol*. 68:4420–6.  Selby MJ, Glazer E, Masiarz F, Houghton M. (1994) Complex processing and protein: Protein interactions in the E2:NS2 region of HCV. Virology. 204:114–22.  Saracco G, Abate ML, Baldi M, Calvo PL, Manzini P, Brunetto MR, Oliveri F, Kuo G, Chien D, Houghton M, Verme G, Rizzetto M, Bonino F. (1994) Hepatitis C virus markers in patients with long-term biochemical and histological remission of chronic hepatitis. *Liver*. 14:65–70.  Chien DY, McFarland J, Tabrizi A, Kuo C, Houghton M, Kuo G. (1994) “Distinct subtypes of hepatitis C virus defined by antibodies directed to the putative core, NS4, and NS5 region polypeptides” *in* Viral Hepatitis and Liver Disease (Nishioka K, Suzuki H, Mishiro S, Oda T. eds.) pp. 320–4. Springer-Verlag, Tokyo.  Yoo BJ, Selby MJ, Choe J, Suh BS, Choi SH, Joh JS, Nuovo GJ, Lee H-S, Houghton M, Han JH. (1995) Transfection of a differentiated human hepatoma cell line (Huh7) with in vitro-transcribed hepatitis C virus (HCV) RNA and establishment of a long-term culture persistently infected with HCV. *J. Virol.* 69:32–8.  Cerny A, McHutchison JG, Pasquinelli C, Brown ME, Brothers MA, Grabscheid B, Fowler P, Houghton M, Chisari FV. (1995) Cytotoxic T lymphocyte response to hepatitis C virus – derived peptides containing the HLA A2.1 binding motif. *J. Clin. Invest.* 95:521–30.  Weiner A, Erickson AL, Kansopon J, Crawford K, Muchmore E, Hughes AL, Houghton M, Walker CM (1995) Persistent hepatitis C virus infection in a chimpanzee is associated with emergence of a cytotoxic T lymphocyte escape variant. *Proc. Natl. Acad. Sci. USA.* 92:2755–9.  Cerny A, Fowler P, Brothers MA, Houghton M, Schlicht HJ, Chisari FV. (1995) Induction in vitro of a primary human antiviral cytotoxic T cell response. *Eur.* *J. Immunol.* 25:627–30.  Houghton M, Choo Q-L, Kuo G, Weiner A, Chien D, Ralston R, Urdea M, Moss B, Purcell R, Cummins L, Muchmore E. (1995) Prospects for prophylactic and therapeutic hepatitis C virus vaccines. *Princess Takamatsu Symp*. 25:237–43.  Weiner AJ, Erickson AL, Kansopon J, Crawford K, Muchmore E, Houghton M, Walker CM. (1995) Association of cytotoxic T lymphocyte (CTL) escape mutations with persistent hepatitis C virus (HCV) infection. *Princess Takamatsu Symp.* 25:227–35.  Lagging LM, Meyer K, Hoft D, Houghton M, Belshe RB, Ray R. (1995) Immune responses to plasmid DNA encoding the hepatitis C virus core protein. *J. Virol.* 69:5859–63.  Koziel MJ, Dudley D, Afdhal N, Grakoui A, Rice C, Choo Q-L, Houghton M, Walker BD. (1995) HLA class I-restricted cytotoxic T lymphocytes specific for hepatitis C virus: Identification of multiple epitopes and characterization of patterns of cytokine release. *J. Clin. Invest.* 96:2311–21.  Piazza M, Chien D, Quan S, Houghton M. (1996) Lack of antibodies to the envelope glycoproteins of hepatitis C virus in immunoglobulin preparations from screened donors. *Boll. Soc. Ital. Biol. Sper*. 72:69–70.  Houghton M. (1996) “Hepatitis C viruses” *in* Fields Virology (Fields BN, Knipe DM, Howley PM et al. eds.) pp. 1035–58. Lippincott-Raven Publishers, Philadelphia.  Rosa D, Campagnoli S, Moretto C, Guenzi E, Cousens L, Chin M, Dong C, Weiner AJ, Lau JY, Choo Q-L, Chien D, Pileri P, Houghton M, Abrignani S. (1996) A quantitative test to estimate neutralizing antibodies to the hepatitis C virus: cytofluorimetric assessment of envelope glycoprotein 2 binding to target cells. *Proc. Natl. Acad. Sci*. USA. 93:1759–63.  Missale G, Bertoni R, Lamonaca V, Valli A, Massari M, Mori C, Rumi MG, Houghton M, Fiaccadori F, Ferrari C. (1996) Different clinical behaviors of acute hepatitis virus infection are associated with different vigor of the anti-viral cell-mediated immune response. *J. Clin. Invest.* 98:706–14.  Rehermann B, Chang KM, McHutchinson JG, Kokka R, Houghton M, Chisari FV. (1996) Quantitative analysis of the peripheral blood cytotoxic T lymphocyte response in patients with chronic hepatitis C virus infection. *J. Clin. Invest.* 98:1432–40.  Rehermann B, Chang KM, McHutchinson J, Kokka R, Houghton M, Rice CM, Chisari FV. (1996) Differential cytotoxic T-lymphocyte responsiveness to the hepatitis B and C viruses in chronically infected patients. *J. Virol.* 70:7092–102.  Houghton M, Choo Q-L, Chien D, Kuo G, Weiner A, Coates S, Cousens L, Wininger M, Selby M, Ralston R, Berger K, Dong C, Crawford K, Kansopon J, Chin M, Wong S, Tabrizi-Weight A, Purcell RH, Muchmore E, Morandi M, Rosa D, Abrignani S. (1996) “Development of an HCV vaccine” *in* Viral Hepatitis and Liver Disease (Rizzetto M, Purcell RH, Gerin JL, Verme G. eds.) pp. 656–9. Edizioni Minerva Medica, Torino, Italy.  Nelson DR, Marousis CG, Davis GL, Rice CM, Wong J, Houghton M, Lau YN (1997) The role of hepatitis C virus-specific cytotoxic T lymphocytes in chronic hepatitis C. *J. Immunol.* 158:1473–81.  Pasquinelli C, Shoenberger JM, Chung J, Chang KM, Guidotti LG, Selby M, Berger K, Lesniewski R, Houghton M, Chisari FV. Hepatitis C virus core and E2 protein expression in transgenic mice. *Hepatology*. 25:719–27.  Diepolder HM, Gerlach J-T, Zachoval R, Hoffmann RM, Jung M-C, Wierenga EA, Scholz S, Santantonio T, Houghton M, Southwood S, Sette A, Pape GR. (1997) Immunodominant CD4+ T-cell epitope within nonstructural protein 3 in acute hepatitis C virus infection. *J. Virol.* 71:6011–9.  Calvo PL, Kansopon J, Sra K, Quan S, DiNello R, Guaschino R, Calabrese G, Danielle F, Brunetto, Bonino F, Massaro AL, Polito A, Houghton M, Weiner AJ. (1998) Hepatitis C virus heteroduplex tracking assay for genotype determination reveals diverging genotype 2 isolates in Italian hemodialysis patients. *J. Clin. Microbiol.* 36:227–33.  Wong DKH, Dudley DD, Afdhal NH, Dienstag J, Rice CM. (1998) Liver-derived CTL in hepatitis C virus infection: Breadth and specificity of responses in a cohort of persons with chronic infection. *J. Immunol*. 160:1479–88.  Ishii K, Rosa D, Watanabe Y, Katayama T, Harada H, Wyatt C, Kiyosawa K, Aizaki H, Matsuura Y, Houghton M, Abrignani S, Miyamura T. (1998) High titers of antibodies inhibiting the binding of envelope to human cells correlate with natural resolution of chronic hepatitis C. *Hepatology*. 28:1117–20.  Pileri P, Uematsu Y, Campagnoli S, Galli G, Falugi F, Petracca R, Weiner AJ, Houghton M, Rosa D, Grandi G, Abrignani S. (1998) Binding of hepatitis C virus to CD81. *Science*. 282:938–41.  Selby M, Erickson A, Dong C, Cooper S, Parham P, Houghton M, Walker CM. (1999) Hepatitis C virus envelope glycoprotein E1 originates in the endoplasmic reticulum and requires cytoplasmic processing for presentation by class I MHC molecules. *J. Immunol.* 162:669–76.  Cooper S, Erickson AL, Adams EJ, Kansopon J, Weiner AJ, Chien DY, Houghton M, Parham P, Walker CM. (1999) Analysis of a successful immune response against hepatitis C virus. *Immunity*. 10:439–49.  Colombatto P, Brunetto MR, Kansopon J, Oliveri F, Maina A, Aragon U, Bortoli ML, Scatena F, Baicchi U, Houghton M, Bonino F, Weiner AJ. (1999) High prevalence of G1 and G2 TT-virus infection in subjects with high and low blood exposure risk: identification of G4 isolates in Italy. *J. Hepatol.* 31:990–6.  Abrignani S, Houghton M, Hsu HH. (1999) Perspectives for a vaccine against hepatitis C virus. *J. Hepatol.* 31 Suppl 1:259–63.  Hsu HH, Abrignani S, Houghton M. (1999) Prospects for a hepatitis C virus vaccine. *Clin. Liver Dis.* 3:901–15.  Liberman E, Fong YL, Selby MJ, Choo QL, Cousens L, Houghton M, Yen TS. (1999) Activation of the grp78 and grp94 promoters by hepatitis C virus E2 envelope protein. *J. Virol.* 73:3718–22.  Mustilli AC, Izzo E, Houghton M, Galeotti CL. (1999) Comparison of secretion of a hepatitis C virus glycoprotein in Saccharomyces cerevisiae and Kluyveromyces lactis. *Res. Microbiol.* 150:179–87.  Rosen HR, Hinrichs DJ, Gretch DR, Koziel MJ, Chou S, Houghton M, Rabkin J, Corless CL, Bouwer HG. (1999) Association of multispecific CD4(+) response to hepatitis C and severity of recurrence after liver transplantation. *Gastroenterology*. 117:926–32.  Allander T, Drakenberg K, Beyene A, Rosa D, Abrignani S, Houghton M, Widell A, Grillner L, Persson MA. (2000) Recombinant human monoclonal antibodies against different conformational epitopes of the E2 envelope glycoprotein of hepatitis C virus that inhibit its interaction with CD81. *J. Gen. Virol.* 81:2451–9.  Alter HJ, Houghton M. (2000) Clinical Medical Research Award. Hepatitis C virus and eliminating post-transfusion hepatitis. *Nat. Med.* 6:1082–6.  Fan XG, Tang FQ, Yi H, Liu WE, Houghton M, Hu GL. (2000) Effect of IL-12 on T-cell immune responses in patients with chronic HCV infection. *APMIS*. 108:531–8.  Heile JM, Fong YL, Rosa D, Berger K, Saletti G, Campagnoli S, Bensi G, Capo S, Coates S, Crawford K, Dong C, Wininger M, Baker G, Cousens L, Chien D, Ng P, Archangel P, Grandi G, Houghton M, Abrignani S. (2000) Evaluation of hepatitis C virus glycoprotein E2 for vaccine design: an endoplasmic reticulum-retained recombinant protein is superior to secreted recombinant protein and DNA-based vaccine candidates. *J. Virol.* 74:6885–92.  Houghton M. (2000) Strategies and prospects for vaccination against the hepatitis C viruses. *Curr. Top. Microbiol. Immunol*. 242:327–39. Review.  Lee AY, Manning WC, Arian CL, Polakos NK, Barajas JL, Ulmer JB, Houghton M, Paliard X. (2000) Priming of hepatitis C virus-specific cytotoxic T lymphocytes in mice following portal vein injection of a liver-specific plasmid DNA. *Hepatology*. 31:1327–33.  Lee AY, Polakos NK, Otten GR, Ulmer JB, Houghton M, Paliard X. (2000) Quantification of the number of cytotoxic T cells specific for an immunodominant HCV-specific CTL epitope primed by DNA immunization. *Vaccine*. 18:1962–8.  Petracca R, Falugi F, Galli G, Norais N, Rosa D, Campagnoli S, Burgio V, Di Stasio E, Giardina B, Houghton M, Abrignani S, Grandi G. (2000) Structure-function analysis of hepatitis C virus envelope-CD81 binding. *J. Virol.* 74:4824–30.  Weiner A, Chien D, Choo Q-L, Coates S, Kuo G, Houghton M. (2000) “Humoral response to HCV” *in* Hepatitis C. (Liang J, Hoofnagle J. eds.), pp. 125–145. Academic Press.  Schirren CA, Jung MC, Gerlach JT, Worzfeld T, Baretton G, Mamin M, Hubert Gruener N, Houghton M, Pape GR. (2000) Liver-derived hepatitis C virus (HCV)-specific CD4(+) T cells recognize multiple HCV epitopes and produce interferon gamma. *Hepatology*. 32:597–603.  Bassett SE, Guerra B, Brasky K, Miskovsky E, Houghton M, Klimpel GR, Lanford RE. (2001) Protective immune response to hepatitis C virus in chimpanzees rechallenged following clearance of primary infection. *Hepatology*. 33:1479–87.  Erickson AL, Kimura Y, Igarashi S, Eichelberger J, Houghton M, Sidney J, McKinney D, Sette A, Hughes AL, Walker CM. (2001) The outcome of hepatitis C virus infection is predicted by escape mutations in epitopes targeted by cytotoxic T lymphocytes. *Immunity*. 15:883–95.  Merola M, Brazzoli M, Cocchiarella F, Heile JM, Helenius A, Weiner AJ, Houghton M, Abrignani S. (2001) Folding of hepatitis C virus E1 glycoprotein in a cell-free system. *J. Virol.* 75:11205–17.  Polakos NK, Drane D, Cox J, Ng P, Selby MJ, Chien D, O’Hagan DT, Houghton M, Paliard X. (2001) Characterization of hepatitis C virus core-specific immune responses primed in rhesus macaques by a nonclassical ISCOM vaccine. *J. Immunol.* 166:3589–98.  Schirren CA, Jung MC, Worzfeld T, Mamin M, Baretton G, Gerlach JT, Gruener NH, Zachoval R, Houghton M, Rau HG, Pape GR. (2001) Hepatitis C virus-specific CD4+ T cell response after liver transplantation occurs early, is multispecific, compartmentalizes to the liver, and does not correlate with recurrent disease*. J. Infect. Dis.* 183:1187–94.  Tseng CT, Miskovsky E, Houghton M, Klimpel GR. (2001) Characterization of liver T-cell receptor gammadelta T cells obtained from individuals chronically infected with hepatitis C virus (HCV): evidence for these T cells playing a role in the liver pathology associated with HCV infections. *Hepatology*. 33:1312–20.  Weiner AJ, Paliard X, Selby MJ, Medina-Selby A, Coit D, Nguyen S, Kansopon J, Arian CL, Ng P, Tucker J, Lee CT, Polakos NK, Han J, Wong S, Lu HH, Rosenberg S, Brasky KM, Chien D, Kuo G, Houghton M. (2001) Intrahepatic genetic inoculation of hepatitis C virus RNA confers cross-protective immunity. *J. Virol.* 75:7142–8.  Legrand E, Neau D, Galperine T, Trimoulet P, Moreau JF, Pitard V, Lacut JY, Ragnaud JM, Dupon M, Le Bail B, Bernard N, Schvoerer E, Houghton M, Fleury H, Lafon ME. (2002) CD4 T lymphocyte proliferative responses to hepatitis C virus (HCV) antigens in patients coinfected with HCV and human immunodeficiency virus who responded to anti-HCV treatment. *J. Infect. Dis.* 186:302–11.  Masciopinto F, Freer G, Burgio VL, Levy S, Galli-Stampino L, Bendinelli M, Houghton M, Abrignani S, Uematsu Y. (2002) Expression of human CD81 in transgenic mice does not confer susceptibility to hepatitis C virus infection. *Virology*. 304:187–96.  Shoukry NH, Grakoui A, Houghton M, Chien DY, Ghrayeb J, Reimann KA, Walker CM. (2003) Memory CD8+ T cells are required for protection from persistent hepatitis C virus infection. *J. Exp. Med*. 197:1645–55.  Seo MY, Abrignani S, Houghton M, Han JH. (2003) Small interfering RNA-mediated inhibition of hepatitis C virus replication in the human hepatoma cell line Huh-7. *J. Virol.* 77:810–2.  Masciopinto F, Giovani C, Campagnoli S, Galli-Stampino L, Colombatto P, Brunetto M, Yen TS, Houghton M, Pileri P, Abrignani S. (2004) Association of hepatitis C virus envelope proteins with exosomes. Eur. *J. Immunol.* 34:2834–42.  Houghton M, Abrignani S. (2004) “Vaccination against the hepatitis C viruses” *in* New Generation Vaccines 3rd Edition (Levine MM, Kaper JB, Rappuoli R, Liu M, Good MF. eds.) pp. 593–606. Marcel Dekker Inc., New York.  O’Hagan DT, Singh M, Dong C, Ugozzoli M, Berger K, Glazer E, Selby M, Wininger M, Ng P, Crawford K, Paliard X, Coates S, Houghton M. (2004) Cationic microparticles are a potent delivery system for a HCV DNA vaccine. *Vaccine*. 23:672–80.  Coates S, Choo Q-L, Kuo G, Crawford K, Dong C, Wininger M, Weiner A, Abrignani S, Houghton M. (2004) “Hepatitis C” *in* Vaccines: Preventing Disease & Protecting Health (De Quadros CA. ed.) pp. 150–6. Pan American Health Organisation.  Song HC, Seo MY, Stadler K, Yoo BJ, Choo QL, Coates SR, Uematsu Y, Harada T, Greer CE, Polo JM, Pileri P, Eickmann M, Rappuoli R, Abrignani S, Houghton M, Han JH. (2004) Synthesis and characterization of a native, oligomeric form of recombinant severe acute respiratory syndrome coronavirus spike glycoprotein. *J. Virol.* 78:10328–35.  Brazzoli M, Helenius A, Foung SK, Houghton M, Abrignani S, Merola M. (2005) Folding and dimerization of hepatitis C virus E1 and E2 glycoproteins in stably transfected CHO cells. *Virology*. 332:438–53.  Coates S, Choo Q-L, Kuo G, Crawford K, Dong C, Wininger M, Weiner A, Berger K, Wong S, Ralston R, Morandi M, Pileri P, Rosa D, Muchmore E, Mahoney J, Brasky K, Purcell R, Abrignani S, Houghton, M. (2005) “Protection of chimpanzees against heterologous 1a viral challenge using a gpE1/gpE2 heterodimer vaccine” *in* Proceedings of the 11th International Symposium on Viral Hepatitis & Liver Disease (Jilbert AR, Grgacic EVL, Vickery K, Burrell CJ, Cossart YE. eds.) pp. 118–123. Australian Center for Hepatitis Virology.  Nattermann J, Schneiders AM, Leifeld L, Langhans B, Schulz M, Inchauspe G, Matz B, Brackmann HH, Houghton M, Sauerbruch T, Spengler U. (2005) Serum antibodies against the hepatitis C virus E2 protein mediate antibody-dependent cellular cytotoxicity (ADCC). *J. Hepatol.* 42:499–504.  Houghton M, Abrignani S. (2005) Prospects for a vaccine against the hepatitis C virus. *Nature*. 436:961–6.  Rosa D, Saletti G, De Gregorio E, Zorat F, Comar C, D’Oro U, Nuti S, Houghton M, Barnaba V, Pozzato G, Abrignani S. (2005) Activation of naive B lymphocytes via CD81, a pathogenic mechanism for hepatitis C virus-associated B lymphocyte disorders. *Proc. Natl. Acad. Sci. USA.* 102:18544–9.  Vajdy M, Selby M, Medina-Selby A, Coit D, Hall J, Tandeske L, Chien D, Hu C, Rosa D, Singh M, Kazzaz J, Nguyen S, Coates S, Ng P, Abrignani S, Lin Y-L, Houghton M, O’Hagan D. (2006) Hepatitis C virus polyprotein vaccine formulations capable of inducing broad antibody and cellular immune responses. *J. Gen. Virol.* 87:2253–62.  Stamataki Z, Coates S, Evans MJ, Wininger M, Crawford K, Dong C, Fong YL, Chien D, Abrignani S, Balfe P, Rice CM, McKeating JA, Houghton M. (2007) Hepatitis C virus envelope glycoprotein immunization of rodents elicits cross-reactive neutralizing antibodies. *Vaccine*. 25:7773–84.  Manns MP, Foster GR, Rockstroh JK, Zeuzem S, Zoulim F, Houghton M. (2007) The way forward in HCV treatment – finding the right path. Nat. Rev. Drug Discov. 6:991–1000. Review. Erratum in: *Nat. Rev. Drug Discov.* (2008) 7:102. *Nat. Rev. Drug Discov.* (2008) 7:458.  Bowen DG, Shoukry NH, Grakoui A, Fuller MJ, Cawthon AG, Dong C, Hasselschwert DL, Brasky KM, Freeman GJ, Seth NP, Wucherpfennig KW, Houghton M, Walker CM. (2008) Variable patterns of programmed death-1 expression on fully functional memory T cells after spontaneous resolution of hepatitis C virus infection. *J. Virol.* 82:5109–14.  Lin Y, Kwon T, Polo J, Zhu YF, Coates S, Crawford K, Dong C, Wininger M, Hall J, Selby M, Coit D, Medina-Selby A, McCoin C, Ng P, Drane D, Chien D, Han J, Vajdy M, Houghton M. (2008) Induction of broad CD4+ and CD8+ T-cell responses and cross-neutralizing antibodies against hepatitis C virus by vaccination with Th1-adjuvanted polypeptides followed by defective alphaviral particles expressing envelope glycoproteins gpE1 and gpE2 and nonstructural proteins 3, 4, and 5. *J. Virol.* 82:7492–503.  Houghton M. (2009) Discovery of the hepatitis C virus. *Liver Int.* 29 Suppl 1:82–8. Review.  Houghton M. (2009) The long and winding road to the identification of the hepatitis C virus. *J. Hepatol.* 51:939–48.  Drane D, Maraskovsky E, Gibson R, Mitchell S, Barnden M, Moskwa A, Shaw D, Gervase B, Coates S, Houghton M, Basser R. (2009) Priming of CD4+ and CD8+ T cell responses using a HCV core ISCOMATRIX vaccine: a phase I study in healthy volunteers. *Hum. Vaccin*. 5:151–7.  Ray R, Meyer K, Banerjee A, Basu A, Coates S, Abrignani S, Houghton M, Frey SE, Belshe RB. (2010) Characterization of antibodies induced by vaccination with hepatitis C virus envelope glycoproteins. *J. Infect. Dis.* 202:862–6.  Frey SE, Houghton M, Coates S, Abrignani S, Chien D, Rosa D, Pileri P, Ray R, Di Bisceglie AM, Rinella P, Hill H, Wolff MC, Schultze V, Han JH, Scharschmidt B, Belshe RB. (2010) Safety and immunogenicity of HCV E1E2 vaccine adjuvanted with MF59 administered to healthy adults. *Vaccine.* 28:6367–73.  Houghton M. (2011) Prospects for prophylactic and therapeutic vaccines against the hepatitis C viruses. *Immunol. Rev.* 239:99–108.  Stamataki Z, Coates S, Abrignani S, Houghton M, McKeating, J. (2011) Immunization of human volunteers with Hepatitis C virus envelope glycoproteins elicits antibodies that cross-neutralize heterologous virus strains. *J. Infect. Dis.* 204:811–3.  Meunier JC, Gottwein JM, Houghton M, Russell RS, Emerson SU, Bukh J, Purcell RH. (2011) Vaccine-induced cross-genotype reactive neutralizing antibodies against hepatitis C virus. *J. Infect. Dis*. 204:1186–90.  Houghton M. (2012) Chimp virus makes a savvy vaccine vector. *Sci. Transl. Med*. 4:115fs1.  Law JLM, Chen C, Wong J, Hockman D, Santer DM, Frey SE, Belshe RB, Wakita T, Bukh J, Jones CT, Rice CM, Abrignani S, Tyrrell DL, Houghton M. (2013) A hepatitis C virus (HCV) vaccine comprising envelope glycoproteins gpE1/ gpE2 derived from a single isolate elicits broad cross-genotype neutralizing antibodies in humans. PLoS ONE. 8:e59776. doi:10.1371/journal. pone.0059776.  Houghton M. (2013) Three isn’t the magic number. Nat. Med. 19:807.  Santer DM, Ma MM, Hockman D, Landi A, Tyrrell DL, Houghton M. (2013) Enhanced activation of memory, but not naïve, B cells in chronic hepatitis C virus-infected patients with cryoglobulinemia and advanced liver fibrosis. *PLoS ONE*. 8:e68308. doi: 10.1371/journal.pone.0068308.  Nourbakhsh M, Douglas DN, Pu CH, Lewis JT, Kawahara T, Lisboa LF, Wei E, Asthana S, Quiroga AD, Law LM, Chen C, Addison WR, Nelson R, Houghton M, Lehner R, Kneteman NM. (2013) Arylacetamide deacetylase: A novel host factor with important roles in the lipolysis of cellular triacylglycerol stores, VLDL assembly and HCV production. *J. Hepatol.* 59:336–43.  Houghton M, Law J, Tyrrell DL. (2013) An inactivated hepatitis C virus vaccine on the horizon? *Gastroenterology*. 145:285–8.  Grebely J, Bilodeau M, Feld JJ, Bruneau J, Fischer B, Raven JF, Roberts E, Choucha N, Myers RP, Sagan SM, Wilson JA, Bialystok F, Tyrrell DL, Houghton M, Krajden M. (2013) The Second Canadian Symposium on Hepatitis C Virus: A call to action. *Can*. *J. Gastroenterol.* 27:627–32.  Steenbergen RH, Joyce MA, Thomas BS, Jones D, Law J, Russell R, Houghton M, Tyrrell DL. (2013) Human serum leads to differentiation of human hepatoma cells, restoration of very-low-density lipoprotein secretion, and a 1000-fold increase in HCV Japanese fulminant hepatitis type 1 titers. *Hepatology*. 58:1907–17.  Law LMJ, Landi A, Magee WC, Tyrrell DL, Houghton M. (2013) Progress towards a hepatitis C virus vaccine. *Emerg. Microbes Infect*. 2:e79. doi:10.1038/emi.2013.79.  Colombatto P, Brunetto MR, Maina AM, Romagnoli V, Almasio P, Rumi MG, Ascione A, Pinzello G, Mondelli M, Muratori L, Rappuoli R, Rosa, D, Houghton M, Abrignani S, Bonino F. (2013) HCV E1E2-MF59 vaccine in chronic hepatitis C patients treated with PEG-IFNα2a and ribavirin: a randomized controlled trial. *J. Viral Hepatitis*. doi: 10.1111/jvh.12163.  Houghton M. (2014) Hepatitis C: the next 25 years. *Antiviral Res.*110:77–8. doi: 10.1016/j.antiviral.2014.06.018.  Wong JA, Bhat R, Hockman D, Logan M, Chen C, Levin A, Frey SE, Belshe RB, Tyrrell DL, Law JL, Houghton M. (2014) Recombinant hepatitis C virus envelope glycoprotein vaccine elicits antibodies targeting multiple epitopes on the envelope glycoproteins associated with broad cross-neutralization. *J Virol.* 88:14278–88. doi: 10.1128/JVI.01911-14.  MacParland SA, Bilodeau M, Grebely J, Bruneau J, Cooper C, Klein M, Sagan S, Choucha N, Balfour L, Bialystok F, Krajden M, Raven J, Roberts E, Russell R, Houghton M, Tyrrell DL, Feld JJ. (2014) National CIHR Research Training Program in Hepatitis C. The 3rd Canadian Symposium on Hepatitis C Virus: expanding care in the interferon-free era. *Can J Gastroenterol Hepatol*. 28:481–7.  Ahmed M, Wang F, Levin A, Le C, Eltayebi Y, Houghton M, Tyrrell L, Barakat K. (2015) Targeting the Achilles heel of the hepatitis B virus: a review of current treatments against covalently closed circular DNA. *Drug Discov Today.* 20:548–61. doi: 10.1016/j.drudis.2015.01.008.  Logan M, Law J, Wong JA, Hockman D, Landi A, Chen C, Crawford K, Kundu J, Baldwin L, Johnson J, Dahiya A, LaChance G, Marcotrigiano J, Law M, Foung S, Tyrrell L, Houghton M.(2016) Native folding of a recombinant gpe1/gpe2 heterodimer vaccine antigen from a precursor protein fused with Fc IgG. *J Virol.* 91:e01552-16 doi:10.1128/JVI.01552-16.  Huang W, Wang Y, Chen C, Law JL, Houghton M, Chen L. (2016) Fabrication of flexible self-standing all-cellulose nanofibrous composite membranes for virus removal. *Carbohydrate Polymers.* 143:9–17. doi: 10.1016/j.carbpol.2016.02.011.  O’Shea D, Law J, Egli A, Douglas D, Lund G, Forester S, Lambert J, Law M, Burton DR, Tyrrell DL, Houghton M, Humar A, Kneteman N. (2016) Prevention of hepatitis C virus infection using a broad cross-neutralizing monoclonal antibody (AR4A) and epigallocatechin gallate. *Liver Transplantation.* 22:324–32. doi: 10.1002/lt.24344.  Freedman H, Logan MR, Law JL, Houghton M. (2016) Structure and Function of the Hepatitis C Virus Envelope Glycoproteins E1 and E2: Antiviral and Vaccine Targets. ACS Infect Dis. 2:749–762. Epub 2016 Aug 16  Freedman H, Logan MR, Hockman D, Leman JK,, Law JL, Houghton M. (2017) Computational Prediction of the Heterodimeric and Higher Order Structure of gpE1/gpE2 Envelope Glycoproteins Encoded by the Hepatitis C Virus (HCV). *J Virol.* doi: 10.1128/JVI.02309-16.  Sarhan MA, Abdel-Hakeem MS, Mason AL, Tyrrell DL, Houghton M. (2017) Glycogen Synthase Kinase 3β Inhibitors Prevent Hepatitis C Virus Release/Assembly through Perturbation of Lipid Metabolism. *Scientific Reports.* doi: 10.1038/ s41598-017-02648-6  Landi A, Law J, Hockman D, Logan M, Crawford K, Chen C, Kundu J, Ebensen T, Guzman CA, Deschatelets L, Krishnan L, Tyrrell DLJ, Houghton M. (2017) Superior immunogenicity of HCV envelope glycoproteins when adjuvanted with cyclic-di-AMP, a STING activator or archaeosomes. *Vaccine*. 35:6949– 6956 doi: 10.1016/j.vaccine.2017.10.072.  Bartenschlager R, Baumert TF, Bukh J, Houghton M, Lemon SM, Lindenbach BD, Lohmann V, Moradpour D, Pietschmann T, Rice CM, Thimme R, Wakita T. (2018). Critical challenges and emerging opportunities in Hepatitis C virus research in an era of potent antiviral therapy: Considerations for scientists and funding agencies. *Virus research.* 248:53–62. doi: 10.1016/j.virusres.2018.02.016  Law JLM, Logan M, Wong J, Kundu J, Hockman D, Landi A, Chen C, Crawford K, Wininger M, Johnson J, Mesa Prince C, Dudek E, Mehta N, Tyrrell DL, Houghton M. (2018) Role of the E2 Hypervariable Region (HVR1) in the Immunogenicity of a Recombinant Hepatitis C Virus Vaccine. *Journal of virology.* 92. pii: e02141-17. doi: 10.1128/JVI.02141-17.  Khera T, Behrendt P, Bankwitz D, Brown RJP, Todt D, Doepke M, Khan AG, Schulze K, Law J, Logan M, Hockman D, Wong JAJ, Dold L, Gonzalez-Motos V, Spengler U, Viejo-Borbolla A, Ströh LJ, Krey T, Tarr AW, Steinmann E, Manns MP, Klein F, Guzman CA, Marcotrigiano J, Houghton M, Pietschmann T. (2018) Functional and immunogenic characterization of diverse HCV glycoprotein E2 variants. *J Hepatol.* doi: 10.1016/j.jhep.2018.11.003  Banda DH, Perin PM, Brown RJP, Todt D, Solodenko W, Hoffmeyer P, Kumar Sahu K, Houghton M, Meuleman P, Müller R, Kirschning A, Pietschmann T.(2019) A central hydrophobic E1 region controls the pH range of hepatitis C virus membrane fusion and susceptibility to fusion inhibitors. *J Hepatol.* 70(6):1082–1092. doi: 10.1016/j.jhep.2019.01.033. Epub 2019 Feb 13.  Houghton M. (2019) Hepatitis C Virus: 30 Years after Its Discovery. *Cold Spring Harb Perspect Med*. 9(12). doi: 10.1101/cshperspect.a037069.  Akache B, Deschatelets L, Harrison BA, Dudani R, Stark FC, Jia Y, Landi A, Law JLM, Logan M, Hockman D, Kundu J, Tyrrell DL, Krishnan L, Houghton M, McCluskie MJ. (2019) Effect of Different Adjuvants on the Longevity and Strength of Humoral and Cellular Immune Responses to the HCV Envelope Glycoproteins. *Vaccines (Basel)*. 7(4). doi: 10.3390/vaccines7040204.  *Immunoregulation*  Egli A, Levin A, Santer DM, Joyce M, O’Shea D, Thomas BS, Lisboa LF, Barakat K, Bhat R, Fischer KP, Houghton M, Tyrrell DL, Kumar D, Humar A. (2014) Immunomodulatory Function of Interleukin 28B during primary infection with cytomegalovirus. *J Infect Dis.* 210:717–27. doi: 10.1093/infdis/jiu144.  Egli A, Santer D, Barakat K, Zand M, Levin A, Vollmer M, Weisser M, Khanna N, Kumar D, Tyrrell L, Houghton M, Battegay M, O’Shea D. (2014) Vaccine adjuvants-understanding molecular mechanisms to improve vaccines. *Swiss Med Wkly.* 144:w13940. doi: 10.4414/smw.2014.13940. eCollection 2014.  Egli A, Santer DM, O’Shea D, Barakat K, Syedbasha M, Vollmer M, Baluch A, Bhat R, Groenendyk J, Joyce MA, Lisboa LF, Thomas BS, Battegay M, Khanna N, Mueller T, Tyrrell DL, Houghton M, Humar A, Kumar D. (2014) IL-28B is a key regulator of B-and T-cell vaccine responses against influenza. *PLoS Pathog.* 10:e1004556. doi: 10.1371/journal.ppat.1004556. eCollection 2014 Dec.  Egli A, Santer DM, O’Shea D, Tyrrell DL, Houghton M. (2014) The impact of the interferon-lambda family on the innate and adaptive immune response to viral infections. *Emerging Microbes Infections.* 3:e51. doi: 10.1038/emi.2014.51.  Egli A, Humar A, Widmer LA, Lisboa LF, Santer DM, Mueller T, Stelling J, Baluch A, O’Shea D, Houghton M, Kumar D. (2015) Effect of Immunosuppression on T-Helper 2 and B-Cell Responses to Influenza Vaccination. *J Infect Dis.* 212:137–46. doi: 10.1093/infdis/jiv015.  Syedbasha M, Linnik J, Santer D, O’Shea D, Barakat K, Joyce M, Khanna N, Tyrrell DL, Houghton M, Egli A. (2016) An ELISA Based Binding and Competition Method to Rapidly Determine Ligand-receptor Interactions. *J Vis Exp*. doi: 10.3791/53575.  Santer DM, Minty GE, Mohamed A, Baldwin L, Bhat R, Joyce M, Egli A, Tyrrell DL, Houghton M. (2017) A novel method for detection of IFN-lambda 3 binding to cells for quantifying IFN-lambda receptor expression. *J Immunol Methods.* doi:10.1016/j.jim.2017.03.001.  Okoye IS, Houghton M, Tyrrell L, Barakat K, Elahi S. (2017) Coinhibitory Receptor Expression and Immune Checkpoint Blockade: Maintaining a Balance in CD8+ T Cell Responses to Chronic Viral Infections and Cancer. *Front Immunol*. doi: 10.3389/fimmu.2017.01215. eCollection 2017.  Santer DM, Minty GES, Golec DP, Lu J, May J, Namdar A, Shah J, Elahi S, Proud D, Joyce M, Tyrrell DL, Houghton M. (2020) Differential expression of interferon-lambda receptor 1 splice variants determines the magnitude of the antiviral response induced by interferon-lambda 3 in human immune cells. *PLoS Pathog.* 16(4):e1008515. doi: 10.1371/journal.ppat.1008515  Freedman H, Kundu J, Tchesnokov EP, Law JLM, Nieman JA, Schinazi RF, Tyrrell DL, Gotte M, Houghton M. (2020) Application of Molecular Dynamics Simulations to the Design of Nucleotide Inhibitors Binding to Norovirus Polymerase. *J Chem Inf Model.* 60(12):6566–6578. doi: 10.1021/acs.jcim.0c00742. Epub 2020 Dec 1. PMID: 33259199; PMCID: PMC7869559.  *Autoimmune Liver Disease*  Landi A, Weismuller TJ, Lankisch TO, Santer DM, Tyrrell DL, Manns MP, Houghton M. (2014) Differential serum levels of eosinophilic eotaxins in primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis. *J Interferon Cytokine Res.* 34(3):204–14. doi: 10.1089/jir.2013.0075.  *Chronic Fatigue Syndrom*e  Steffen I, Tyrrell DL, Stein E, Montalvo L, Lee TH, Zhou Y, Lu K, Switzer WM, Tang S, Jia H, Hockman D, Santer DM, Logan M, Landi A, Law J, Houghton M, Simmons G. (2011) No evidence for XMRV nucleic acids, infectious virus or anti-XMRV antibodies in Canadian patients with chronic fatigue syndrome. *PLoS ONE.* 6:e27870.  Jason LA, Unger ER, Dimitrakoff JD, Fagin AP, Houghton M, Cook DB, Marshall GD Jr, Klimas N, Snell C. (2012) Minimum data elements for research reports on CFS. *Brain Behav. Imm*un. 26:401–6.  Landi A, Broadhurst D, Vernon SD, Tyrrell DL, Houghton M. (2015) Reductions in circulating levels of IL-16, IL-7 and VEGF-A in myalgic encephalomyelitis/ chronic fatigue syndrome. *Cytokine*. 78:27–36. doi: 10.1016/j.cyto.2015.11.018.  Gindin Y, Chung C, Jiang Z, Zhou JZ, Xu J, Billin AN, Myers RP, Goodman Z, Landi A, Houghton M, Green RM, Levy C, Kowdley KV, Bowlus CL, Muir AJ, Trauner M. (2021) A Fibrosis-Independent Hepatic Transcriptomic Signature Identifies Drivers of Disease Progression in Primary Sclerosing Cholangitis. *Hepatology*. 73(3):1105–1116. doi: 10.1002/hep.31488. Epub 2021 Feb 28. PMID: 32745270; PMCID: PMC8048608.  *Computational Modeling*  Barakat KH, Huzil JT, Jordan KE, Evangelinos C, Houghton M, Tuszynski J. (2013) A computational model for overcoming drug resistance using selective dual-inhibitors for aurora kinase A and its T217D variant. *Mol. Pharm.* 10:4572–89.  Barakat KH, Law J, Prunotto A, Magee WC, Evans DH, Tyrrell DL, Tuszynski J, Houghton M. (2013) Detailed computational study of the active site of the hepatitis C viral RNA polymerase to aid novel drug design. *J. Chem. Inf. Mode*l. 53:3031–43.  Anwar-Mohamed A, Barakat KH, Bhat R, Noskov SY, Tyrrell DL, Tuszynski JA,Houghton M. (2014) A human ether-á-go-go-related (hERG) ion channel atomistic model generated by long supercomputer molecular dynamics simulations and its use in predicting drug cardiotoxicity. *Toxicology Letters.* 230:382–92. doi: 10.1016/j.toxlet.2014.08.007.  Barakat KH, Anwar-Mohamed A, Tuszynski JA, Robins MJ, Tyrrell DL, Houghton M. (2015) A Refined Model of the HCV NS5A protein bound to daclatasvir explains drug-resistant mutations and activity against divergent genotypes. *J Chem Inf Model.* 55:362–73. doi: 10.1021/ci400631n.  Ahmed M, Pal A, Houghton M, Barakat K. (2016) A Comprehensive Computational Analysis for the Binding Modes of Hepatitis C Virus NS5A Inhibitors: The Question of Symmetry. *ACS Infect Dis.* 2:872–881.  Ahmed M, Jalily Hasani H, Ganesan A, Houghton M, Barakat K. (2017) Modeling the human Nav1.5 sodium channel: structural and mechanistic insights of ion permeation and drug blockade. *Drug Des Devel Ther*. doi: 10.2147/DDDT. S133944. eCollection 2017.  Barakat KH, Houghton M, Tyrrell DL, Tuszynski JA. (2017) Rational Drug Design Rational Drug Design: One Target, Many Paths to It. *IGI Global*. doi: 10.4018/978-1-5225-1762-7.ch044  Freedman H, Winter P, Tuszynski J, Tyrrell DL, Houghton M. (2018) A computational approach for predicting off-target toxicity of antiviral ribonucleoside analogues to mitochondrial RNA polymerase*. The Journal of biological chemistry.* 293:9696–9705. doi: 10.1074/jbc.RA118.002588  Ganesan A, Ahmed M, Okoye I, Arutyunova E, Babu D, Turnbull W, Kundu JK, Shields J, Agopsowicz K, Xu L, Tabana Y, Srivastava N, Zhang G, Moon T, Belovodskiy A, Hena M, Kandadai AS, Hosseini S, Hitt M, Walker J, Smylie M, West FG, Siraki AG, Lemieux MJ, Elahi S, Nieman JA, Tyrrell DL, Houghton M, Barakat K. (2019) Comprehensive in vitro characterization of PD-L1 small molecule inhibitors. *Scientific Reports.* 9(1):12392. doi: 10.1038/s41598-019-48826-6.  Kalyaanamoorthy S, Lamothe SM, Hou X, Moon TC, Kurata HT, Houghton M, Barakat KH. (2020) A structure-based computational workflow to predict liability and binding modes of small molecules to hERG. Sci Rep. 10(1):16262. doi: 10.1038/s41598-020-72889-5.  Freedman H, Kundu J, Tchesnokov EP, Law JLM, Nieman JA, Schinazi RF, Tyrrell DL, Gotte M, Houghton M. (2020) Application of Molecular Dynamics Simulations to the Design of Nucleotide Inhibitors Binding to Norovirus Polymerase. *J Chem Inf Model*.; 60(12):6566–6578. doi: 10.1021/acs.jcim.0c00742.  *COVID-19*  Law JLM, Logan M, Joyce MA, Landi A, Hockman D, Crawford K, Johnson J, LaChance G, Saffran HA, Shields J, Hobart E, Brassard R, Arutyunova E, Pabbaraju K, Croxen M, Tipples G, Lemieux MJ, Tyrrell DL, Houghton M. (2021) SARS-COV-2 recombinant Receptor-Binding-Domain (RBD) induces neutralizing antibodies against variant strains of SARS-CoV-2 and SARS-CoV-1. *Vaccine*. 39(40):5769–5779. doi: 10.1016/j.vaccine.2021.08.081. Epub 2021 Aug 26. PMID: 34481699; PMCID: PMC8387217. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0509=MH  Michael Houghton: Hello?  Adam Smith: Hello, this is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize in Stockholm. Is this Michael Houghton?  MH: Yes it is, hello Adam.  AS: How nice to speak to you. Well, first of all congratulations on the award of the Nobel Prize.  MH: Thank you very much. It’s a great honour of course, and I’m very, very, very pleased. Thank you.  AS: How did you actually hear the news?  MH: My colleague in Alberta, Dr Tyrell, he called me at three o’clock in the morning, and told me that I’d won it, and of course it was a big surprise and I was very sleepy. But I tried to go back to sleep afterwards but couldn’t quite manage it. But … And yes, it was wonderful.  AS: I think it’s very sanguine to try and go back to sleep afterwards. I think one of the economics laureates last year, Abhijit Banerjee, did that, but it requires some cool.  MH: Well, it wasn’t too successful. I kind of dosed off and on, so it wasn’t a particularly good sleep. In the end I gave up. And then of course got on emails and there’s hundreds and hundreds of emails, which is all very nice of course.  AS: Yeah, it’s going to be a busy day.  MH: Yeah.  AS: It’s an extraordinary story of people working together and with your cloning of the virus and development of the blood test in 1990, the ability to remove the danger of the disease for millions of people, it’s quite extraordinary.  MH: Well, thank you very much. You know, at the time of trying to discover Hep C in the ‘80s, it was a difficult task. We didn’t have the tools available then that we do now of course, so it was a lot of effort actually, a lot of brute force, and just trying to use and apply all the methods available then. And we must have tried 30 different approaches at least over 7 or 8 years, and eventually we got one clone, after screening probably hundreds of millions of clones. So, yes, I work with some great people, without whom I would not have had this success. And we worked very hard, and so a lot of hard work and persistence was part of our success story, for sure.  AS: When students hear that sort of story, they often ask ‘how did you keep going, what kept your belief alive?’.  MH: Well, you know, I got into microbiology when I was 17 having read about Louis Pasteur’s life and his work, so he was my inspiration, and I think trying to discover a major virus is kind of incentive enough, you know. I remember driving to work during those 7 or 8 years where we were frustrated for so long and watching all these new hotels going up around the institution that I worked at, and I was thinking ‘Oh well, they just started this big hotel, I’m sure we will have found it by the time it’s finished’. But no, it wasn’t. I think they had to erect about 10 hotels before we finally found it!  AS: I’m left with an extraordinary vision of measuring the progress of research through the erection of large buildings.  MH: [Laughs] It was hard. I was working at a biotech company in California, as you may know, and so biotech companies in the States, they want results, right? They have investors that give a lot of money, and they want results sooner than later, especially in the US. So you know it’s great that the company I worked at was willing to work on it and to persist in funding it, and all of our venture capitalists and so forth. And I think in a real way it was a testament to the power of the biotechnology industry, but also it was a lot of pressure on me to manage the programme and to keep it going, with years and years of failure basically. Yeah, so I got pretty desperate: ‘Surely we’ll do it before this one’s completed!’. [Laughs]  AS: Well you did it! Indeed, indeed. And you’re now working on the development of a vaccine.  MH: Yes, yes. You know, quickly after we discovered the virus we developed a blood test, that was the most urgent need to protect the blood supply. And as you said earlier, we did that quite quickly. And then of course the two big challenges were trying to find therapeutics for the virus, and that took a long time. It took, you know, the whole field and the pharmaceutical industry working for more than 20 years. But eventually, we’ve got these wonderful drugs now that can cure nearly everybody quite quickly and safely. But it is a, you know, it is an epidemic, global epidemic. It is a pandemic. HCV today kills around 400,000 people every year. If you put that in the context of COVID, which we’re all obviously very concerned with, that’s already killed 1 million people. So, you know, the way eventually you have to control an epidemic like this is with a vaccine. After many years of work I think our field feels that it is now feasible, at least a partially effective vaccine. So yes, I’m at the University of Alberta I’ve been working on an improved version that we think has a good chance of success, or at least being partially effective.  AS: That’s exciting. I do hope we’ll have the chance to speak about this at greater length very soon. But now I should let you get on, you’ve got so many people to talk to. So, it’s been a great pleasure speaking to you. Thank you very much indeed, and many, many congratulations.  MH: Thank you Adam. Much appreciated. Bye bye. |
| Interview |  |
| Q1 | What did you want to be when you were younger? Did you want to be a scientist? |
|  | Yes, I did. At high school I was interested in biology. I was interested in physics. So when I got my A-levels, I was trying to figure out what to do: physics or biology. But I didn’t get a very good grade in my physics A-level. So I thought, ‘Well maybe I’m not going to be too good at that’.  I went to the local library where I lived and looked at all the various career choices. I spent a week in the library thinking seriously about what career I wanted. I got to ‘M’ – microbiology – and I read about Louis Pasteur’s work and his life story. And then I thought, this is what I want to do. That was when I think I decided I was going to do medical research. |
| Q5 | What was it about Louis Pasteur’s story that spoke to you? |
|  | I think two things. His daughter died of bacterial disease so obviously with his work, he was able to prevent that in so many people. There was that medical innovation and altruistic aspect to his life along with his tragedy. But also it was very interesting to actually study the mechanism of bacteria and life organisms in general. I was very interested in the difference between an organism and a rock. I found the organism much more interesting than the rock. As you change and develop through life, you realise rocks are very interesting, you can get a lot of information from rocks! But at the time I was more interested in living organisms than physical objects. |
| Q25 | Besides Louis Pasteur was there any other person in your life, perhaps a teacher or mentor, that influenced you to take the path you went down? |
|  | Not really but growing up in England, when the structure of DNA was elucidated in that magnificent work by [Watson, Crick and Wilkins](https://www.nobelprize.org/prizes/medicine/1962/summary/), the BBC ran programmes about it on Sunday mornings. I used to get up quite early on Sunday mornings just to watch it. That really influenced me too. I knew I wanted to do biology and medical research. And I also knew from listening to those programmes that I wanted to get involved with gene regulation – what these days is termed molecular medicine. |
| Q40 | And that’s what you were interested in at university. What type of student were you? Were you very studious? |
|  | I started off studious for the first two terms, but then after that, I discovered a lot of interesting things to do socially! The usual student things – I played a lot of sport, drank a lot of beer and just enjoyed a much freer community for the first time in my life. I went to a traditional high school in the UK where you were told what to do, and often what to think. So being released into a really open community at the University of East Anglia, I wouldn’t say I went off the rails, but it was an important period of growth for me. But actually the work suffered! |
| Q12 | Looking back is there any advice that you would give to yourself, or that you like to give to students who are starting to think about their career? |
|  | I feel like it’s very important to find what your passion is in life, find out what you’re really motivated to do, and it doesn’t matter what it is. It could be a ballet dancer. It could be a travel writer, but find out what really motivates you. Secondly spend a lot of effort on finding out because I think a lot of young people drift from one thing to another, to another. It’s okay to change but I think you’ve got to put a lot of thought into what you really want to do, and you’ve got to put some effort into that. It’s not an easy decision.  So in summary – find what you’re passionate about, find out what your vocation is and spend time and spend the effort to do that. |
| Q24 | What makes you passionate about science and your work? |
|  | I like the idea of looking at disease and then working with other scientists to figure out ways to prevent that disease. I work at the level of molecular medicine, and there’s a lot of tools available to us now, a lot of methodologies and a lot of technology we can bring to diseases. I very much like exploring ways to solve disease. We have so many diseases that affect humans.  Although we’ve made progress, I don’t think it’s good enough. There are too many diseases that humans suffer from about which we know very little – Alzheimer’s, inflammatory bowel disease, multiple sclerosis. Cancer of course gets a lot of effort and there has been some progress there, but there are so many diseases that really afflict mankind that I feel we should be doing a better job on. |
| Q17 | How does it feel to do work that has such a tangible impact on people’s lives? |
|  | It’s great. After our discovery of the hepatitis C virus, I organised an international meeting on the disease with a colleague in Italy. I remember sitting in the audience during the conference and hepatitis C virus was up there on the screen. And I thought, wow finally we’ve been able to identify a field and to have people all over the world, working on it, to actually help patients. That was a good feeling.  But it took us a lot of effort to find the virus, the best part of seven years. When you’ve been trying so, so long, so hard, it was very satisfying after spending so much work and effort. And there was a fair bit of pressure. It was done in a biotech company where the investors are always asking when, when, when, where’s the virus?  But the bottom line is if you can impact disease and prevent disease in patients, that’s what medicine is all about. Whether you’re a clinician or whether you’re a medical researcher, like me, that’s the most important thing. Everything else is just icing on the cake. |
| Q26 | You mentioned that discovering hepatitis C took a lot of persistence. What qualities do you think are important to be a successful scientist? |
|  | I think for me, it’s working with good people. I think that’s important because you can kick ideas around with each other and often the best ideas come from chance, random conversations. You schedule meetings all the time to update progress and review problems, but it’s really the conversations around the coffee pot at work, or sometimes over lunch. It’s environments that are not scheduled that really stimulate the germ of, ‘well, okay, this is a direction we should take’.  I think number two is, as I said before, being very passionate about what you’re doing, because that gives you determination and that gives you the persistence. Persistence is very important.  What else? Good old fashioned hard work and getting the funding. It’s not easy getting funding for something like hepatitis C – seven years without making any progress. That’s tough to do in academia and it’s tough in industry because people want returns quite quickly.  So working with good people, persistence, determination, and don’t give up. If you think you have a good chance, a reasonable chance, don’t give up. |
| Q38 | How did you manage to convince your company to keep going then? |
|  | That’s a great question. I think you always get conflicting opinions in any group of humans. Some people think it’s time to stop the program. Some people think even if we don’t discover it, we’ll be there and able to contribute to the growth of the field and in some way make a contribution, medically and commercially. And then other people feel, like I did, that it’s worth the effort. What else could I be doing that has the potential of trying to discover the hepatitis C virus?  So there’s a whole range of different emotions. There’s the commercial, there’s the impatience, and then there’s the philosophical: ‘what else could I be doing that was more important than trying to find a major virus?’ |
| Q3 | What keeps you going, when you encounter problems or failure? |
|  | I think first of all you’ve got to believe with realism that you have a real chance. You don’t want people trying to become astronauts and going to Mars if they don’t like heights! That’s an extreme example, but you’ve got to believe with some reality that you have a chance to do it.  If you feel confidence that you can do it when you have setbacks, which we had all the time for seven years. I was very philosophical about it. When colleagues showed me disappointing data often I would laugh and say, ‘Well, okay, that’s too bad. Let’s try something else.’ So good old human traits of confidence and persistence, that’s part of what the human race has, doesn’t it? |
| Q7 | And outside of science how do you like to spend your free time? Is there something you do to feel more creative or relax? |
|  | I played a lot of sports since the age of four actually, so I love sport. I love cricket, it’s my favorite game. I used to play a lot of it at high school and at college and afterwards. Nowadays I just watch it!  And I’m interested in the world around us. We’re all on a learning curve. We’re still trying to figure out what we are and where we are. I read books on physics. I read books on cosmology. I’m very interested in understanding who we are. A sort of philosopher I suppose like millions of human beings – we’re trying to figure out what we are. |
| ID | 0510 |
| Biographical | I was born on August 25, 1952 in Sacramento, California to Roberta Helen Rice and Charles Moen Rice Jr. (Fig. 1). My mother originated in Colorado Springs, Colorado, my father from Worcester, Massachusetts. I was the third Charles Moen Rice; we were all only children. I never met my paternal grandparents who were long gone by the time I was born. For most of my early years, we lived in Sacramento with a short interlude in San Jose (Fig. 2). My father worked as an insurance claims adjuster, my mother as a suburban housewife. My “brothers and sisters” growing up were a series of canine friends, largely dachshunds (Fig. 3). My parents and I loved dogs, a passion that endures to the present. A neighbor once said of my father, “if I believed in reincarnation, I would want to come back as one of your dad’s dogs.” No finer life could be imagined. I was an avid reader as a child, often staying up late into the night much to my parents’ chagrin. Music was a large part of my early home life nourished in part from my father who was a fanatic stereophile and had to have the latest high-end equipment. I was exposed to classical music and musicals, but later degenerated to listening to the Rolling Stones and the Doors on a low-end record player in my room.  Amongst my most cherished boyhood items were the usual chemistry set and very basic microscope, but my real love of biology and nature came from frequent camping and hiking trips in the Sierra Nevada mountains. My education was exclusively in public schools. I did reasonably well, despite having a series of odd jobs including cleaning up after parties at a nearby clubhouse. My custodial skills are still quite good. All in all, I had a fairly normal trajectory for someone growing up in the 1960s, which was anything but a “normal” decade: Vietnam, the cold war, the moon landing, assassinations of JFK, MLK and RFK, sex, drugs and rock-n-roll, etc.  The last years of high school (Rio Americano), forced the choice of what to do next. The default trajectory for a middle-class kid was “go to college”, so that’s what I did. I applied to UC Davis and was accepted (with a small scholarship). For those of you unfamiliar with Northern California geography, Davis is about 15 miles west of Sacramento. So, for me, close to home, but far enough away. Given my love of animals, including even rats, I chose UC Davis given its veterinary medicine reputation, a vocation I thought I might pursue after finishing my undergraduate degree. In those days, going to a state university in your home state had an added bonus – it was cheap. I had no idea what major I was going to pursue but was leaning towards math until that was derailed by an advanced statistics course some years later. I blame this on my instructor, who had the appearance of wizard-like Gandalf, but the wisdom he was attempting to convey was lost on me.  An introductory biology course my freshman year turned out to be perhaps the most important chance encounter of my career. The course was taught by a Caltech-trained developmental biologist, Dennis Barrett. Dennis was/is a terrific biologist, and his lectures were captivating. Even more engaging were his exams, which were made up of multiple-choice questions. The exam was taken in class and the students could then take it home and revise their answers using any means available – textbooks, literature, or discussions with other students. This take-home portion of the exam, and the quest to get a perfect score, was an incredible learning experience because the correct answers to these multiple-choice questions were not the obvious ones and required a deeper dive and a real understanding of the biology. I don’t recall the details now, but Dennis became a key advisor and advocate for me during my undergraduate years and beyond.  My first undergraduate research experience was in the chemistry department studying tunicates (sea squirts) who manage to concentrate vanadium from sea water over six orders of magnitude in specialized blood cells. While I didn’t mind bleeding tunicates and doing elemental analysis, this wasn’t my cup of tea. I switched to working with Dennis on his favorite organism, the purple sea urchin, *Strongylocentrotus purpuratas.* “Purps” as we would call them are commonly found off the US Western coast; we collected them on field trips in the area near the Bodega Bay Marine Station. These animals can be induced to shed their gametes with an electrical jolt or injection of potassium chloride. Fertilization ensues by mixing the eggs and sperm in sea water, and you can watch early development proceed with a simple microscope – amazing. I was hooked, but this was just a part-time, sporadic research experience interspersed with working at the UCD library, the Memorial Union food service, and spending my first few summers working at a cannery or as a tomato inspector. It was some years before I could stomach eating ketchup again.  The summer of 1973 provided the chance to really immerse myself in research. Dennis was an instructor in the Physiology Course at the Woods Hole Marine Biology Laboratory (MBL) in Massachusetts and suggested that I apply to their summer program. This worked out. I arrived and found myself immersed in science 24/7. The course covered developmental biology, immunology, biophysical biochemistry and was taught by world class scientists through lectures, reading material and intense hands-on lab work. I turned 21 at the MBL and had a memorable (that I don’t actually remember) celebration (Fig. 4). After that, it was difficult to return to the undergraduate grind for my senior year at UCD.  Nonetheless, I survived and graduated in 1974 with a degree in Zoology. I’ve so far highlighted academic pursuits but in reality there was quite a bit going on outside of the classroom – soccer, softball, basketball, frequent backpacking trips and other activities that I will not detail here. Also in my academic wanderings, I had taken advantage of some “fun” classes, like the introduction to viticulture and enology anchored by the book “Wine: An Introduction” by UCD professors Maynard Amerine and Vernon Singleton. Growing up in California near the wine country, coupled with this course, seeded a real passion for wine. I found myself waffling between a career in wine and developmental biology research. Somewhat different trajectories …  Given this dilemma, I recruited a few college friends, we bought a used VW bus and departed for an extended trip to Central and South America. Before I left, I applied to two PhD programs strong in developmental biology: UC San Diego and Caltech. Uncertain as to my future, off we went, slowly making our way through Central America. After several months, a failing VW bus was abandoned in Costa Rica and we flew to Colombia to continue the South American leg of the adventure to Lima, Peru, where a telegram from my father awaited me: “you have been accepted at UCSD and Caltech and they want to know if you are coming”. I was having a great time traveling and meeting an amazing cast of wanderers, but a decision had to be made. Continuing from Lima to Cuzco, to Machu Picchu, La Paz and Salta in Northern Argentina, and after an exchange of letters with Dennis, I decided on Caltech, despite its lower stipend. A transition back to reality was needed. Fortunately, Dennis needed a teaching assistant for the MBL physiology course and some help moving from Davis to Denver, where he was joining the University of Denver faculty. The cheapest flight back to the US was to Miami. From there, an attempt by a scruffy vagabond with a backpack to hitchhike back to California failed, requiring a multiday Greyhound bus ride to Sacramento. After a few days back home, we loaded up a rental truck, drove from Davis to Denver and after a short stop to unload, headed to Woods Hole for another memorable summer. Besides the science, there was healthy competition between the various MBL courses, including a long-standing rivalry between the Physiology Course, headed by immunologist John Cebra, and the Embryology Course headed by the intensely competitive Eric Davidson, a Caltech professor who studied sea urchin development. This rivalry was played out on a softball diamond and a flag football field. My recollection is that the Physiology Course usually triumphed at softball whereas Eric’s team dominated the more physical football encounters. As you might have guessed, Eric’s sea urchin lab was one of the main reasons I was going to Caltech.  The summer ended and I was off to Pasadena, driving a yellow-orange 1975 VW Rabbit that my parents helped me buy. Being raised in Northern California, I approached this transition with great trepidation. How could I defect to Southern California? It was going to be smoggy, crowded, and terrible. My goal was to get my PhD and move on to greener pastures ASAP. But … I ended up loving it and spent nearly a decade at Caltech. However, there was a surprise upon my arrival. Rather than being assigned to Eric’s lab, as I’d hoped, I was placed in an animal virus lab, headed by James H. “Jim” Strauss and his wife Ellen Glowacki Strauss. In those days, laboratory rotations weren’t necessarily required or even encouraged. As I learned more about the Davidson lab I began to have second thoughts – Eric was brilliant but rumored to be tough, demanding and he didn’t suffer fools. I was pretty sure I belonged squarely in the “fools” category so I decided that this might not be the best fit. You could chalk it up to “no guts” and a lack of self-confidence, but at the same time the field of animal RNA viruses was still in its infancy and the Strauss lab was at the cutting edge of studying a model enveloped RNA virus, Sindbis virus, the prototype alphavirus. The lab was small with 3 PhD students, 2 techs, Jim and Ellen, and an excellent environment for someone entering a new field. Jim’s office was inhabited by two free-flying parakeets who didn’t necessarily take kindly to graduate students barging in for advice.  There had been extensive work in the lab on Sindbis virus RNA replication; less was known about the virus particle. Jim suggested that I work on a small, secreted glycoprotein called E3, which was processed from an envelope glycoprotein precursor during virion maturation and released into the cell culture supernatant. In the case of Sindbis, E3 was not virion associated whereas in the case of a related alphavirus, Semliki Forest virus, it stayed bound to the virus particle. I wasn’t enamored with this project. Fortunately, we were given a great deal of freedom to come up with and test our own ideas. I did end up doing quite a bit of work on the Sindbis virus glycoproteins, and that comprised the bulk of my thesis. But the larger Caltech research environment was playing a key role in shaping my research interests. This included a remarkable group of fellow PhD students and postdocs, the Caltech faculty and, of course, the undergrads. Recombinant DNA was exploding, we could now “easily” sequence nucleic acids and our lab was conveniently positioned right down the hall from the Maniatis lab, with its freezer full of enzymes and cutting-edge molecular biology expertise. Rather than being left out of this revolution, it seemed obvious that we should determine the sequences of the Sindbis structural proteins. The only catch was that concerns about recombinant DNA cloning and safety prevented molecular cloning of these animal RNA viruses. I was left to figure out how to sequence the structural protein coding region without complementary DNA (cDNA) cloning. Without delving into the gory details, it turns out that some restriction enzymes can cleave single-stranded cDNA or RNA-cDNA hybrids, providing discrete fragments that can be end-labeled, gel purified and sequenced using the laborious Maxim-Gilbert chemical sequencing method. This eventually provided the sequence of Sindbis subgenomic mRNA revealing a single open reading frame (ORF) that encoded the capsid protein followed by E3 and the two virion glycoproteins, E2 and E1. This capped off my PhD work, which I defended in 1981.  At this point, if not before, I should have been charting my future and lining up a postdoc. But to be honest, I was having too much fun collaborating with other labs, finishing ongoing work, and starting new projects. Again, this was possible because of the freedom granted, as long as good science ensued. I made a few half-hearted attempts, sending out feelers to Ron Davis at Stanford and Tom Cech in Colorado, but they either didn’t answer or weren’t interested (which is perhaps not surprising for an applicant working on an obscure RNA virus). So, ignoring the “academic kiss of death” I just stayed in the Strauss lab.  There were two ongoing efforts that made this an easy decision. The first revolved around an undying belief in the power of genetics. For me, this had been nurtured at UC Davis as an undergraduate by the great evolutionary geneticists Theodosius Dobzhansky and G. Ledyard Stebbins, and at Caltech surrounded by Max Delbruck in his waning years and the “next generation” including Bill Wood, Seymour Benzer, and Ed Lewis. One of the many attractions of working on viruses is their small genome size yet a highly evolved ability to infect cells, replicate and survive in nature despite a complete dependence on cellular functions. Inert on their own, they provide a perturbation to probe cell and organismal biology. As highly efficient machines, we can learn much from viruses themselves and their replicative mechanisms. Classically, chemical mutagenesis, selection of conditional mutants and their characterization under permissive and non-permissive conditions were the mainstay of animal RNA virus genetics. For Sindbis, this had certainly been the case for an immensely useful panel of temperature-sensitive (ts) mutants. But now, given reverse transcriptase and the ability to copy RNA into cDNA and recombinant DNA methods, how could we exploit these new tools to allow site-directed genetic manipulation of positive-sense RNA viruses?  In concept, this should be simple: isolate viral genome RNA, make a cDNA copy, and clone it into a plasmid that allows transcription of a functional viral genome RNA using either cellular machinery or in vitro transcription. This was shown to work for the bacteriophage QB by Taniguchi and Weissman in 1978. Shortly thereafter we began working towards the same objective for Sindbis. This was a collaborative effort with Henry Huang, a brilliant postdoc in Leroy Hood’s group. Cloning was now allowed and we were fortunate that Eugene Butler, a postdoc in the Maniatis lab, had purified and characterized the DNA-dependent RNA polymerase of Salmonella phage 6 (SP6) for his PhD and defined the 17-base promoter and initiating base. This turned out to be a highly efficient way to make unlimited quantities of synthetic Sindbis genome RNA with proper 5’ and 3’ terminal sequences. It took several more years, and additional work after I moved to St. Louis, before we published our first paper on the Sindbis infectious clone: “Production of infectious RNA transcripts from Sindbis virus cDNA clones: mapping of lethal mutations, rescue of a temperature-sensitive marker, and in vitro mutagenesis to generate defined mutants”. In the meantime, Vincent Racaniello and David Baltimore had reported success with poliovirus and Paul Ahlquist for the plant RNA virus, bromegrass mosaic virus. Many other examples followed, including recent work with SARS-CoV-2. This opened up an almost limitless landscape of possibilities for virologists since in theory, for any positive-sense RNA virus, these so-called “infectious clones” could be manipulated to generate mutations and phenotypes could be tested.  The second area cooking in the Strauss lab was an effort to understand more about another group of enveloped RNA viruses, the flaviviruses. Given their similar virion morphology and physical properties, alphaviruses and flaviviruses had been lumped together in the family *Togaviridae*. However, there was no serological cross-reactivity between these groups, so the flaviviruses had recently become a separate family, the *Flaviviridae*. Not much was known about flavivirus genome structure and how this might be similar or different from the alphaviruses or other positive strand RNA virus families.  The prototype flavivirus was the famous yellow fever virus (YFV), shown to be a filterable agent, transmitted by the bite of infected mosquitoes, and the cause of the often fatal viscerotropic disease by Walter Reed and his colleagues at the turn of the last century. Decades later, by passaging a human isolate from a young Ghanaian named Asibi in mouse and chicken embryo tissues, [Max Theiler](https://www.nobelprize.org/prizes/medicine/1951/theiler/facts/) derived an attenuated yellow fever strain, called 17D, that was no longer virulent in non-human primates (NHP) and protected them from lethal YFV infection. This vaccine, which has been administered to more than 500 million people, is still used today. A single shot confers broad and long-lasting protection. Max, who was then working at the Rockefeller Foundation, was awarded the Nobel Prize in Physiology or Medicine in 1951 for his work on the yellow fever vaccine.  Given the choice of working with virulent flaviviruses like dengue virus, yellow fever virus or the Japanese, St. Louis, Murray Valley, West Nile and tick-borne encephalitis viruses, the YF 17D vaccine strain seemed like a no brainer. With great help from Edith Lenches, a stoic Hungarian technician in the Strauss lab, we spent years optimizing conditions for virus growth and partial purification of the virus. With high quality genome RNA in hand, and the assistance of three Caltech undergrads, we were able to clone and determine the sequence of YF 17D and, a few years later, the Asibi strain. Our YF sequences, together with the West Nile virus sequences reported by Gerd and Gisa Wengler, revealed a genome organization more like the picornaviruses than the alphaviruses – a genome of ~11 kb consisting of a single long ORF flanked by two short non-coding regions. Work from the Wengler lab had shown that flavivirus genome RNAs were capped but not polyadenylated. Rather, the new sequences revealed a potential stable 3’-terminal RNA secondary structure. This set the stage for a new era in flavivirus molecular biology, but what was needed were “infectious clones”.  Given our ongoing Sindbis work, which was beginning to show promise, I decided to make the YF infectious clone effort a priority. Lynn Dalgarno from Australia was on sabbatical in the Strauss lab (Fig. 5) and we had been working together on another flavivirus, Murray Valley encephalitis virus. We became quite good friends and he extended an offer for me to spend some time in his lab at Australia National University. This seemed reasonable since it would allow me to really focus on the YF project. Before I left, I interviewed at a few places for a faculty position and received an offer from Washington University. Earlier, Henry Huang had joined their Microbiology and Immunology department (later changed to Molecular Microbiology). This was an especially attractive option since Henry and I had active Sindbis projects with Sondra Schlesinger in the Micro department. We had gotten to know Sondra well during her visit to Caltech to do some sequencing of Sindbis defective-interfering particle RNAs. I decided that Wash U was the best option for hitting the ground running, with the added bonus of not going out on any more job interviews. This was despite the not-so-generous start-up package of 60K offered by then department chair, immunologist Joe Davie, and a chorus of warnings from coast-biased colleagues about taking a position in the Midwest. This was surely “career suicide”.  Lynn warned me about the long lag time between ordering and receiving supplies at ANU so I packed up a complete collection of molecular biology enzymes and reagents before heading off to Canberra. My time in the Dalgarno lab was spent trying to assemble a full-length cDNA clone of YF 17D. I made literally hundreds of attempts but failed miserably. The reason: toxicity in *E. coli.* I did make some progress on learning which YF cDNA regions were tolerated versus toxic, which came in handy later. It was frustrating but the process was helped by frequent squash matches, an introduction to Aussie Rules football and a memorable stay on Heron Island, a beautiful coral gem on the Great Barrier Reef. There were some lasting upsides on the science front. With help from my future Wash U colleagues, we submitted a grant to the US Army to continue our YF efforts and I was selected to apply for the second class of the Pew Scholars Program. Fortunately, both were successful. Some years later, residual Pew funds helped jump start our work on hepatitis C.  Having survived left side drivers and a highly territorial Aussie magpie that swooped me whenever I wasn’t looking, it was time to return to Pasadena, pack up and head to St. Louis. The VW Rabbit, now 10 years older and showing its age, was loaded up with precious lab samples and my wine collection. I drove straight to St. Louis, acquiring two speeding tickets on the way. Besides setting up the lab, my first task was to write an NIH grant on the Sindbis work for the February 1986 deadline. It was painful (I wanted to be doing experiments), but I was excited: we finally had a functional Sindbis clone and I was able to borrow an Apple Macintosh 512K computer to help streamline the writing. What fun! Temperature sensitive mutants could finally be assigned to specific viral proteins, the Sindbis machinery could be engineered to express heterologous proteins rapidly and at high levels, and variants could be selected that were non-cytopathic in vertebrate cells.  The early years of the lab were a bit slow but productive. We “worked” all the time but also took time off to have fun outside the lab. I also met my life partner, Peggy MacDonald, and her chocolate Labrador retriever, Bonnie. Most of the first crop of PhD students worked on Sindbis projects, I continued slogging away on YF 17D. I tried installing dual transcription terminators at the 5’ and 3’ YF-plasmid boundaries, low copy plasmids, different *E. coli* hosts, and finally I just abandoned plasmids altogether and tried lambda phage. I figured that if lambda was going to lyse the bacterial host anyway, maybe flavivirus cDNA toxicity wouldn’t be an issue. Not so – it did work but the recombinant phage was unstable and the burst size was so small that DNA yields were too low to be useful. The polymerase chain reaction was seeing increased use but in those days the error rate was high, and it was difficult to amplify long templates. From my failed attempts in Australia and at Wash U, I knew that the full-length cDNA could be propagated in *E. coli* as two plasmids that could be designed to overlap by unique restriction enzyme sites. Why not try assembling the full-length template for SP6 transcription by in vitro ligation and completely avoid trying to amplify the full-length YF cDNA in bacteria? This took some optimization, but it worked. A modern version of this strategy is still used today to assemble flavivirus and coronavirus DNA templates for in vitro transcription of full-length genome RNAs.  Energized and hopeful, we sent the paper off to *Science*. As I recall, it went through 2 rounds of reviews that were largely favorable, but it was ultimately rejected because of a perceived “lack of general interest”. A new journal, *The New Biologist*, offered to publish the work and it finally appeared in 1989. *The New Biologist* perished a few years later, making these reprints a real collector’s item. I don’t have any, so don’t bother contacting me.  Nonetheless, we were finally poised to explore the molecular genetics of YFV. The top priority was to understand the molecular basis of the attenuated YF 17D vaccine strain. This would involve making an Asibi infectious clone, testing the resulting virus for virulence in rhesus macaques, and then making a series of 17D/Asibi recombinant viruses to map the changes responsible for attenuation. This was a collaboration with Joel Dalrymple at USAMRIID who had made the Asibi RNA that we used for cloning and sequencing. Joel would undertake the NHP work, my lab would make and characterize the chimeras in cell culture models and make stocks for animal inoculation. Tragically, Joel developed aggressive kidney cancer and passed away a few years later at the age of 53. Without our USAMRIID collaborator and internal advocate, the project stalled and remains unfinished to this day.  Other work on YF was progressing. We determined the order and boundaries of the mature flavivirus proteins and began to unravel the complex proteolytic processing scheme involved in their production. One key player was a viral serine protease embedded in the polyprotein that mediated cleavages required for assembly of infectious virus and the membrane associated RNA replication machinery. We could show that this protease activity was essential, as were each of its seven site-specific cleavages in the YF polyprotein.  At the time, we were not working on non-A, non-B post-transfusion hepatitis. From work in the chimpanzee model, the mystery agent appeared to be a small, enveloped virus, but its true identity was unknown; attempts to culture it in the laboratory had failed. Unexplained cases of hepatitis were on my mind, however, given the death of a close friend’s mother from acute liver failure, cause unknown.  This changed shortly after the 1989 publication of landmark papers from Michael Houghton, Harvey Alter and their colleagues, identifying a new positive-strand RNA virus (called hepatitis C virus, HCV), with a genome of about 10 kb, as the cause of non-A, non-B post transfusion hepatitis. HCV infection was widespread, usually chronic and associated with mild to advanced liver disease, including cirrhosis and cancer. The sequence of the virus revealed a single long open reading frame encoding a polyprotein with features strikingly similar to members of the *Flaviviridae*, including the classical flaviviruses and the animal pestiviruses. A new virus member had joined our family.  As a relatively new Assistant Professor, it didn’t make much sense to start working on a virus that couldn’t be grown in the laboratory. This brief period of sanity was derailed by a phone call from Steve Feinstone at the FDA who had read our YF 17D infectious clone paper. Steve wondered if this couldn’t be leveraged to produce a vaccine against HCV. Steve, a co-discoverer of HAV, had been characterizing the non-A, non-B agent in the chimpanzee model and, like many others, was attempting to identify the causal virus.  With Steve’s nudge and encouragement, we decided to collaborate and started working on HCV, with the initial goal of learning more about HCV polyprotein processing and the functions of the resulting mature viral proteins – very similar to what we had done for YF. Steve had access to some of Harvey Alter’s famous patient H plasma obtained in 1977 during the acute phase of infection and shown to be highly infectious in chimpanzees. The first step was to make HCV H-strain cDNA clones for expression studies in mammalian cells and in bacteria, to make regionspecific antigens, and a panel of HCV-specific antisera. The problem? No one in the lab wanted to work on HCV. Generating antisera was boring and besides, there was no “virus” to work with in the lab.  Arash Grakoui (Fig. 6) stepped up to the plate in my lab, Steve and his team pitched in and together we managed to generate a near complete map of the HCV polyprotein cleavage products, identify two HCV-encoded proteases and their cleavage sites, and start some collaborative work on other predicted HCV enzymes. We weren’t alone. Other groups in the US, Europe and Japan were reporting similar results and the HCV research community was growing. There was a sense of the field’s importance, a mutual respect for our colleagues and competitors, and open sharing of ideas and materials. This nurturing atmosphere was seeded in large part by Michael Houghton, who initiated and anchored a yearly international HCV meeting where he would highlight and applaud every advance in the field.  But the central problem persisted. Advances were being made, but we still didn’t have an HCV permissive cell culture system. I seemed to be on a downward spiral, starting with a virologist-friendly alphavirus, then a more challenging flavivirus and now, a virus that we couldn’t even grow in the lab. We began to work on the animal pestiviruses, the closest relatives to HCV at the time, and which replicated in cell culture. This provided some needed experimental “relief”, but we hadn’t given up on HCV.  Early on, we had decided to try a “reverse” strategy. If we couldn’t get infectious patient or chimpanzee serum to infect cells in culture, perhaps we could raise our chances by using infectious clone-derived HCV RNA. We would have an unlimited supply of infectious material to screen for permissive cells and conditions. The dilemma was how to assay infectivity – there was only the chimpanzee model and intra hepatic injection of a 9.6 kb RNA and hoping it would be taken up by hepatocytes, intact, seemed like a stretch. It wasn’t completely far-fetched though, given that Susan Emerson and Robert Purcell had successfully taken this approach years earlier for hepatitis A virus RNA in marmosets.  We assembled what we believed was a full-length cDNA clone from Harvey Alter’s H77 material, made RNA and Steve injected this intrahepatically into chimpanzees. Nothing happened – no evidence of HCV RNA in circulation but we did learn the input RNA was very rapidly degraded and quickly became undetectable. Disappointing but perhaps not too surprising given this crude and likely inefficient RNA transfection attempt.  At this time, we began to wonder about our full-length clone. Was it really full-length, or might there be something missing? HCV sequences were being reported around the world and while the original sequence reported by the Houghton group terminated with polyA, the subsequent sequences suggested polyU. A careful analysis of the cDNA cloning methods used suggested that they could be biased. Alexander “Sasha” Kolykhalov, a superbly talented molecular biologist who had immigrated from Russia, took on the challenging task of confirming or extending the 5’ and 3’ terminal sequences of the HCV genome. Had Sasha not joined my group, I doubt that I would be writing this piece. Immigrants have and continue to make some of the most impactful contributions to US and global success stories. Isolating ourselves from this flow of untapped talent is a sure formula for disaster.  I will keep the next specifics to a minimum since they are covered in my [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2020/rice/lecture/). Sasha went on to discover a missing piece at the 3’ end of the HCV genome RNA. This later turned out to be absolutely required for virus replication. However, modifying our existing clones with this new sequence still failed to initiate productive replication in chimpanzees. Why was this? We worried about everything. Missing sequences, transfection method, a requirement for RNA modifications or a viral protein for infectivity, lethal mistakes in our clone, and more. The list was daunting. Sasha cloned and assembled hundreds of full-length cDNA clones, tested them with restriction enzyme digestions and in culture for polyprotein translation. He sequenced a subset that passed these criteria and used this information to assemble a clone that reflected the dominant H77 consensus sequence. When Steve inoculated this RNA into two animals, we saw a rise in circulating HCV RNA, characteristic liver inflammation and delayed seroconversion; both animals went on to chronic infection. After eight years of working on HCV, we finally had an infectious clone; more examples followed soon thereafter. The journal *Science* did accept this one.  Despite being validated *in vivo*, transcripts from HCV consensus clones were unable to replicate in cell culture. Another breakthrough, another roadblock. Many laboratories tried different HCV isolates, diverse cell types and conditions, but nothing worked. The ability to launch infection in the chimp model opened up new possibilities to study HCV evolution, immunity and test the impact of mutations on virus viability but the cell culture roadblock remained. Overcoming this was important, not just for studying the virus lifecycle but also for developing antiviral drugs. Without a cell-based assay supporting virus replication, potent inhibitors could be developed using biochemical assays but there was no convenient pre-clinical assay to test and optimize their efficacy at blocking virus replication.  The next breakthrough, reported in *Science* in 1999, was from Ralf Bartenschlager’s lab at the University of Mainz in Germany. Like many in the field, Ralf and his student, Volker Lohmann, were close to quitting their efforts on HCV and moving on but decided to try one more last-ditch effort. Starting with a consensus clone for a German isolate, they engineered an HCV RNA where the portion of the ORF encoding the virus structural proteins was replaced by the gene for neomycin resistance. This was followed by an internal ribosome entry site from encephalomyocarditis virus (EMCV) to drive translation of the HCV proteins needed for viral RNA amplification. If this engineered RNA could replicate and express the drug resistance gene, then cells would be resistant to the drug and able grow in its presence. It worked – a few drug-resistant colonies appeared and the HCV subgenomic replicon system was born. We had been trying a similar approach with our H77 infectious clone but failed to detect any drug-resistant colonies. In need of a positive control, we assembled the Bartenschlager subgenomic replicon using synthetic oligonucleotides and confirmed their results. Remarkably, when we and others sequenced the HCV RNA present in these rare colonies, it was not the sequence of the input RNA. When even single changes were engineered back into the original replicon sequence, some of them raised the efficiency of drug resistant colony formation by more that 10,000-fold. Ten years after HCV’s discovery, we finally had a robust cell culture system for studying RNA replication and aiding drug development.  At this point, another phone call ushered in a major change in my life. Steve Goff, a virologist at Columbia, was on the line asking if I would visit Rockefeller University and advise a committee tasked with finding someone to head a new Tri-Institutional “Center for the Study of Hepatitis C”. One thing led to another, and I was offered the position. But I was perfectly happy at Wash U. My stint as interim chair of Micro was finished so I could really focus on research, and, being an outdoor, non-city type, I had always done my best to avoid New York City. Not to mention that Rockefeller, with its stratospheric reputation, didn’t seem like the right landing pad for a plodding molecular virologist. After some tough soul searching and a nudge from my scientific grandfather, Jim Darnell (you should do this!), Peggy and I decided to make the move. Peggy gave up her tenure track faculty position at Wash U, and we moved to NYC in mid-2000 to an apartment that was about 50 yards from the Rockefeller campus. Our two rescue dogs, Sadie and Wrangler, were not happy with the loss of their yard and the new digs. But we all managed to adjust aided by the vibrant scientific atmosphere at Rockefeller, wonderful colleagues who, after all, were not that scary, and a beautiful park-like campus.  Not many of the Wash U crew were able to relocate from St. Louis to NYC so the first years were spent rebuilding the group, closing the Wash U lab and waiting for our renovated space in the RU Hospital building to be finished. I was fortunate to have a few previous trainees return to the lab for postdocs as well as two senior scientists who joined the Center and formed groups working on HCV immunology and virus entry (using pseudovirus approaches since we still lacked cell culture infectious HCV). We also solidified interactions with clinical colleagues and the Clinical Director of the Center, Ira Jacobson, who is a renowned clinical hepatologist working at the time at Weill-Cornell and New York Presbyterian Hospital. Ira shared over the years a wealth of knowledge regarding important aspects of HCV diagnosis, treatment, and challenges that HCV infected individuals face, helping to keep the ultimate goal of the research clearly in sight.  From the HCV replicon work, the next step was obvious but when adaptive mutations were placed in full-length, otherwise unmodified HCV RNAs, they replicated and expressed the expected HCV proteins, but no virus was produced. A major advance, another roadblock. This became yet another annoyance for the field that persisted for another 5 years. This was finally solved by a serendipitous finding in Japan by Takaji Wakita. Takaji was studying an HCV isolate from a rare case of acute fulminant disease (Japanese fulminant hepatitis 1, or JFH1). Perhaps this virus, given its atypical pathogenesis in the patient might be able to replicate in culture. When he tested a JFH replicon, it replicated efficiently in human hepatoma cells with no need for adaptation. Later work by three groups, including ours, showed that JHF1 or chimeric HCV derivatives could produce virus that was infectious in cell culture, chimpanzees, and mice engrafted with human hepatocytes. More than 15 years after HCV’s discovery, we finally had a complete cell culture replication system.  It was another six years before the first HCV protease inhibitors entered the clinic and several more years before IFN was abandoned in favor of effective drug cocktails that could eliminate the virus in virtually everyone treated, with minimal side effects. In the intervening years, much was learned about the intricacies of HCV RNA replication, virus entry, and the host cell factors important for virus infection. Efforts ramped up in the biotech and pharma sectors working to identify and optimize drugs for inhibition, to identify resistance mutations and their effect on viral fitness, and to test combinations of drugs for efficacy against the diversity of HCV genotypes present in the infected population and to determine the minimal duration to achieve a cure – elimination of the virus from an infected individual! The ultimate outcome, combination drug cocktails capable of achieving virological cure in two to three months across multiple HCV genotypes, was an amazing culmination of the hard work of so many individuals, across a diverse spectrum of fields. Looking back, I feel incredibly fortunate to have had, by a series of chance events in my life, the opportunity to be a part of this effort, and to see first-hand the role that basic science can play towards helping patients afflicted with a devastating disease. Not every basic scientist will be so lucky to be in such a “right place at the right time”, but the future cannot be predicted, and random chance could strike at any time. I urge all young (and not so young) scientists to embrace their passion, follow their curiosity where it leads them, work hard, and to be fair and open in sharing ideas and reagents. No one discovery is likely to change the world, but the collective work of all of you will. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0510=CR  Charles M. Rice: Hello?  Adam Smith: Hello, am I speaking Charles Rice?  CR: You are.  AS: Well, first of all congratulations on the award of the Nobel Prize.  CR: Well, I am absolutely stunned. I guess when you get it… when you get a call like this and you’re not expecting it, you pretty much don’t know what to say. But this is really a big surprise, not the fact that Hepatitis C is being you know sort of recognised. I heard just a short time ago that Harvey Altern and Mike Haughton were also co-laureates for this Prize, and, you know, they really deserve an incredible amount of credit. I feel as though I’m just kind of a representative of the sort of molecular virologist community that contributed something to this fight against this disease.  AS: I mean it’s a beautiful story of a kind of chain of discovery over a long period of time. People… One person handing to the next, one team handing to the next. It’s how science should work, isn’t it?  CR: Yeah. No, I think it was really a, you know, has been, just a joy actually to work in this community. I think people have been very generous, you know, sort of with ideas and reagents. And that, together with the input of biotech and pharma, finally sort of came to the finish line in terms of developing these drugs that are so effective, that we have today. Now we still have some challenges in terms of making sure that everybody that needs them gets them and gets treated, but it is, I think, a success story for biomedical science and team science. And we’re seeing really an amazing follow-up example of that with the pandemic and the number of groups that have stepped up to the plate to work on SARS-CoV-2. And, you know, the pace at which new discoveries are being made, and I hope will impact the control of the pandemic is really staggering. It’s really amazing.  AS: Indeed, because at Rockefeller for instance, your lab and others are very much involved in this current race.  CR: Yeah, I mean it’s interesting because I think it has become a priority, particularly for virologists I guess, but, you know, this week we are sort of preparing some papers that we hope to get submitted on various aspects of coronaviruses that we’ve really been spending a lot of attention on over the last six months. And, as I said, the activity around the world on this virus is breath taking, and it’s changing the way that science is done. It shows you what can be done if people really mobilise and work together and bring different expertise to a common problem.  AS: The award of the Nobel Prize can often be a bit of a distraction. I guess it’s especially important in your case that you don’t get distracted at this point.  CR: Well, yeah, I mean this does come as a bit of a distracting influence I suspect. Maybe not quite as much as it would under normal circumstances. I’ll probably shortly be sending an email to the group, you know, sort of working on these subjects and papers to tell them to, you know, keep it up.  AS: Well, yes, I guess it’s an extra boost for all virologists, everyone working on viruses around the world, that viruses are again recognised by the Prize.  CR: Yes, I guess you know that’s the other thing that you know we don’t engage in these activities to win prizes.  AS: Indeed. Well I must say that for somebody who’s had a surprise call very early in the morning, you do sound remarkably collected and …  CR: I don’t know, you know it’s… On this particular phone the only calls that we seem to get are you know sort of robo-calls, so when the phone went off you know at sort of 4:30 in the morning I thought ‘well, it’s probably one of our minus 80 freezers that’s warming up’. I didn’t pick it up the first time, because I was sort of half asleep, and it rang again and it was, you know, it’s still dark here so you know I couldn’t really see which button to push. But I guess I pushed the sort of talk button and there was the secretariat. It still took a few minutes to click.  AS: Well I look forward to speaking again at greater length. But, for now, congratulations and thank you for the call.  CR: Okay, thank you Adam.  AS: Thank you. Bye.  CR: Take care, bye bye. |
| Interview |  |
| Q1 | Why did you decide to pursue science? |
|  | I think it’s really just fundamental curiosity. I’ve always been interested in sort of nature, biology and the outdoors, amongst many other things. So I think I was somewhat unfocused coming out of my early education. And that was certainly the case when I went to college. I wasn’t really sure what I wanted to do. |
| Q25 | Were there any defining moments that influenced your career? |
|  | There were really just a series of experiences. One of them was just a really talented teacher of an introductory biology class, Dennis Barrett, who just really was a great teacher and got the class motivated and got people interacting with each other to sort of discuss different aspects of concepts that he was trying to get across. I think that connection really sort of changed my life in a sense because we actually became pretty good friends and I did some research as an undergraduate with him.  Then he actually sort of guided me towards going to the Marine biology laboratory in Massachusetts. This was a summer program for very young science learning (sort of) trainees. I did this in between my junior and senior year. It was just an amazing experience because it was basically several months in the summer where you’re just doing nothing but listening to the scientists, that are hanging out in Woods Hole (which is a nice place to spend the summer) and sort of listening to lectures, spending a lot of time in the lab, just experiencing different kinds of research techniques ranging from biophysical things to immunology and other stuff. It was a life changing experience, but I still wasn’t a hundred percent sure that I wanted to do research when I graduated from college. So I kind of wandered in central and South America because I was also growing up in California. You get exposed to a lot Spanish speaking people so I was kind of a Spanish literature minor in college. I decided to just take some time off and I applied to graduate school and then basically took off on the road and became a vagabond for the better part of a year, and then ended up returning to go to graduate school. |
| Q1 | Were there more reasons for why you became a scientist? |
|  | It was really those experiences in college I think that got me hooked on research and then the experience of actually doing a PhD at a fantastic institution with a great group of peers and role models at Caltech. I was hooked and that was another random occurrence in the sense that I was really interested in fundamental sort of developmental biology, what happens when an egg gets fertilised and sort of early events in embryogenesis. Then I ended up, when I arrived at Caltech, getting placed in a biology lab instead of a developmental biology lab. And that was that. I enjoyed it and just sort of kept working on viruses from that time on and throughout my career. |
| Q3 | How do you deal with failure? |
|  | Well, I don’t know. It sort of depends on how you view failure, because I guess there are different degrees of failure. I mean, one is that you sort of designed an experiment and then you just screwed it up. There was some sort of technical glitch or whatever that makes the results uninterpretable and if you can identify that and troubleshoot and then get the experiment back on track so that you get an answer that you can believe in – that’s part of the scientific process. But even when an experiment works, you have probably an idea as to what the expected outcome is going to be. If it’s a hypothesis driven experiment and the results don’t often support your hypothesis so you may end up with a well-executed experiment, really nice data and it’s just unexpected and you don’t know how to explain those results.  I guess there are two sorts of mentalities when you’re sort of confronted with that situation. One is, ‘Oh, these results don’t fit my hypothesis, I’m going to just give up.’ The other mentality is, ‘Well, this is a well-executed experiment, I’ve got the right controls. It’s giving me an answer that I didn’t expect.’ And that is, I think, the greatest opportunity in science – to actually view a result and you can either view it as failure or something unexpected and an opportunity. I think that the results of an initial experiment are usually not the end of the sort of investigation there, they’re more of the beginning. So maybe [failure] is a matter of semantics in a way and a matter of perception. |
| Q12 | What advice do you usually give to young researchers? |
|  | I think to really make an advance is hard work. I think to be a successful scientist, you almost have to deal with our vocation as not a job as it’s more of a hobby and that we’re fortunately allowed to continue at least to some extent, depending upon what the funding agencies will let us get away with. So I think you have to have a passion for what you’re doing, so that some of these results they could be discouraging now, you just take them as a matter of course and move on. I think it’s hard work, but if it’s work for you, then you should probably do something else.  I think the successful scientists are really doing it because they’re curious and they’re doing this because there’s nothing else we’d rather be doing. I guess we sometimes get called workaholics or things like that. I would say maybe we’re more hobbyholics in the sense that we have been fortunate enough to have what we get paid to do as our hobby. I think that’s, to me, the sort of guiding principle for young scientists. You want to try and find something that you have a passion for, and then really just sort of follow that. |
| Q39 | Do you have a lot of pets? |
|  | I am a dog fan. I’m an only child, so I didn’t have brothers and sisters but I had a continuous series of dogs from the time that I was a little boy. One of the pictures that I still have is something that my parents had taken with me when I was, I think, three years old and a basket with a bunch of puppies.  Today we have two dogs. We have a fairly dog-friendly campus here so the students that live on campus can have dogs and the sort of housing that we have right next to campus is pet friendly. My dogs sometimes come in here to the office. |
| Q7 | What do you like to do in your spare time? |
|  | I like the outdoors. We try and get away to a hideaway and a mountain range in Wyoming. We drive out there with the dogs. It’s about a 31 hour track to get to this spot. But it’s about as different as you can imagine from Manhattan. A log cabin that is, 15 miles away from the nearest paved road that’s completely surrounded by undeveloped land that is controlled by the forest service. The dogs of course love this. The only thing we have to contend with is that it does sort of overlap with some cattle grazing rights so that some of the folks that raise cattle allow them to graze in this area. That can create some issues with the dogs who sometimes take an interest in these cows when they’re not supposed to. |
| Q19 | How did you receive the news about your Nobel Prize? |
|  | It was a phone call from the committee secretary. I was by myself here in New York and the call came on a landline at 4:30 in the morning. I was completely asleep. I couldn’t imagine who would be calling me at 4:30 and I got up to sort of go out there and pick it up and yell at whoever was calling me. Then I thought, ‘Oh, it’s just gotta be somebody that hit the wrong number or whatever.’ So I turned around to go back to bed and it stopped ringing and then it started again, and then I kind of stormed into the living room and it was pitch black and I grabbed the phone, which didn’t have a lit dial.  I don’t use this phone very often. I knew there was a connect button and a disconnect button, but I didn’t really know which one I was pushing, but I guess it was the connect button. As a consequence of that the secretary came on the phone and there was this voice with a sort of Swedish accent and it still just really didn’t dawn on me until he said more about the fact that this had to do with hepatitis C and Nobel Prize and [Harvey Alter](https://www.nobelprize.org/prizes/medicine/2020/alter/facts/) and [Michael Houghton](https://www.nobelprize.org/prizes/medicine/2020/houghton/facts/). And I thought, ‘Oh, this is beginning to sound like it might be real.’ It was quite an awakening. After something like that, you don’t go back to sleep. |
| ID | 0511 |
| Biographical | I was born November 23, 1957 in Jamaica, New York City, to William George and Nancy Priscilla (Horn) Kaelin. My mother’s first pregnancy ended in a miscarriage. The obstetrician who delivered me was a friend of my mother’s family. He initially thought I was stillborn and lamented that such obstetrical problems seemed to disproportionately affect his friends. He apparently gave me one last whack, whether for his benefit or mine. Regardless, I began to cry. Eventually, my mother would have four more children, each spaced 2 years apart.  My father went to college and law school at Duke University before becoming an international tax and estate lawyer in Manhattan. My mother majored in mathematics at Adelphi College before becoming an actuary at the Metropolitan Life Insurance Company. She became a homemaker after my birth.  We lived in Jamaica, New York until I was two, at which point we moved to Rockville Centre – a middle-class suburb of New York City on Long Island. There I was enrolled in a public elementary school. I recall the fear of polio and remember being given the oral polio vaccine. That was perhaps my first introduction to the miracles that modern medicine could produce.  On the second day of first grade some male classmates came to my house to play in our small backyard. At one point, while we were roughhousing, I became pinned to the ground under the other boys. Among them was a boy who, I later learned, had been held back in first grade twice for behavioral issues. He was bigger and stronger than the rest of us. He twisted my leg like it was a propeller on a toy airplane (perhaps to emulate the antics of the Three Stooges). I screamed in pain until the boys finally dispersed. I crawled on the ground, unable to walk, until I got to our back door and found my mother. She couldn’t believe that my leg could be broken, so she asked me to stand. I promptly collapsed onto the ground. She drove me to my pediatrician, who confirmed that my leg was broken and put me into a plaster cast to my midthigh. I remember looking at my XRAY on our way home (even I could tell my leg was broken).  For the next 8 weeks I was homebound and largely immobilized, although I could motor around the house if I slid on my buttocks. A tutor came to my house each day so that I wouldn’t fall behind in my classwork. When I returned to school, I was actually so far ahead that I thought I might somehow get in trouble. I remember sitting at my desk and surreptitiously erasing and then redoing afresh the assignments that my classmates were being given for the first time. I sometimes wonder whether all of the individual attention I received while homeschooled contributed to my intellectual development and academic achievements later on. At the same time, I also wonder whether it contributed to my feeling of not quite belonging. This was exacerbated further when I changed schools the next year to attend a Catholic elementary school (St. Agnes). There, I found myself once again immersed among students who already knew one another.  At St. Agnes I was taught by lay women and nuns. This was an era, sadly, when most bright women were told that their career options were: nurse, teacher, or nun. I am sure that some of my female teachers in elementary school (and later high school) would today be lawyers, doctors, college professors, or CEOs. I did extremely well at school until the fifth grade, when two things happened. First, the coolest kid in the class befriended me. By association, I suddenly became cool. Second, I was taught by a young, attractive, nun rather than a lay sexagenarian (at least that’s how old they felt to me). Both of these things led to a lot of acting out on my part, including misbehavior and failure to do my homework. The standard punishments included afterschool detentions and writing out multiple copies of the multiplication table from 1×1 to 12×12. The worse the offense, the more copies you had to write out. I remember once sitting in my backyard writing out 40 copies of the multiplication table. The silver lining was that I was already good in math and now knew multiplication (and hence division) cold.  In those days, I was getting in the low 90s or high 80s (out of 100) in my subjects despite my antics. One day, my fifth grade teacher called my parents and told them that I should be doing *much* better in school given my aptitude (i.e. I was coasting). After that, my study habits improved somewhat, but they were not exemplary.  My father loved to fish, and we spent many hours fishing together. I think there are many analogies between fishing and science. Two keys to success in fishing are technical expertise (e.g., how to bait a hook) and intuition (e.g., knowing where to fish). Both are easier to learn by apprenticeship than from a book. Similar considerations apply in science. But technical expertise and intuition only get you so far; you also need luck. On any given day the biggest fish might be caught by a novice rather than an expert. The same is true of scientific discovery.  In the 1960s, science was celebrated in the United States due to the cold war and the space race. Like many young boys, I had a toy microscope, chemistry sets (with chemicals that were actually dangerous), electric cars and trains, an erector set, and other toys that stimulated an interest in science. I threw tickertape and confetti at the triumphant Apollo astronauts from my father’s Wall Street office. I also had ample unstructured time to play, whether it was going to the beach, tossing a ball, collecting postage stamps, running a lemonade stand, or making up games with neighborhood children. I regret, however, spending so much time watching television rather than reading.  By the late 1960s, my father could afford a much larger home. He wanted to live in a town within commuting distance of New York that had strong public schools rather than pay five private school tuitions. We moved to Fairfield, Connecticut in the summer of 1970, and I began the eighth grade that September. Entering adolescence is always challenging. In this case, it was complicated by entering a new school system. This exacerbated my shyness. We now had a beautiful house with a swimming pool, but only a handful of other children lived within walking or bicycling distance. Fortunately, I had a few neighborhood friends with whom to play touch football or ice hockey when a nearby pond froze over in winter.  The other problem was that many of my school subjects were taught in tracks, with track one reserved for the most gifted students. As a newcomer, I was placed into track two. This lack of stimulation likely contributed to my poor study habits until and including my high school junior year. I would typically sit in the back of the room and silently scoff at the kids who sat at the front, raising their hands obsequiously at every opportunity. I did the minimum amount of homework necessary and never reviewed the material covered in class that day. My one saving grace was that I did well in mathematics without really trying, and consistently did well on mathematic aptitude tests. As a result, my report cards usually contained an “A” in mathematics and a mixture of “A”s and (mostly) “B”s in other subjects. During this period, it became even clearer that I liked quantitative/objective subjects and disliked qualitative/subjective subjects. I liked learning concepts and ideas and abhorred rote memorization. I was interested in science, but I found biology pretty boring because it was largely descriptive. Chemistry and physics were more my speed. During this time, I learned that I tended to like the things that I was good at and tended to be good at the things that I liked.  During my junior year, my high school, Roger Ludlowe, got a computer terminal that was connected to a mainframe at Fairfield University. Although I was good at mathematics, I did not see a career for myself in mathematics. Computers seemed like an exciting way to put mathematics to work. And I liked that in computer science, as in mathematics, there were objective ways of knowing whether your solutions were correct or “worked”. I began learning various programming languages and would sometimes bicycle to Fairfield University after school to get input from the faculty there.  One day, during my junior year, I was sitting at the Roger Ludlowe computer terminal and saw a lone pamphlet in the waste bin. It described an eight-week National Science Foundation Student Science Training Program in Mathematics and Computer Science held at Florida Atlantic University for 32 “gifted” high school students. I applied and was accepted.  On my flight to Florida, I met another boy on his way to the same program. He had many books he was reading simply for pleasure, including mathematics books and challenging fiction books such as “Gravity’s Rainbow”. He, like all of the other high school students that summer, were amongst the brightest students I had ever met. I was pleasantly surprised, however, to discover that I could hold my own with them in the college level courses that we took that summer. And I discovered that I did better in school when the material was interesting and challenging and when I was surrounded by exceptionally smart people. For the first time in my academic life, I went to the library to checkout extra books to supplement my assigned reading and would work past midnight solving mathematics problems or writing code.  My fellow summer students and I were given a Russian Math Olympiad test (or its equivalent). It contained the kind of advanced, abstract mathematics problems that could be solved without having had prior formal instruction if you were naturally gifted in mathematics. It was the most challenging test I had ever seen. I was initially crestfallen when I received a score of ~45, the worst grade I had ever gotten. I then looked around and saw that many other students had done much worse. My ego fleetingly recovered until I saw that one of the other students, however, had scored ~145. I shouldn’t have been surprised. He was the one student who was a much better programmer than I was. For example, while I wrote a computer program for playing draw poker as one of my final projects, he wrote a program for playing bridge. I decided that he was the kind of genius who would become an academic mathematician, whereas I better find something more practical. I didn’t see the personal computer revolution coming and didn’t want to write computer code for industrial or military applications. I thought a career in medicine could be the answer (ironically, “Mr. 145” also became a medical doctor).  Although I was delighted to learn that I wasn’t the dumbest of the 32 students that summer, I certainly had the worst high school grades because of my prior poor study habits. I decided I would try an experiment for my senior year. I would sit in the front of the classroom and actively participate, befriend (rather than belittle) the smart kids in class, do all my homework (and extra credit problems) on time, and review the lessons that we had each day. I successfully petitioned to be placed in all track “1” classes and to take precalculus and advanced placement calculus in parallel rather than in series. I put a bulletin board in my bedroom for my hoped for “A”s. And I determined that I would only have fun on the weekends if had done well at school that week.  My plan worked. I got straight “A”s. I also did very well on the scholastic aptitude test (SAT) and achievement tests required for college. I was a “late bloomer”.  My father, the son of a laborer, was the first member of his family to attend college. Given his parents’ modest means, he sought an up-and-coming school that was still affordable. He applied to Duke, which seemed to fit the bill, and was rejected. He then hitchhiked from his Long Island home to Durham, North Carolina (in the 1950s, this took him several days) to plead his case. The admissions staff, either due to admiration or pity, interviewed him and gave him an aptitude test. His performance earned him admission. While at Duke, my father did a number of odd jobs to pay for his education, including illegally selling sandwiches in the dormitories. He received a scholarship to attend Duke Law School and was allowed to combine his senior year of college with his first year of law school to defray costs. My father was fiercely loyal to Duke and dreamt that I, his eldest son, would also attend Duke.  I applied to Duke and flew to Durham to be interviewed. My father was elated because the associate admissions director, who was one of his former Duke classmates, winked at him as I left the interview to let him know that I would likely be admitted.  I also applied to Harvard and MIT (in those days, “late bloomers” could still get into an elite school. Sadly, this doesn’t seem true today). I visited Harvard with “Mr. 145” and one of his classmates. We stayed overnight in a small dormitory. The 12 students it housed had us stand in the middle of their commons area that evening to tell them our name, our hometown, and our SAT scores. When “Mr. 145” and his friend finished both were told “you will get in”. When I gave my SAT scores, they said “you might want to apply to Brown”. In fairness, my verbal score wasn’t as strong as my math score, and they were correct because I was waitlisted.  I was immensely proud, however, when I was accepted to MIT. I walked into my father’s den and told him I was leaning toward MIT. He put down his scotch and asked, “Don’t you have to be good in math to get into MIT?”, to which I of course said “Yes”. He then said, “I am going to give you a math problem, if you go to MIT, you’ll pay your tuition, but if you go to Duke, I’ll pay your tuition”. I quickly did the math. Truthfully, however, I did go back and forth as to whether Duke might be a better choice for a future physician. And I thought I might get more attention at Duke than at MIT (where I assumed they had a sea of “145”s).  My Duke freshman class contained many students who clearly had functioned at a high level for years. I felt like I was just getting started, and I was fascinated to see what kind of grades I could get if I really applied myself (I am embarrassed that it was still largely about grades for me back then).  I majored in mathematics and, partly to fulfill premedical requirements, chemistry. There were many premedical students at Duke, and it was widely believed that you needed an “A” in Organic Chemistry to get into medical school. I excelled at freshman Inorganic Chemistry because it was logical, conceptual, and quantitative (plus I had an outstanding high school chemistry teacher, Mr. Ralph Minopoli). Organic Chemistry required much more rote memorization. My first Organic Chemistry exam I got a “C” despite studying very hard. The next two exams I got a “B” and then an “A–.” Miraculously, I got an “A+” on the final exam and therefore got an “A” for the term. I had dodged a bullet. I promised myself that I would not dig myself into such a hole the next term, and yet the same test score pattern repeated itself. My assumption is that the rote memorizers couldn’t remember the material from the first exam by the time they got to the final, whereas perhaps I assimilated some concepts after all. However, I haven’t excluded divine intervention.  I earned a higher grade point average at Duke than I did in high school. Ironically, one of my few “Bs” was in Human Physiology, which only reaffirmed my inclination to avoid (largely descriptive) biology courses. I was one of the best mathematics students at Duke, but I worried that I was simply a big fish in a smallish pond. I therefore continued to think about medicine. A friend suggested that I do a laboratory research project to embellish my medical school applications.  My junior year, I met with a physical chemist at Duke about a research project that involved studying the folding of cytochrome C using electron paramagnetic resonance (EPR). I could begin the following summer and continue into the fall semester. He told me that the seven undergraduates who had worked on this project previously had all gone onto medical school. I left his office thinking I had found the golden ticket to medical school.  Now, looking back, I realize I should have asked why my seven predecessors couldn’t bring this project to completion. I soon discovered why. I was given a bench to work at and my predecessors’ notebooks, but no real instructions from my mentor. In fact, he and I barely interacted. None of the other scientists in his laboratory worked on anything even remotely related to my project. Many of them did exclusively dry bench research, and none of them were protein biochemists. I was supposed to covalently couple a spin label to cytochrome C, separate the modified cytochrome C from the unmodified cytochrome C, and then study the labeled Cytochrome by EPR in response to chemical denaturants. I was lost. I assumed that some people intuitively knew what to do in the laboratory and that others, including me, did not. This experience convinced me that I could assimilate old knowledge but lacked what it took to create new knowledge (at least in the laboratory).  That fall, I attended a lecture by a visiting cytochrome C expert. He was kind enough to briefly discuss my project. His first question was simply to ask me “why?” – specifically, “why are you doing this?” He proceeded to tell me that the conditions proposed to covalently add the spin label were already going to denature my protein, and that the purification method recommended by my mentor was going to separate denatured protein from native protein rather than labeled native protein from unlabeled native protein.  I presented my various concerns about my project to my professor. During my senior year Christmas break, I received a special delivery letter indicating that he had given me a “C–” for my independent study project. He also wrote in the margin that “Mr. Kaelin appears to be a bright young man whose future lies outside the laboratory.”  Despite this debacle, I was accepted to several medical schools, including Duke (I was again rejected by Harvard). The medical school basic science curriculum in those days involved a mind-numbing amount of memorization. One thing that saved me was that Duke compressed the standard two years of basic science into one year. The first year was hard for me, but I felt I could withstand anything for one year (although I did wonder if I had made a mistake not pursuing mathematics and computer science). The other saving grace was that the courses were honors/pass/fail, and it was understood that almost no one got honors. You just plowed through.  In the second year, I took the classical clinical rotations of obstetrics/ gynecology, internal medicine, psychiatry, surgery, and pediatrics. I loved each of my rotations and could now see the knowledge gained in the first year in action. It was exhilarating and reaffirmed my decision to go to medical school. My internal medicine chief resident was Dr. Paul Klotman. I thought he was the smartest, funniest, coolest person I had ever met. I decided then and there that I would be a chief resident one day.  Duke medical students were encouraged to work in a laboratory fulltime for their third year. With some trepidation, I gave laboratory research another try. I worked with Dr. Randy Jirtle, studying tumor blood flow. Randy, in contrast to my first mentor, was very helpful and encouraging. During this time, I read about tumor angiogenesis and the highly vascular tumors linked to von Hippel-Lindau (VHL) disease.  During my third year, Dr. [Michael Bishop](https://www.nobelprize.org/prizes/medicine/1989/bishop/facts/) came to Duke Medical School to give a lecture, which was exhilarating. In it he described the first oncogenes, some of which encoded kinases. I was sure I was seeing the future of oncology and assumed that this would lead to new therapeutics (e.g., kinase inhibitors). Sadly, over the ensuing years, naysayers would tell me why this was naive. It would take people like Alex Levitzki and Alex Matter to prove them wrong.  Although my second laboratory experience was much better than my first, it wasn’t enough to convince me that I had a future in the laboratory. I did my internship and residency in Internal Medicine at Johns Hopkins. I liked Internal Medicine partly because I liked solving complex clinical puzzles.  My chairman when I was an intern was Dr. Victor McKusick. He taught me the importance of medical history and the power of human genetics. My chairman when I was a resident was Dr. Jack Stobo. He conducted weekly “bench to bedside” chalk talks that introduced me to emerging molecular techniques, such as DNA restriction and Southern blotting. It was pretty clear a revolution was about to happen, even if I didn’t think I would be part of it.  A colleague introduced me to Eric Fearon, who was then a medical student with Dr. Bert Vogelstein. Eric had already published several landmark papers in which he applied modern molecular techniques to gain new insights into cancer genetics. He encouraged me to attend one of Bert’s seminars. At the time, it was believed that solid tumors, in contrast to hematological malignancies, were too heterogeneous and complex to study with modern molecular techniques. Bert’s colon cancer studies shattered that view. This was the second lecture, after Michael Bishop’s lecture, where I knew I was seeing the future.  I loved clinical medicine and was honored to be selected to spend an extra year at Johns Hopkins as one of four assistant chiefs of service (equivalent to chief resident). I learned even more clinical medicine that year and, more importantly, met a beautiful fourth year medical student (although she never reported to me!). Carolyn Scerbo would later become my wife, and the mother of my two beautiful children, Kathryn Grace and Tripp.  Chief residents typically love to learn about rare eponymous syndromes, such as von Hippel-Lindau (VHL) Disease. That way, if a trainee challenges their authority on rounds, they can silence them with questions about diseases the trainee has never heard of. For the same reason, chief residents like long differential diagnoses for various signs and symptoms. I had memorized, for example, all of the causes of polycythemia. It struck me as odd that the three hallmark tumors of VHL Disease – kidney cancers, hemangioblastomas, and pheochromocytomas – were among them. This, together with their increased vascularity, suggested to me that the VHL gene was involved in oxygen sensing because angiogenesis and erythropoiesis are normally induced by hypoxia (low oxygen level).  I decided to specialize in medical oncology because I liked multisystem disorders and thought cancer biology was fascinating. I also appreciated that the bane of any internist is distinguishing the sick from the not so sick. This is not an issue with cancer patients.  I moved to Boston in 1987 to be a medical oncology fellow at the Dana-Farber Cancer Institute. I was finally arriving at Harvard, which prompted me to wonder whether Harvard (or I!) had made a mistake. My seven fellow fellows were extremely impressive and most of them had more research experience than I did. I was deemed the most likely of us to become a clinical oncologist rather than a laboratory-based researcher.  One path to medical oncology board certification involves working in a laboratory for 2 years. I thought it would be exciting to see what life was like in a top laboratory, even if I didn’t expect to succeed myself. I interviewed with Dr. Robert Weinberg at MIT, who had just cloned the retinoblastoma gene *RB1*. He was clearly receptive to having a physician-scientist in the laboratory, having trained Dr. Steven Friend, who cloned *RB1*. Bob then got out a ledger and determined that he would have space for me in 3 years. My heart sank because I needed to start that year.  While researching Bob’s laboratory I met Dr. Shelly Bernstein. Shelly, a Weinberg physician-scientist trainee, had just established his own laboratory at the DFCI to study metastasis. I joined Shelly, but I can now appreciate that I was a bit adrift. In my free time, I read a *Science* paper that described PCR-amplification of a K-Ras exon from a paraffin block. Just for fun, I tried to replicate the experiment. To my astonishment it worked! I remember the exhilaration when I turned on the UV box and saw an ethidium-stained band of the correct size. About 4 months after joining Shelly, he told me that he would be closing his laboratory to return to clinical practice. This seemed like another sign that I was not meant to do science! I was an orphan.  My last attending physician during my clinical oncology year was Dr. David Livingston. I knew he ran a laboratory and I went to him for advice. I showed him my PCR result, which perhaps impressed him. Or maybe he saw something else. In any event, he invited me to join his laboratory. It turned out that he, like Bob Weinberg, was studying the *RB1* gene. David’s group and Ed Harlow’s group had discovered that the SV40 T and the adenovirus E1A proteins, respectively, bound to the *RB1* gene product pRB. I was to map the T/E1A-binding region of pRB, and the PCR technique I had learned proved useful for rapidly making pRB mutants. The minimal T/E1A-binding region, which we called the pRB “pocket”, turned out to be a hotspot for cancer-associated *RB1* mutations. We therefore hypothesized that the pRB pocket might bind to one or more cellular proteins. Our initial strategy to find them was to look for coimmunoprecipitating proteins in anti-pRB immunoprecipitates from cells. The problem, however, was that the supply of our workhorse anti-pRB antibody was unreliable.  David decided we needed to make our own anti-pRB antibodies. I was to express pRB fragments in E.Coli and then inject them into rabbits. The trick was to find a suitable prokaryotic expression vector, since protein expression in E.Coli was still fickle back then.  One day, a company representative left me a brochure for a new prokaryotic expression vector that encoded glutathione S-transferase fused to a protein of interest. Such GST fusions were frequently more soluble than their unfused counterparts and could be purified using glutathione sepharose. Ordinarily, the captured protein would be eluted with glutathione prior to its intended use. I realized, however, that I could express GST fused to the pRB pocket, capture it with glutathione sepharose, and then use the immobilized fusion protein to capture pRB-binding proteins. I eventually found a series of anonymous 35S-labelled proteins that had the properties I was looking for: they bound to wild-type, but not mutant, pRB, and were displaced by T/E1A-derived peptides.  I was thrilled when my findings were published in *Cell* and when I was allowed to present it at major meetings. After speaking at the 1990 Cold Spring Harbor Symposium, I walked down to the Robertson House pool, where a lone person was enjoying the afternoon. He told me that my talk was wonderful. I told him that his praise was much appreciated because I had just learned that my National Institutes of Health (NIH) K08 physician-scientist fellowship application to support my work had received a very unfavorable score. Indignant, he asked me which study section evaluated my application. When I told him, he said, “that’s outrageous, I chair that study section”. Shortly thereafter, I was notified by the NIH that my grant would be funded after all.  I still didn’t know the identities of my pRB-binding proteins, or which of them bound directly to pRB. My colleague Myles Brown then told me about the work of Michael Blanar, who had radiolabeled a recombinant protein using radioactive ATP, heart muscle kinase, and a genetically encoded phosphoacceptor site. I redesigned my GST fusion vector so that this phosphoacceptor site was encoded between the GST and pRB moieties. After considerable troubleshooting, I finally produced biologically active, radiolabeled GST-pRB, which I used to probe whole cell extracts in “far western blot” assays. I knew the system worked because I could detect E1A and T in appropriate cell extracts. I also saw a doublet of ~50 kD, which prompted me to team up with one of Dr. Sam Speck’s postdoctoral fellows, Erik Flemington. Erik helped me screen a lambda phage expression library with my radiolabeled GST-pRB. David Livingston, Joe Nevins, and Pradid Raychaudhuri had reported that pRB could bind (directly or indirectly) to a DNA-binding activity called “E2F”. I was elated when my expression cloning strategy yielded the first E2F cDNA (coined E2F1).  Why was I so successful as a postdoctoral fellow? In stark contrast to my first laboratory experience, I was given a great project to work on, in a great laboratory, and with a great mentor. My expectations of myself were so low that I was exhilarated when even the most prosaic experiment, such as restricting DNA or transforming bacteria, actually worked! Importantly, I was still relatively naïve, which can be a blessing in the laboratory. I ambitiously tried many experiments that a more jaded scientist would dismiss as being too risky. And I didn’t know the usual solutions for many problems. This forced me to be resourceful and to look at problems afresh.  In 1992, I started my own laboratory down the hallway from David’s laboratory. I initially did a few E2F experiments, but it was obvious that there were many good laboratories ready to work on this protein. I didn’t want to look back on my scientific career and realize that everything I had done would have been done with or without me. That would hardly justify leaving clinical medicine, which I loved. Moreover, people wisely advised me to begin differentiating my science from David’s science. I briefly attempted to expression clone the *ATM* gene using a functional complementation assay, but without success. In the summer of 1993, however, I read a *Science* paper describing the cloning of the *VHL* tumor suppressor gene and decided that it would be my focus. I assumed that studying the VHL gene would teach us about the pathogenesis of kidney cancer (which is one of the ten most common cancers), about the control of angiogenesis, and potentially about oxygen sensing. This work is described more fully in my written [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2019/kaelin/lecture/). It was supported by the NIH, the Howard Hughes Medical Institute (which I joined in 1998), the Doris Duke Charitable Foundation, the Murray Foundation, and the late Dr. William Shelton.  As a young faculty member, I served as an inpatient clinical attending physician one month a year and would also “moonlight” several nights a month in a community hospital intensive care unit. I stopped seeing patients, however, by the late 1990s. Firstly, I never wanted people to say I was a good scientist for a *physician*-scientist. I tell young physicians that if their choice is to be an “A” clinician or a “B” scientist, they should choose the former. If I was going to try to be an “A” scientist, I knew I had to do it full-time. Second, I soon realized that most of the cancer patients referred to the DFCI had already been diagnosed. The diagnostic puzzles I was solving often related to the iatrogenic complications of their treatments. There is also a saying on the wards that common things are common. There are many things in medicine that are interesting the first or second time you see them, but much less interesting the 20th time you see them. Solving puzzles in the laboratory began to give me the joy I had once found seeing patients. It was also painfully clear that the therapies available for most of my cancer patients were woefully inadequate. I thought that more effective therapies would require the kind of deep insights into cancer pathogenesis that modern molecular biology offered. Lastly, you can’t, by definition, devote yourself fully to two careers. When I was younger, I believed that my patients were lucky to have me as a doctor and I promised myself that I would stop seeing patients if I could no longer defend that view. I had too much respect for my full-time clinical colleagues and my patients to become a part-time clinician with waning skills.  In 2003, several years after the work that led to my Nobel Prize, my wife Carolyn, herself a beloved breast cancer surgeon, developed breast cancer. She ultimately required a mastectomy and chemotherapy. Even though I had taken care of hundreds of cancer patients and their families, I now had a much more visceral understanding of their anguish and pain. Carolyn survived her breast cancer only to develop an unrelated glioblastoma in 2010. She underwent two major brain operations, each requiring months of rehabilitation in order for her to walk again, as well as radiation therapy and chemotherapy. We assembled a “dream team” of talented clinicians and scientists who helped us. For example, her tumor’s genome was sequenced early on as a guide to specific targeted agents. Ultimately, however, we lost her in 2015. Carolyn and I would often joke about what it would be like if I ever won the Nobel Prize. It was bittersweet to receive the Prize without her at my side. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0511=WG  William G. Kaelin: Dr Kaelin speaking.  Adam Smith: Good morning, my name is Adam Smith, I’m calling from Nobelprize.org. Well congratulations on the award of the Nobel Prize.  WK: Thank you.  AS: So, it’s early there, 5am.  WK: Yes it is, yes.  AS: Were you sleeping, or …  WK: Oh I was absolutely … I was asleep. And I’m still in a state of shock so I hope I’ll speak coherently.  AS: You sound very coherent at the moment.  WK: [Laughs] You know, I think every scientist in the world dreams of this possibility and knows what today is, but if you’re realistic you don’t think it’s really going to happen, so I try … I try to treat it like any other night so I was asleep.  AS: May I ask you what your first action was on hanging up the phone after hearing?  WK: I was … again I’m in a state of shock, it’s … obviously it’s absolutely wonderful news, but my heart’s still racing and I think it’s all just sinking in, and unfortunately I lost my wife several years ago so I live alone.  AS: I’m sorry.  WK: And so my first thought was that this is something I’d always, if it did happen, wanted to share with her. But I’m just terribly honoured and I’m glad I can share this with so many people, scientifically and otherwise who have supported me throughout the years.  AS: But that must be a great sadness, I’m sorry.  WK: Thank you.  AS: The link that you discovered, the unexpected link between VHL and HIF-1 is an example of just never knowing where knowledge will come from and where questions will take you.  WK: Yes, absolutely. You know, I’m a big believer of curiosity-driven, hypothesis-driven research. I know that’s complimentary to other ways of generating knowledge but I think in the end what drew me to science and what draws a lot of scientists to science is that we like interesting puzzles, like clinical features of patients who had mutations in the VHL gene were a curious constellation of findings but one way to unify them was there was some abnormality in the way the tumours they were developing were sensing and responding to oxygen, and we thought if we could understand that we could understand more globally how cells and tissues sense and respond to changes in oxygen. And since I, like my co-awardees, am trained as a physician, we understood very well the importance of oxygen in so many human diseases. It appeared that in these particular cancers that were linked to VHL mutations that somehow the tumours had co-opted this process for their own benefit, and that, as you know, has turned out to be correct. So now that we understand the pathway there are a lot of opportunities for pharmacological intervention, in diseases such as cancer but also other diseases including heart attacks and stroke. But I come back to what you said earlier – I think in the end it was a very interesting puzzle to try to solve.  AS: You raise a very interesting point that all three of you are physician scientists. That does, I guess, give you a different perspective on your work. Do you think it’s very important that there are more physician scientists coming along?  WK: Well, first of all I’m very proud to share the Prize with two wonderful physician scientists, but I also like to point out to people that I think scientists in general, and in particular physician scientists, are under tremendous pressure these days, to try to justify the importance of their work in terms of potential clinical applicability. And yet I like to point out that our story is one of trying to generate knowledge and to understand how things work. And if you go deep enough and you understand things well enough, occasionally opportunities for translation or therapeutic application will arise. So I’m so happy to be involved with this story because I think that’s how real translation happens. People like to take short cuts, or they are sometimes told to try to take short cuts, but there are no short cuts as far as I’m concerned. I think you have to understand the system that you’re studying, and if you’re lucky once in a while you’ll understand it well enough that, you know, the light bulb goes off and you say ‘Ah-ha, now I can finally do this’. So I hope when people gain a greater appreciation of our stories that, you know, they’ll see that yes we’ve now in some cases enabled new drugs that are starting to be approved or, certainly in some cases, deep into testing, but it really began with some curious clinical phenomena that we were trying to understand mechanistically. And so to answer your question I certainly think we need more physician scientists but I think they also need to be trained to have the tools to do that sort of mechanistic work, rather than taking short cuts and doing things that in many cases turn out to be rather descriptive and don’t really give you the type of knowledge you need to do meaningful translation.  AS: Thank you, that’s a very important point, and beautifully coherently argued at this time in the morning.  WK: [Laughs] Well, I’m trying to listen to myself talk wondering just how I’m doing here, but thank you.  AS: I think you’re doing brilliantly, and no doubt once you’ve had the chance to have a cup of coffee it’ll get even better, because you’re going to have a day of it now aren’t you. Congratulations, and we very, very much look forward to welcoming you to Stockholm in December.  WK: Thank you so much, thank you. Okay, bye bye now.  AS: Thank you, bye bye. |
| Interview |  |
| Q33 | Was it your dream to be a Nobel Laureate? |
|  | Was this my dream to become a Nobel Laureate when I was a child? To be honest, when I was a child, I had heard of this prize and I think like many people, it quickly takes on sort of this mythological proportion. Like a lot of children growing up in the sixties, I had an interest in science and engineering because of the space race. I had a lot of toys that fostered an interest in science, one of which I’m going to donate to the museum today. I remember hearing a scientist speak for the first time, who visited my elementary school when I was in the fifth grade. I think there was a little part of my brain that imagined I might eventually become a scientist. I think I did have a little part of my brain that dreamt maybe what would it be like to win a Nobel Prize one day. |
| Q1 | How did you decide to pursue medical research? |
|  | As a young boy, my favourite subject was mathematics, because mathematics to me was a subject where you didn’t have to study very much. If you understood the concept, you understood the concept and it stayed with you. I didn’t particularly like courses where you had to take the books home and memorise lots of facts and information. I loved mathematics initially, and then later when computers came along, I became interested in computer science because I thought that was a way of applying math in everyday life. But I’m embarrassed to say, I wasn’t Bill Gates and I wasn’t Steve Jobs, I didn’t see the personal computer revolution that was going to eventually come. I didn’t imagine smartphones. I couldn’t imagine a career in computer science, and I frankly didn’t think I was quite gifted enough in mathematics to be an academic mathematician. So, I started to look for other ways I could use a mathematical mindset, if you will, and still make a living.  I started to gravitate a little bit more towards science and medicine. Medicine it seemed to me was a way that I could have science and math in my life and use that hopefully for the betterment of mankind. My father growing up was a lawyer, so maybe I was slightly inclined to follow a profession. Now, from watching him, I had decided I didn’t necessarily want to become a lawyer, but I knew there were some benefits to following a profession, and so I decided to pursue medicine. |
| Q3 | How do you deal with failure? |
|  | I think failure comes in different flavours. For example, the first time I attempted to work in a laboratory to do research, I was an undergraduate in college. In hindsight, I now appreciate the project that was given was simply undoable, unimportant and uninteresting, which is a very bad combination for a young person trying to become a scientist. Then during the last month in the laboratory, I correctly told my professor that by doing a little reading, I had determined that this project would never be completed because it was all based on a mistake of one of my predecessors, a so-called artifact. Of course, he rewarded me by giving me a bad grade and telling me I should never work in the laboratory again. That’s one type of failure. The lesson I took from that is, sometimes if you’re struggling in a laboratory the problem might be you, but it might also be the laboratory. But then there’s another type of failure where perhaps you’re having a challenge mastering a particularly sophisticated technique. I think any scientist knows that’s part of the territory. Sometimes you muddle through and you master the technique, or perhaps instead, you identify a collaborator who’s already good at the technique, who can help you get over that barrier.  But the final type of frustration, which I think is the most important one for any young scientist to consider, is that, as you say many times, our guesses and hunches are simply wrong. Sometimes we obtain results that are frankly disappointing given our perhaps prior expectations. But I try to remind especially young scientists that if every time you do an experiment, you get the expected results, you’re probably doing engineering, but you’re not really doing science, and frankly, science would be terribly boring if every time you did an experiment, you got exactly the results you thought you were going to get. In fact, I’ve even gone one step further and said that a good scientist should actually live for unexpected results. Because as you probably well know, there are many, many major discoveries that actually began with a completely unexpected result, where fortunately, there was someone with a receptive mind who decided that they would perhaps pursue this further, even though initially perhaps they couldn’t comprehend the significance of what they were seeing.  In fact, I’ve heard one Nobel Laureate say that many results that might have led to a Nobel Prize probably wind up in the waste paper bin because someone refused to actually look objectively at the data simply because it didn’t conform to their prior expectations. I think what any type of frustration that we’ve talked about, persistence is key. Whether it’s having the persistence to overcome various forms of rejection whether it’s a mentor who doesn’t have confidence in you, as was the case with my first mentor. Whether it’s reviewers and editors telling you your papers are not worthy of publication. Whether it’s a study section rejecting one of your grants. This just goes with the territory, and you have to be persistent, perhaps even a little thick-skinned. But likewise in the laboratory, you have to be persistent because as you know, in science, seldom are things straightforward and linear. There are going to be obstacles to overcome, and occasionally your data will take you off the path you thought you were traveling on into a different area. I think you just have to be persistent and to live for those occasional moments where you do have those ‘eureka moments’ where you suddenly have the privilege of seeing something and understanding something that’s never been seen or understood before. I think knowing that if you’re lucky, you will occasionally have those ‘eureka moments’ that provides you the fuel to get through the frustrating periods. |
| Q12 | What would you advise a young person starting a career in science? |
|  | I would have several pieces of advice. The first thing I would tell them is everything else being equal. I’m a big advocate of focusing on studies that teach you how to think rigorously and clearly and logically, because those things never go out of fashion. You can study and memorise facts and factoids, but sometimes those facts and factoids eventually turn out to be wrong or irrelevant, and they’re often quite specific to various disciplines. Whereas if you take courses that really train you to think clearly, that will serve you well, no matter what you do. For example, I actually didn’t like biology as a young person because at the time biology was quite descriptive and wasn’t particularly mechanistic. I found that terribly boring, whereas I thought courses like mathematics, computer science, and physics were very good for helping me to think clearly and to arrive at answers that were objectively true. I tended to steer away, for example, from some of the subjects that I found overly subjective.  The next thing I would tell them is I think one of the keys to happiness in life is to find something you find so rewarding and so fulfilling, you would do it even if you didn’t need the money, right? Most people go to work every day because they need a roof over their head, and they need food on their table and clothes on their back. I fully understand that, but what a great privilege it is to do a job that you would do even if you didn’t need the money. One of the great joys of my life has been … I discovered I enjoyed science so much I would do it even if I wasn’t getting paid. In fact, there are many times I feel guilty I’m getting paid to do this because it feels like I’m playing rather than working. I think if you can find such a thing, I think that’s priceless. If you have any interest in science whatsoever, I would give it a chance and find out whether you really enjoy it. Because I think it is such a great privilege to do something where you come to work every day, you’re surrounded by bright people, and you get to follow your curiosity, and if you’re lucky, occasionally actually discover something useful. |
| Q19 | How did you react when you heard you had been awarded the Nobel Prize? |
|  | The night before, someone asked me whether I would be able to sleep knowing that the following morning would be the announcement of the Nobel Prize. I told them that I thought I would sleep quite well, because I thought that the chance of winning was no greater than one or two percent, maybe even that was optimistic. I said, at one to two percent, I’ll be able to sleep tonight, but at one to two percent, I will leave my phone ringer on, on my bedside table, which I don’t normally do. I went to bed at the normal hour, and I had a very vivid dream where I looked at the alarm clock, and the time had already passed when I would’ve gotten the phone call. In my dream, I was already rationalising why this might even be a good thing. I was happy before, I’ll be happy now, and now I can go back to my work without this distraction. Then I unfortunately woke up from my dream and saw that the alarm clock said 2:00 a.m. and I said to myself, I have to do this all over again and go back to sleep. Then the phone rang at 4:40 a.m. and at that point, first of all, I was again wondering, is this now a dream? Or is this now reality? It was almost, I’ve described it as almost like an out-of-body experience, because I’m listening to this lovely gentleman with a Swedish accent telling me I’ve won the Nobel Prize. It was like overwhelming emotions of just gratitude and the overwhelming sense of what a privileged life I’ve had because so much luck goes into this. Clearly this is a dream for so many scientists. To think I now have the privilege of being a Nobel Laureate, it was just quite overwhelming. My next thought was how wonderful it was going to be to share this with all the important people in my life who’ve made it possible. |
| Q23 | Can you explain your Nobel Prize-awarded discovery? |
|  | I think most people are aware that you need oxygen to live, but less appreciated is the fact that too much oxygen would also be quite toxic and potentially lethal. All of the animals on the planet, including us, had to evolve a system that would allow the cells and tissues to know whether they were getting enough oxygen and to respond accordingly. So just as you might have a thermostat in your room to adjust the temperature properly, your cells need a system to adjust how much oxygen they’re being exposed to. It turns out precisely because oxygen is important, there are many human diseases where part of the problem is inadequate oxygen delivery to a tissue, such as in a heart attack or a stroke. Those two diseases are caused because the heart or the brain are not getting enough blood and hence are not getting enough oxygen. We also know that cancers, in order to grow, have to obtain oxygen. We now understand how in some cases they’ve hijacked the system that we use to sense and adapt to oxygen for their own evil purposes, so that they can trick the body into providing them with an oxygen supply. |
| Q41 | Where are we today in understanding cancer? |
|  | It started to become clear in the middle to the late part of the last century that cancers arose because of alterations, or scientists called them mutations in specific genes. But frankly, until the year 2000, we didn’t have the complete list of human genes, and we didn’t even know what the normal sequences of those genes were. It had always occurred to me back in the 1980s, when I was still a doctor taking care of cancer patients, that treating cancer was a little bit like trying to fix the engine of your car with a hammer. We really needed to understand this disease much better. Fortunately, in the year 2000, we finally obtained the complete list of human genes and their normal sequences that allowed us for the first time to start to understand which genes are altered or again, mutated in specific cancers, and then to start to use that information to develop better, more targeted, more precise drugs. I think we’re in a phase now where things are starting to accelerate, because we’re starting to reap the harvest of that knowledge that started to emerge in the year 2000.  More and more now we have new treatments for cancer that are helping many, many patients. But along the way, we’ve learned that no two types of cancer are genetically identical. Even within a given type of cancer, such as breast cancer, the cancer for one patient might be genetically dissimilar from another breast cancer. That’s why progress is sometimes frustratingly slow. I don’t think there’s going to be a single magic bullet that will cure all cancers. I think we have to continue to methodically make progress on all of the different cancers because as I said, sometimes the treatment for one cancer might not be applicable at all to another because of their different genetic makeup. |
| Q16 | What are your thoughts on how science is perceived today? |
|  | One source of great sadness and concern for me is this trend in certain quarters to disparage science and to disparage expertise. I was born in 1957, which was the year of Sputnik, so when I grew up as a young boy in the sixties in the New York area, the scientists and engineers, they were the heroes. I can remember going to ticker-tape parades for the returning astronauts. Like a lot of young children at the time, especially, unfortunately it was mostly young boys at the time, I had a chemistry set and a microscope and electric cars and a rock collection and a number of things that I think indirectly or directly were fostering an interest in science and engineering. I think for most of my adult life there was great support for investments in science because I think it was held as indisputable that creating new knowledge was intrinsically good, and that this was a gift we gave to ourselves and to future generations.  Now increasingly, at least again, in certain quarters, you hear people disparage science, especially when they don’t like the conclusions of the scientist. For example, I think about the current debate, and it’s sad that I even have to use the word debate because it’s no longer debatable, but when you hear a certain climate change, deniers make comments about science as though you get to pick and choose what the data tells you. You simply can ignore if it’s expedient to do so, what the best minds in the world are telling you you should be doing. I think we do this at great peril, and I think this is simply a road to the dark ages. If the pendulum shifts to the point where expertise is a bad thing, and we no longer celebrate science and engineering. |
| ID | 0512 |
| Biographical | I was born 14 may 1954, and my childhood in Carnforth, Lancashire was idyllic. At the time I would have said it was unremarkable, as are most things when not viewed by comparison. The near-total freedom I enjoyed seemed perfectly natural. The town was an unpretentious rail­way town in North Lancashire, England. My father was the local law­yer; my mother left her work as a telephonist when she married, as was the custom. And I was their only child. They were good enough not be overly protective and I survived as much foolhardy behaviour as most young people. I was neither pushed nor discouraged in schoolwork and again saw that as entirely normal. Appreciation of my parents came to me much later, with the recognition that *other* people saw them as special people in the community. My world was a simple one of building tree houses, lighting fires, mock (and occasionally real) combat with other groups of children. But I was always concerned with improving things: a better catapult, a hotter fire, a bigger explo­sion. I had an encyclopaedic knowledge of the melting temperature of metals; molten lead was a joy; an ambition to create the 2800OF nec­essary to melt iron was sadly never fulfilled. I learnt that it was possi­ble to create something akin to a hand grenade by compressing thou­sands of the tiny ‘caps’, as supplied for toy guns, between two large bolts threaded onto a single nut, then hurled at a brick wall. The result was a neat hole in a nearby garage door. Fortunately, before the inevi­table calamity, life evolved.  Aged 11, I started at Lancaster Royal Grammar School. The school was good and undoubtedly the single most formative experience in my educa­tion. But it was not idyllic. There will be others who recall their trials with school meals; the UK was not at the top of the culinary league in the 1960s and the Lancaster Royal Grammar School kitchen was not the *cor­don bleu* of the nation. When a good meal cropped up there was no ques­tion of equal shares: the older boys, in charge of the table, would take the large majority. Again, without a comparator, I saw this as the way of the world. But that blissful childhood was over.  I was good at most subjects, with the exception of English. Lack of tal­ent was reinforced by lack of effort and sadly this dichotomy in my abili­ties grew until I eventually came to recognise the importance of commu­nication, a decade or two later. Actually, my ethos was not out of keeping with that of the school; little time was wasted on things other than sport (particularly Rugby Football) and University Entrance (particularly entrance to Oxford or Cambridge). This rather blinkered approach to life did exact its penalty in due course. But I was comfortable at the time. The school had some good teachers; several were truly excellent. I remember in particular Gary Sleightholme, who taught me chemistry. The accent was on finding simplicity in complexity, which is of course the essence of molecular biology. I have heard many scientists describe their first appre­ciation of this, at the hands of some esteemed mentor in a famous research institution. But for me (and I suspect for many others) I’m pretty sure it was the school. Of the two acceptable school options, excellence in sport or Oxbridge entrance, the pathway for myself was the latter, by default. For various reasons I didn’t think I’d enjoy either Oxford or Cam­bridge, but never had quite the bravery to refuse the entrance examina­tion, which I duly took. Most of the questions were opaque to me, but I remember creating and solving a set of equations relating to a complex chemistry problem. When several variables cancelled out and the answer was simple integer, I felt confident of success. Beyond this I hardly man­aged a single answer. But rather to my own surprise, and greatly to that of some at the school, a telegram arrived announcing an open scholarship to Gonville and Caius College, Cambridge. This was to study medicine.  I remember that decision, as follows. I had intended to study chemis­try; my chemistry teacher was inspiring and, as I was told by my parents, a distant relative had been a successful pharmaceutical chemist. But it wasn’t to be. The Headmaster, John Lorraine Spencer MA, a rather ethe­real figure, who somewhat incongruously wore a gown as he walked about the rough and tumble school, appeared one day in the chemistry classroom. ‘Ratcliffe,’ he said, ‘may I have a word?’ I duly followed him with some trepidation to his study. ‘Ratcliffe,’ he said, ‘I think you should study medicine.’ His views were never to be taken lightly. ‘Yes sir,’ I responded, and the University application form was altered without fur­ther exchange. I have never been sure whether he thought I would be a good doctor or a bad a chemist, or really whether he was right or wrong in the end.  But I was pleased with myself. Even though I didn’t want to go, I had got the Scholarship to Cambridge a year early and there was a little time to kill. The previous obsession with explosive dynamics resurfaced, in a slightly more dangerous guise. I had always wanted to be good at sport, not chemistry; but though the spirit was strong, the flesh was weak. Now, however improbable, I saw a potential solution; motorsport. I took a job in the analytical laboratory of a local textile firm and earned enough money to buy a racing kart (not a go-kart). Here was a real thrill; the acceleration over a short span was truly mind-blowing. It suited my basic interest in combustion. I learnt to ‘mechanic’ it (the most important bit) and drive tolerably, though not brilliantly well. It held prestige amongst a set of peers I admired. Though I never possessed a powerful motorcycle I had the gear to tune them for my friends. Mercifully for my poor parents, this period came to an effective end when I finally took up the place at University.  As might be predicted from this preparation, medicine at Cambridge was not an unqualified success. I am not going to go into detail; suffice it to say this was not the fault of the University, or the College, or my tutors. Though I readily saw the potential in a different approach to life, it was simply too far away from two-stroke racing engines and the associated culture. Though I made good friends, I couldn’t quite adjust. The saving grace was that the clinical three years of the six-year course were gener­ally undertaken elsewhere, usually in London. This offered a second chance.  The clinical medicine course at St. Bartholomew’s Hospital was well organised and I found much of it, particularly the process of medical diagnosis, very interesting. There were other good things. I met my wife Fiona there; Fiona was also a medical student. But, after Cambridge, I wasn’t taking any chances with examinations. I wasn’t quite sure what I wanted to do, but I wanted the freedom to choose. Still lacking those skills in Rugby Football, the easiest route to first choice in a House Physi­cian job (and hence it seemed, to everything beyond) was a good perfor­mance in the final examinations. In these, the majority of marks were awarded through ‘multiple-choice’ questions. Now, as most of those who have set these examinations will know, there are only certain types of information that are suitable for the exercise. Besides, even when a ques­tion is not set properly it is possible to discern what question the exam­iner is trying to set and answer it. I greatly enjoyed the medical course in a wider sense and flirted with a career in most every speciality covered in the curriculum, but I applied the above logic to the examinations with a brutality that still makes me blush. The result, in the main examination, was substantially more marks than any other student. Perhaps naively, I had not seen the difficulty that this might create. I was surprised by a summons to meet with the sub-dean. Most likely drawing on his experi­ence as a former member of the Hospital Rugby Club, he could think of only one explanation; I had acquired copies of the examination papers in advance of the event. The interview has forever made me sympathetic to the cause of minority groups in police stations. In the end however, he was good enough to recognise that without a confession, the evidence was at best circumstantial and I was duly appointed to the House Physi­cian post of my choice, on a ‘firm’ specialising in Gastroenterology and Nephrology.  During that time, Larry Baker, the Consultant Nephrologist, kindly suggested that I should become a Nephrologist myself. As with the Head­master at Lancaster Royal Grammar School, I didn’t doubt his wisdom and planned my career accordingly. Others were more cautious: Nephrol­ogy is an expensive speciality, and the UK National Health Service was not well resourced. I well remember being told by one of leaders in the speciality that there would only be two consultant positions coming up between then (circa 1980) and year 2000, so I had better distinguish myself, somehow. The first statement turned out to be untrue; but the second was chastening. As a busy trainee Nephrologist there was no real opportunity for laboratory research. So, as the necessary route to distinc­tion, I took to writing medical case reports. In most scientific circles this would not be seen as a useful, let alone a distinguished, training. Later, I became adept at re-arranging my publication list, so this phase of my sci­entific development was less apparent. Later still, I have come to see it as critical. What is important in embarking on a research career is selecting the question; once the question is clear, answers may follow. For most of us this is the joy of academic research; we are free to pick our questions. I moved from London to Oxford to complete my clinical training in Neph­rology. The experience of surveying the patients of London postgraduate and Oxford hospitals for case histories from which something new might be securely deduced, was without doubt a key experience. It didn’t directly inform the question I eventually chose, but it taught me how to look for potentially soluble problems amidst a mass of insoluble distrac­tions.  There were a few false starts. I thought it would be possible to under­stand the physico-chemical properties of myoglobin that led to myoglobi­nuric kidney failure, using isolated perfused kidneys. I learnt kidney per­fusion from Brian Ross, who had developed the technology under [Hans Krebs](https://www.nobelprize.org/prizes/medicine/1953/krebs/facts/), but myoglobin even at massive concentration had no effect on the preparation. I then thought it would be possible to use 31Phosphorus NMR measurements of cellular energetics to understand why the kidneys are susceptible to injury in shock and joined George Radda’s laboratory to study this, but the spatial resolution of the method was not sufficient. I thought it would be possible to understand why the kidneys make eryth­ropoietin (the hormone that stimulates red blood cell production) in response to blood loss, but not to reduction in blood flow. I hadn’t prop­erly considered the technical difficulty of measuring intra-renal haemody­namics and oxygen fluxes, under those conditions. So, none of these problems were solved, but they brought me progressively closer to the ‘oxygen sensing’ question.  Most of my colleagues in Nephrology worked on quite different topics in immunology, genetics or the control of blood pressure. The combina­tion of a slightly awkward, non-compliant nature that led me to avoid these subjects, and the experience of looking for soluble problems, derived from that case-report era, brought me to the question. The sensi­tivity and precision of regulated erythropoietin production by the kidneys in responses to changes in blood oxygen content must, I felt, reflect an answerable and important question as to the nature of the underlying ‘oxygen sensing’ process. Not everyone agreed; recombinant erythropoie­tin was being used to great effect in kidney patients, why worry about its regulation? But I was convinced there would be an answer and that it would be interesting. Besides, the identification of the erythropoietin gene opened a new possibility to trace the transduction pathway from the erythropoietin gene locus ‘outwards’ to the putative oxygen sensor.  I had finished my clinical training in Nephrology and there was a deci­sion to make; should I move from Oxford to take up one of those rare opportunities to become a Consultant Nephrologist in the National Health Service, one with supposedly protected research time? Or should I stay amongst friends in Oxford? By now I had made, at least in part, a cul­tural adjustment towards the ‘Oxbridge’ environment. A combination of kind personal assurances of support from David Weatherall and John Ledingham in the Department of Medicine, miserably heavy rainfall when I travelled to look at a Consultant position at a hospital in Wales, and extreme good fortune in an interview at the Wellcome Trust, conspired to convert what was surely a truly impossible ambition (to solve the problem as a working Consultant Nephrologist) to one which, as a well-funded Wellcome Trust Senior Fellow in Clinical Science, might just be possible.  But there were still problems to overcome. I had no technical knowl­edge at all of molecular cell biology. At the time, I wasn’t greatly con­cerned, though looking back, the level of ignorance must have raised a few eyebrows amongst my colleagues. This attitude owed a lot to my early experience as a junior doctor. The National Health Service was in perpet­ual crisis. My years as House Physician coincided with the end of the Cal­laghan government, and the UK’s ‘winter of discontent.’ Practically every­one was on strike and nothing worked. As far as I could see, in the eyes of the all-powerful senior staff, the solution to each and every problem within the hospital (and on occasion outside it) was that the House Phy­sician or Registrar (the next grade up) would sort it out. Against this background, it had never before struck me that total lack of knowledge was a barrier to engagement with a problem. But now, even I could see that some external means of acquiring skills in molecular cell biology was necessary. I invested in a copy of Benjamin’s Lewin book *Genes III* and went to see a friend, John Bell, who I had met as a House Physician at the National Hospital for Nervous Diseases in London. John was generous in giving me a bench place, to work on erythropoietin regulation, in the midst of his crowded HLA immunogenetics laboratory. This was critical and set me up. So, here is my advice to the aspiring clinician scientist, take your time, look around carefully, pick your *own* question, *then* find a friend to help.  In fact, I had a number of friends who helped, most importantly David Weatherall, who, after my initiation in John’s laboratory, gave me some laboratory space of my own within his newly commissioned Institute of Molecular Medicine. In the adjacent bay was Richard Jones, to whom I owe a lot. Richard taught me much of the gene regulation technology we used in the early stages of the work. Carole Beaumont (on sabbatical with Richard) taught me tissue culture. Martin Johnson at Cambridge made transgenic mice for me, an attempt to derive the erythropoietin producing cells in kidney by expressing ‘T’ antigen at the erythropoietin locus. By now, there was growing confidence in the project, at least locally; a series of excellent trainee Nephrologists, Tan Chorh Chuan, Chris Pugh, Patrick Maxwell, John Firth, Jonathan Gleadle came, or were steered my way. Ben Ebert joined the laboratory as a Rhodes Scholar from the US; Masaya Nagao joined us from Japan. All were taking a risk, as I had no track record in the field.  It was a busy time. Fiona had also moved from London to Oxford. We married in 1983 and she was by then a trainee anaesthetist. During that critical period when I was finishing my own Nephrology training, decid­ing what to do and then setting up the laboratory, she bore our four chil­dren: Anna, Alice, Robert and David. I occasionally brought the very young children to the laboratory and entertained them with tricks with the dry ice, another iteration of my own childhood theme of explosives. I interfaced week-end experiments with family walks and trips to the sea­side, and generally thought I was managing well. It is only in retrospect that I see the sheer enormity of Fiona’s task, managing her own training, the children and the household, almost single-handed. I owe so much to her fortitude.  There had been many unsuccessful attempts to understand the nature of the oxygen sensing process through pharmacological interventions on erythropoietin response to hypoxic stimuli. But identification of the erythropoietin gene gave us a new opportunity. It had been established that the erythropoietin gene was regulated by transcription. So, we argued, working from the gene it should be possible define oxygen-regu­lated control sequences at the locus and then dissect our way through the transcriptional and signal transduction pathways to the putative oxygen sensor. Nevertheless, despite a lot of talent and enthusiasm in the labora­tory, none of us had a biochemical training. And beyond the identification of the oxygen-regulated control sequences by gene transfer, the most obvious approaches to dissecting those pathways were biochemical. As Richard Jones explained, the new molecular approaches based around the gene had opened research questions in cell biology to amateurs like myself, who had come into the laboratory with no training in biochemis­try, but there were limitations to this. Even the environment David Weatherall had created with his Institute of Molecular Medicine could not address this deficiency. We spent a lot of time discussing alternative genetic approaches to the problem. One of these led directly, but unex­pectedly, to our first breakthrough.  It had long been assumed that the extraordinary sensitivity of erythro­poietin to reduction in blood oxygen reflected the function of a high spe­cialised oxygen sensor that was specific to the erythropoietin producing cells themselves. Erythropoietin is produced by cells in the kidneys and to a lesser extent the liver. We had spent a lot of time trying unsuccessfully to culture these cells from the kidneys of the erythropoietin – T antigen transgenic mice. In the end, it was cell lines from the liver, shown by Franklin Bunn and colleagues at Harvard to produce erythropoietin in response to hypoxia, which opened the molecular approach. We and oth­ers used these cells as the vehicle to define the oxygen-sensing control sequences at the erythropoietin locus. But then there was my biochemis­try problem; how to get to the target, that oxygen sensing mechanism lying further upstream. Another scientist in the Institute, Dave Simmons, was successfully using ‘expression cloning’ in Cos7 cells to identify sur­face receptors and cell adhesion molecules. I thought I would use this technology to identify upstream components of the oxygen-sensitive pathway by gene transfer. This would be from Franklin Bunn’s oxy­gen-sensitive hepatoma cells to the Cos7 cells, which I believed would not be intrinsically oxygen sensitive as they do not make erythropoietin. To my great surprise, control experiments – designed to check the absence of oxygen sensitivity prior to gene transfer – clearly showed the same oxy­gen sensitivity of those control sequences isolated from the erythropoie­tin locus, in Cos7 cells.  This of course disqualified the intended experiment but changed everything in my scientific life. It was the first evidence of a widespread human oxygen sensing system, manifestly operating beyond erythropoie­tin. The implications were clear, there must be other targets in non-eryth­ropoietin producing cells, which are also regulated with great sensitivity by oxygen levels. We found the first of these: enzymes encoding specific isoforms glycolytic genes that are also upregulated in cancer, connecting us with the cancer metabolism and oncology communities. Although the work didn’t immediately attract so much attention, and there were initial difficulties in publication, from that moment we were confident we were on to something important. Nevertheless, the lag between the tremen­dous excitement running through the still small group of scientists work­ing on this problem, and interest developing in the general scientific com­munity, was very striking. It still colours my advice to young scientists; when deciding what to do, try very hard to ignore the interests and preju­dices of those around you, they will likely be a very long way behind the curve. However, the field grew steadily as more and more people found new pathways that responded to HIF (Hypoxia Inducible Factor, the tran­scription factor binding those oxygen-regulated sequences, which was discovered by Gregg Semenza). However, I think all of us were surprised by the extent of the HIF transcriptional cascade and the extent to which so many responses to hypoxia (low tissue oxygen levels) had previously been overlooked. Many of the new responses to hypoxia were fascinating in their own right, but our intention had always been to work our way upstream to the oxygen sensing mechanism itself and our attention shifted back.  By now we were an established group in David’s Institute of Molecular Medicine and we took advantage of everything it had to offer. Half of an entire floor in the building was given over to the Institute’s coffee room. David had clearly been impressed by this much championed facility at the Laboratory of Molecular Biology in Cambridge. Coffee was made in advance, dispensed with impressive efficiency and consumed in arm­chairs of exactly the correct design and spacing to support conversation. The room was carpeted. For those considering institutional design, every detail of this matters. We sat there with anyone who would listen and speculated (mainly unproductively) about what the mechanism of oxygen sensing might be, and (a little more productively) on experimental strate­gies that we might use to define it. With every visitor I considered their work from the perspective of its potential to solve the oxygen sensing problem, my problem. We tried to harness a whole range of gene transfer and expression cloning methodologies, we examined model organisms for conservation of the pathway, hoping to harness genetic methods in flies, nematodes worms, or even yeast. I was impressed by George Stark’s use of somatic cell genetics for dissection of interferon response pathways. Morwenna Wood and Emma Vaux, two highly competent trainee Neph­rologists, spent vast amounts of time engineering Chinese Hamster Ovary cells to express hypoxia inducible transgenes encoding cell surface mark­ers, and then selecting mutants with defective responses to hypoxia. To their enormous credit, they did isolate valuable mutants, but it proved dif­ficult to identify the defective genes beyond those encoding components such as HIF that we already knew about.  In the end, it was a mixture of genetic and biochemical approaches that brought us step by step towards the solution. Each advance was incre­mental, to use that favourite word of editors when declining manuscripts. Defining the regulatory domains in HIF that mediated oxygen sensitivity of the complex, demonstrating the physical association of those domains with the von Hippel-Lindau protein (pVHL), showing the function of pVHL as a ubiquitin ligase that degrades HIF, the discovery of prolyl hydroxylation as the mechanism governing oxygen-regulated association of pVHL with HIF, evidence that the enzymes catalysing HIF prolyl hydroxylation belonged to the 2-oxoglutarate dependent dioxygenase family, identification of the actual enzymes and their oxygen sensitivity, were all *incremental* steps. I was one of those fortunate enough to be called to Stockholm for our contributions to this work, but there were many others whose work contributed to, and was informed by, the timely publi­cation of all those incremental advances.  The final steps, involving the identification of the actual oxygen sens­ing 2-oxoglutarate dependent dioxygenases that catalyse the prolyl hydroxylation of HIF, were taken together with my friend and colleague Christopher Schofield, with whom my laboratory continues to enjoy great collaborations. Chris (Professor of Organic Chemistry at Oxford) brought the biochemical perspective that I lacked to the work. But the original collaborative work was not a large-scale biochemical purification, which I had previously envisaged being necessary at some stage in the pro­gramme. Rather, based on his earlier structural analyses of 2-oxoglutarate dependent dioxygenases and related enzymes, Chris was able to predict genes that might encode the putative oxygen sensing prolyl hydroxylase. Meantime one of our earlier exploratory ventures, hatched in the Weath­erall coffee room, had involved identifying the HIF orthologue in *Caenor­rhabditis elegans* and, very importantly, raising an antibody against the protein. This enabled us to assess mutants for their impact on the proteo­lytic regulation of the HIF by hypoxia, but so far none had shown an abnormality. One of Chris’s predicted 2-oxoglutarate dependent dioxy­genases was represented in the libraries of mutant *C. elegans* that were so beautifully catalogued and efficiently provided by the nematode worm genetics community. Worms bearing mutant alleles of the relevant gene were identified via WormBase and duly ordered.  I have a vivid recall of one morning in March 2001; Andy Epstein, a PhD student in the lab burst into my office, exclaiming, ‘here’s your gene, *Egl9*’. Three different alleles of the mutant *Egl9* gene, previously charac­terised by the Nobel Laureate [Bob Horvitz](https://www.nobelprize.org/prizes/medicine/2002/horvitz/facts/) on the mechanistically agnos­tic basis of defective expulsion of their eggs, all showed upregulation of their HIF, irrespective of oxygen levels, as would be predicted for a defec­tive enzyme whose oxygen-dependent catalysis of prolyl hydroxylation was physiologically deployed to signal oxygen levels. We were rapidly able to confirm this and identify three human orthologues. Jonathan Gleadle, one of the trainee Nephrologists who joined the laboratory and did some of early work defining HIF-target genes, had returned to the group after completing his clinical training. Jonathan identified the human ortho­logue of *Egl9* on the basis of a highly conserved catalytic domain and called their products the PHD (prolyl hydroxylase domain) enzymes. Those findings completed that journey I embarked on as a young Neph­rologist, from erythropoietin to oxygen. The high points in that journey were exciting, very exciting; the low points I tend to forget. The experi­ence was addictive, and I am always looking for the next of those ‘eureka’ discovery moments.  Though the work provided an answer to a question, defence of oxygen homeostasis is clearly more complex. Severe hypoxia is fatal within min­utes and oxygen homeostasis must be maintained over much shorter and longer timescales than those mediated by the transcriptional pathways we have so far unravelled. For instance, the oxygen sensitive signals by which the carotid body controls breathing, part of the work for which the Nobel Prize for Physiology or Medicine was awarded to [Corneille Hey­mans](https://www.nobelprize.org/prizes/medicine/1938/heymans/facts/) in 1939, are still not understood at the molecular level. The labora­tory works on these and other as yet unsolved problems in the physiology of oxygen homeostasis. Although we were at first surprised to find that the HIF system operated generally in mammalian cells, and was not restricted to erythropoietin producing cells, we were then surprised that it was apparently restricted to animal life, there being no obvious HIF ort­hologue in non-metazoan species. It is now clear that species in all four eukaryotic kingdoms deploy enzymatic protein oxidations coupled to protein degradation to signal oxygen levels in their cells. However, the oxidations are of different types and coupled in different ways to the sig­nalling systems, raising questions as to the origins of these systems, their inter-relations and whether they also function in human oxygen sensing. I also became interested in cancer, in particular the implications of onco­genic ‘switching’ of very extensive interconnected physiological path­ways, such as occurs when the pVHL ubiquitin ligase is inactivated and the HIF system is unphysiologically activated in kidney cancer. I imagine that this paradigm, in particular the mechanisms by which the developing cancer ‘accommodates’ adverse components of the oncogenically-acti­vated pathway will be important in understanding the disease. For these reasons, supported by loyal staff who have stayed with me for years, the laboratory remains as active, or at least as hopeful, as ever, and I remain as addicted as ever to the discovery process.  But there have been new experiences. I worked with small and large companies on the development of HIF hydroxylase inhibitors for the treatment of anaemia, and perhaps other ischaemic/hypoxic diseases. This is an interesting experience for an experimental scientist used to near-total control of an experimental research programme. It is very satis­fying to see the work progressing towards a medicine, though somewhat alarming not to have that control. But there is the same unpredictability. Given that the field started with the regulation of erythropoietin, it is no surprise that the 2-oxoglutarate analogues being developed as HIF hydroxylase inhibitors will induce erythropoietin production and correct the anaemia of erythropoietin deficiency. But given the extent of the HIF transcriptional cascade that became apparent, I don’t think the scientific community would have predicted that this could be done without a major dysregulation of other responses to hypoxia, as appears from current clinical experience to be the case. I learned a certain respect for those taking the risks that are intrinsic to the medicine development process.  In 2003, I was approached about taking on the Headship of the Depart­ment of Clinical Medicine. John Bell had succeeded David Weatherall into this chair and was now moving (as David had) to the Regius Chair. I hesi­tated, knowing very well that University administration was not a natural suit. But the Department was interesting. Under the successful tenure of David and John it had grown well beyond the norms of a University Department, more the size of a small University, with a research budget that would come well up the UK university league. It was and is (in accordance with the name) a Department of *Clinical* Medicine but encompassed an extraordinary range of disciplines ranging across struc­tural biology, large-scale human genetics, clinical trials, epidemiology, molecular cell biology, to tropical medicine and the teaching of clinical medicine within the National Health Service. An expectation was that the senior professorial staff would contribute to the Acute Medicine Rota and teach medical students in that context. With my training in Clinical Neph­rology and continuing practice in both Nephrology and Acute Medicine for much of the period I have just described, I could actually do this. My perception was that this was slightly to the surprise of a number of the other medical and nursing staff working in the relevant service; it cer­tainty filled some of my post-docs in the laboratory with horror. They felt that this sort of ‘high tension’ medicine should only be performed by highly professional, and very good-looking staff in surgical scrubs, as they had seen on TV. I have never been completely sure as to which attributes, they felt to be lacking in myself. However, clinical medicine was only part of the experience. Across all its domains the Department encompassed more than 2000 staff, including many working in tropical South-East Asia and Sub-Saharan Africa. Academic management of this scale is a chal­lenge, by and large I learned not to attempt it. I learned a lot about people, particularly creative people. In the Department, as in the laboratory, the most surprising things (to me) turned out to have their value. I learned tolerance and firmly believe that science is, or should be, one of the great unifying forces in a world of diversity. Of course, a persistent problem was balancing Departmental matters with the running of the laboratory, and I’m grateful to many on both sides of that equation who ensured at least a modicum of success. But I avoided further progression in aca­demic management, and after more than a decade in the position, looked for opportunities that might give me more time in the laboratory and new scientific horizons.  It was therefore a piece of good fortune when, in 2015, [Paul Nurse](https://www.nobelprize.org/prizes/medicine/2001/nurse/facts/) approached me about a position at the shortly-to-be-opened [Francis Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/) Institute, to develop its interface with clinical practitioners and clinical medicine. Here, I thought my unusual experience of different sides of medicine might be useful. And there were new scientific horizons. The key point about the journey that I have just described is that it is the selecting of the research question that matters. The purpose of bringing clinical practitioners to a major biomedical research institute such as the Crick is that they will ask new questions, not necessarily clinical ones, simply different ones. I combined the Crick position on a 50/50 basis with running my laboratory in Oxford as a member of the Ludwig Institute of Cancer Research and felt I had things under control, at least until one morning in October.  I had heard mention of the Nobel in discussions of the merits or other­wise of the work on oxygen sensing, but the news that morning was a sur­prise. I had reached that all-too-familiar crisis point in writing a grant application with colleagues from Finland and had been writing most of the weekend. In the frenzy of activity, I had quite forgotten the signifi­cance of the first Monday in October. But my personal assistant, Cathe­rine, does not forget things. It was Catherine who pulled me out of the Monday morning laboratory meeting to take the call from Thomas Perl­mann and then replaced my strong coffee with a calming mug of tea when I returned to finish the meeting. A great deal of champagne was subse­quently consumed in the laboratory throughout the day and, as television viewers observed, standards of safety became lax. Many have recounted the rather surreal experience of being bestowed with omniscience, over­night. Even the children (now grown up) thought I might have a useful opinion on things, for a short period of time. But the experience in Stock­holm is worth restating.  The attention to making Nobel Week a celebration, and a happy time in every way possible way, was truly remarkable. Every event was managed to perfection, every microphone tuned precisely, all electronic projection flawless. The King was majestic, the Queen was gracious and Princesses stunning. Breakfast in the Grand Hôtel, overlooking the Stockholms ström, is one of most pleasurable experiences on the planet. The week’s hectic schedule was efficiently managed by our attaché Jane Viol. It even seemed my motor-racing aspirations had been considered; our driver Bo Cravell was an ex-rally champion. There was just one hiccup. The family travelled to Stockholm with our new-born granddaughter, her mother (Anna) and father (Rupert) having hastily obtained a passport. At the point of maximum tension, dressing for the ceremony, it emerged that it would not be possible to accommodate the baby at the five-hour banquet, in any way whatsoever. My wife Fiona took the matter seriously. After 37 years of marriage, I did not doubt the outcome. I carried on wrestling with buttons on the formal attire. I think Miss Elizabeth Merryn Ever­leigh is youngest to attend that magnificent Nobel banquet, safely tucked away under that very grand staircase through which we had entered the Hall. What a day. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0512=PR  Sir Peter J Ratcliffe: Hello?  Adam Smith: Hello, this is Adam Smith from Nobelprize.org.  PR: Hi.  AS: It’s very nice to hear you. Many congratulations.  PR: It’s very nice to hear you, actually, yes, in your capacity, thank you.  AS: It is a working morning for you so what were you doing when the call came?  PR: Well, very interesting question. I was writing and will continue to write an EU Synergy grant for a collaborative work with friends and colleagues in Finland, and also my good friend and colleague Christopher Schofield, so of course the EU’s on our minds at the moment, and we’re writing a Synergy grant. And despite this good news I guess I’ll continue doing that and meet the deadline.  AS: Yes, they don’t go away for anything.  PR: No.  AS: Talking about the EU is kind of apposite at the moment; these are fevered times in Britain.  PR: Indeed.  AS: Are you … the Prize will bring some publicity and you’ll be in lots of interviews over the coming days.  PR: Yes.  AS: Will you take the opportunity to talk about the current situation, Brexit and all that sort of thing?  PR: I probably will, yes. Well, I think there is a responsibility and a platform to make one’s views known. And I do have views on this, and I think they are important for science and for society. So let’s hope this is a happy event that helps in some way.  AS: Your Prize is really an illustration, I think, of never knowing where a question will lead you. Your search for regulators of EPO, has opened up a whole new sphere of hypoxia biology. It’s so exciting.  PR: Yeah, sure. It very much was. You’re right, we set about the problem of EPO regulation, which might have seemed, and did seem to some a niche area, but I believed that it was tractable, i.e. could be solved by someone, and that’s a very important thing that the problem has a potential solution. And of course as with almost any discovery science the impact of that becomes evident later, and we didn’t really foresee the broad reach of this system when we started the work. That’s true.  AS: But it underlines the importance of having the courage to ask the questions, doesn’t it?  PR: Yes, I think the courage, and I think this is an important issue, that we make knowledge, that’s what I do as a publicly-funded scientist. That knowledge has only one quality that’s definable really: it’s good knowledge, it’s true, it’s correct. The idea at the outset that some knowledge might be more valuable than some other knowledge, well probably that’s true also, but it’s extremely difficult to assess in prospect, and this is an example where we set out on a journey without the clear understanding of the value of that knowledge, and I guess it has gained in value. Quite what the future holds of course is yet another question, but it is important that scientists have the courage and are allowed to derive knowledge for its own sake, i.e. independent of the perceived value at the point of creation. And history of science tells us over and over again that the value of that knowledge can increase with the impact on other people’s research, other circumstances, all sorts of random and unpredictable issues brought to bear.  AS: Because now, unexpectedly, the hope is that tweaking the system is going to be useful in all sorts of diseases.  PR: That’s our hope, and of course the slightly odd thing is that the leading indication is where we started, the regulation of erythropoietin to correct anaemia … now … so we’ve gone full circle: from private to EPO to a general system to trying to keep it private to EPO. And that’s the aim of drugs that are being developed to do that in an effective and safe way, and some of these trials are still to declare and that’ll be exciting news to come in the next year or so.  AS: It’s a lovely story. Good, well we look forward to continuing to watch it. You sound, as ever, wonderfully calm and collected.  PR: No, no I’m not calm! [Laughs] But carry on.  AS: Are you … are you looking forward to the storm that’s about to unleash on you?  PR: Um … I’m not a tiger for publicity. It’s a very happy event, obviously very satisfying and a reward for me. I’m happy about it. Yes, I think it’s a … and comfortable with talking to people such as yourself. Um … I’m not ecstatic about the possibility of being a public figure, if that’s what one is. I’ll do my duty I hope.  AS: We very much look forward to welcoming you to Stockholm in December.  PR: Yes indeed, no I look forward to that too.  AS: Thank you.  PR: Thank you very much and good to talk.  AS: Thank you, congratulations again. Bye.  PR: Bye bye. |
| Interview |  |
| Q1 | Did you always plan on studying medicine? |
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| Q2 | What do you enjoy about medicine? |
|  |  |
| Q3 | How do you deal with failures? |
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| Q5 | Did anyone influence you? |
|  |  |
| Q12 | What would you say to a young person going into science? |
|  |  |
| Q19 | How did you react to finding out you had been awarded the Nobel Prize? |
|  |  |
| Q23 | Can you describe your Nobel Prize-awarded discovery? |
|  |  |
| Q16 | What practical uses are there for your discovery? |
|  |  |
| Q41 | Is there good balance between basic and applied research in medicine today? |
|  |  |
| ID | 0513 |
| Biographical | I was born on July 12, 1956 in Flushing, which is a neighborhood in the Borough of Queens, in New York City. My mother’s family was of German-English-Irish descent and lived in Queens, whereas my father’s family was of Italian descent and lived in the Bronx. I was the first born of five children, followed by Laurie, Beth, Matt and Paul. Our family lived in Old Bridge, New Jersey for five years, not far from Bruce Springsteen’s childhood home. When I was nine years old, we moved to the village of Tarrytown in New York. Tarrytown is basically one long uphill climb, extending from the Hudson River to Main Street and Broadway (the center of town) and further up the hill to the aptly named Altamont Avenue, where my family resided.  I attended *Sleepy Hollow High School,* so named because Washington Irving had set his famous story The Legend of Sleepy Hollow in Tarrytown. In the story, a Headless Horseman chases a superstitious schoolmaster named Ichabod Crane, who is never seen again. The mascot of the high school’s sports teams was the Headless Horseman and the players were referred to as the Horsemen. My freshman biology teacher, Rose S. Nelson (Figure 1), was the inspiration for my career in biomedical research. Dr. Nelson had earned a Ph.D. in Endocrinology and then worked as a postdoc at Woods Hole. Because of her research training, she did not recite facts but instead described discoveries in vivid detail and told us about the scientists who had made those discoveries. She transmitted to us the thrill of performing biomedical research. I also took Advanced Placement (AP) Biology with Dr. Nelson in my junior year and she recommended that I apply to attend a National Science Foundation-sponsored summer program at the Boyce-Thompson Institute for Plant Research in Yonkers, New York. I was accepted into the program, which was my first hands-on laboratory research experience and, despite the fact that my pipetting was clumsy, I loved it. During Dr. Nelson’s AP Biology course, I became particularly intrigued by genetics. **College life** In the fall of 1973, I made a road trip with my mother to visit Cornell University in Ithaca, New York. I had recently visited Harvard, where a former Sleepy Hollow High student who had graduated the previous year was enrolled. I had purchased a Harvard t-shirt as a souvenir of my visit and was wearing it when we stopped in Albany for the night. My mother’s cousin looked at me and said with disdain: “Why are you wearing that shirt? You will never get in there.”  My first year at Harvard, I lived in Wigglesworth Hall, which had several unique attributes that made it a memorable college residence. We occupied the first-floor suite, under which was located the terminus of the Red Line. When the subway train rumbled into Harvard Square station, the floor of my bedroom rumbled with it. Fortunately, the last train came into the station around midnight during the week and around 1 a.m. on the weekends. Wigglesworth also served as a sound barrier between the noise of Harvard Square and the tranquility of Harvard Yard. Public transit buses queued outside my bedroom window and the hustle and bustle of the Square was just a few feet away. On Saturday mornings in the fall, when the football team was playing at home, I would wake up to the sound of the Harvard Band marching up Massachusetts Avenue performing the fight song “Ten Thousand Men of Harvard Want Victory Today.”  The first two years as a Harvard undergraduate were challenging and at times unpleasant for me, as they were filled with math and chemistry courses about which I possessed neither interest nor ability, which I attributed, at least in part, to my prior experiences. I took chemistry as a high school sophomore. The class met right after lunch and the teacher often had a strong odor of liquor on her breath. She did not inspire me. I took AP Calculus in my senior year of high school and had great difficulty with it. I decided that I would need to take Calculus over again in college, so there was no reason to take the AP exam. My teacher was quite displeased to learn about my plans. He informed me that if I did not take the AP exam, I would have to take his exam. I told him that because I was a senior with an 85 grade-average in the class, I was exempt from final exams. He replied that I did not have an 85 average, because he was giving me a 65 for the final quarter. My guidance counselor, Bill Burnette, who was a man of infinite wisdom and patience, brokered a compromise, in which I received a grade of 65 for the final quarter but did not have to take either exam. My indifferent attendance also led to a 65 in physical education, so my high school career ended not with a bang, but a Bronx cheer.  Starting in the spring of my junior year at Harvard, I worked in the laboratory of Dr. Park Gerald on the Genetics Unit of Children’s Hospital in Boston. My introduction to the lab involved helping to prepare karyotypes from blood samples. Karyotypes identify chromosome abnormalities, such as the extra copy of chromosome 21 that is present in the cells of children with Down syndrome. After several months spent “paying my dues” in the karyotype lab, I was invited to move down the hall to the research lab. The goal was to map a human gene encoding glutathione peroxidase (GPX) using somatic cell hybrids. Increased GPX enzyme activity had been reported in cells from patients with Down syndrome, which suggested that a gene coding for GPX might be located on chromosome 21. We now know that there are eight genes encoding GPX in the human genome. Sadly, none of them are located on chromosome 21. Nevertheless, as I was working out the conditions for assaying GPX activity, which took several months of trial and error, Dr. Gerald provided me with valuable advice regarding the nature of the scientific enterprise. He told me: “Search and re-search.” **Penn, CHOP, and MSTP** Although I had planned to go to graduate school to study genetics, the human gene-mapping project increased my interest in medical genetics, and I decided to apply to MD-PhD programs with the intention of pursuing both a clinical and a research career in human genetics. I was accepted into the Medical Scientist Training Program (MSTP) at the University of Pennsylvania School of Medicine. The National Institutes of Health had funded the MSTP at two-dozen medical schools in order to encourage training of clinician investigators. The MSTP covered my medical and graduate school tuition and provided a small monthly stipend, all of which I would be required to repay only if I chose a career other than biomedical research. During my first semester at Penn, I spent pretty much all of my savings on Gray’s Anatomy and other expensive medical school textbooks. I had a meal plan that covered Monday through Saturday. On Sundays, when the dining hall was closed, I would venture to a greasy spoon called Troy’s, which featured a 99-cent breakfast that would tide me over until Monday morning.  My initial efforts to earn a PhD in genetics did not go well. I started my thesis research in a lab as a junior faculty member’s first graduate student. After a year attempting two projects, neither of which was generating any encouraging data, I sought advice from the graduate program director and then, with his blessing, met with Elias Schwartz, who was the director of the hematology division at Children’s Hospital of Philadelphia (CHOP), and Saul Surrey, who was in charge of Eli’s research laboratory. They generously provided me with the opportunity to join their lab team.  The goal of my thesis project at CHOP was to perform a molecular analysis of the β-globin gene in a family with a variant form of β-thalassemia known as the silent carrier. β-thalassemia is a caused by defects in the expression of the β-globin polypeptide, which associates with the α-globin polypeptide and a heme ring to form hemoglobin, the protein in red blood cells that carries O2. In patients with β-thalassemia, β-globin production is defective, leading to the precipitation of α-globin and subsequent destruction of red blood cells, causing anemia. Affected individuals carry two mutant copies of the β-globin gene, one inherited from the mother and one inherited from the father. Because the parents have one mutated and one wild-type copy of the β-globin gene, they do not develop the severe anemia associated with β-thalassemia, but they usually have smaller red blood cells that contain less hemoglobin than normal and can thus be identified as carriers of a mutant β-globin gene.  In the family that I studied, the son and daughter had β-thalassemia, indicating that both parents were carriers. The mother’s red blood cells showed typical findings of a carrier, whereas the father’s red cells appeared completely normal and thus he was described as a ‘silent’ carrier. My goal was to determine whether the silent carrier allele, like all other β-thalassemia alleles that had been studied so far, contained a mutation in the β-globin gene. We hoped that the mutation would have some unique feature at the molecular level that was responsible for its unique clinical presentation.  I drew blood samples from the parents and children, isolated genomic DNA, constructed a library of DNA fragments in a bacteriophage vector, and then isolated and sequenced a 4.4-kilobase DNA fragment containing the β-globin gene that the affected daughter had inherited from her father. At that time, obtaining the sequence of 4 kilobases of DNA on both strands of the double helix was a manual process that took about a year to complete. To my horror, after a year’s work, I identified the same mutation that had been previously discovered by someone else in the lab studying an unrelated patient. Further analysis indicated that the mutation was not present in the daughter’s DNA but was apparently the result of contamination with another DNA sample somewhere along the process of the gene cloning and sequencing. The source of the contamination will forever remain a mystery.  At this point, I was quite depressed and went to see a psychiatrist, who happened to be the father of two of my medical school classmates. I told him my tale of woe regarding the prospect of starting my thesis research over yet again. He looked at me and said “Gregg, it certainly seems that you have good reason to be depressed!” After that validation, I felt much better and went back to the lab with renewed enthusiasm. I found that the β-thalassemia allele that the daughter had inherited from her mother contained a mutation in the β-globin gene at the junction between exon 1 and intron 1 that prevented proper processing of β-globin mRNA, leading to a failure to translate the β-globin mRNA into protein. In contrast, the β-globin gene that the daughter had inherited from her father had a completely normal DNA sequence. Moreover, the analysis of DNA polymorphisms spanning the entire β-globin gene cluster, which includes the genes for embryonic and fetal as well as adult β-globin, revealed that the two affected children did not even inherit the same β-globin gene cluster from their father, indicating that the silent carrier allele was due to a mutation somewhere else in the genome, a truly novel finding.  After my thesis presentation, I sat in the hallway for an hour while my committee members debated whether the bar was lower for MD-PhD students, who needed to apply for internship and residency well in advance of their thesis defense, thus exerting “pressure” on thesis committees to approve the student’s work in time for graduation and commencement of clinical training. The implication was that the work I had done was in some way not up to the lofty standards associated with a PhD from Penn. Fortunately, the editors of the *Journal of Biological Chemistry* and *Cell* did not have such misgivings when they accepted for publication the manuscripts I had written reporting the results of my thesis research. **Duke** Following graduation from Penn, I spent two years as a pediatrics intern and resident at Duke University Medical Center. When I drove a rented U-Haul truck into Durham, North Carolina in June of 1984, I was greeted by the pungent aroma of tobacco, which was still being made into cigarettes in a downtown factory. Mr. Duke had made his fortune in the tobacco trade and cigarettes were still offered for sale from a vending machine in the hospital cafeteria. My residency training there preceded the major national reforms that placed limits on the amount of time that house officers were permitted to spend on the wards, both in terms of consecutive hours and hours per week. Our schedule involved working more than a hundred hours per week, and being “on call” every third night, which meant that all or part of that night would be spent awake taking care of acutely ill children (except for a month on the Pediatric Surgery service, when the call was every other night).  The most difficult rotation was the neonatal intensive care unit (the “NICU”), where extremely premature infants with severely immature lungs were kept alive on ventilators. Two residents would split the night’s work when possible, thereby allowing each to have a few hours of sleep, provided that no emergencies arose that required the simultaneous efforts of both physicians. During my first rotation as an intern in the NICU, I had managed a brief sleep and then reported for duty; the senior resident observed my half-awake state and said “Gregg, go back and splash some water on your face.” Working a full day, then a full night, then a full day again before finally going home was a grueling experience, especially when repeated over many weeks.  Another feature of the Duke pediatrics residency at the time was that the delivery room was located in the old South hospital, whereas the NICU and pediatric wards were in the new North hospital. There was an electric tram that ferried patients, staff, and visitors at a leisurely pace between the two buildings. However, when a newborn baby required resuscitation at night, the on call resident literally had to sprint from North to South and hope to arrive in time to save the neonate’s life.  When I reminisce about my time at Duke, I usually mention that by some miracle, I only fell asleep at the wheel driving from the hospital to my apartment once. Fortunately, the car did not drift across the centerline, but rather towards the side of the road, which was covered with gravel, and the noise of the tires on the rough surface woke me before an accident occurred. **The fast track to Baltimore** Sue Church, who was one of the senior pediatric residents at Duke, noticed that I did not appear to be particularly happy in my position as a house officer. She suggested that I forego my final year of residency and fast track to a medical genetics fellowship. The pediatric genetics unit at Johns Hopkins was well known to me because Haig Kazazian and Stylianos Antonarakis (Figure 1), in collaboration with Stuart Orkin at Harvard, had led the effort to identify and characterize the functional consequences of mutations in the β-globin gene that caused β-thalassemia. I had read their papers with the intensity and devotion reserved by others for the Bible. In addition to the fantastic research environment, the Johns Hopkins fellowship provided the opportunity to learn Medical Genetics at the foot of the master, Victor McKusick (Figure 1). I interviewed at several genetics programs and when Haig Kazazian offered me a position at Hopkins, I immediately accepted. In order to fulfill the requirements for board certification in Pediatrics, I worked in the pediatric emergency department at Johns Hopkins Hospital on those evenings when I was not already on call as a Medical Genetics fellow.  During this first year in Baltimore, I also contemplated the possibilities for a research project. I was interested in studying the regulation of gene expression in vivo using transgenic mice. The Kazazian and Antonarakis labs had moved on from identifying mutations in the β-globin gene that cause β-thalassemia to identification of mutations in the gene encoding factor VIII that cause hemophilia A. I contacted Chuck Shoemaker at Genetics Institute, who had isolated the factor VIII gene, to ask whether he could provide me with cloned genomic DNA. After I told him what I had in mind, he said that he could provide factor VIII gene sequences, but that there was this other gene that I might want to consider studying called *EPO*, which he had cloned before starting work on factor VIII.  My education about EPO was facilitated by the happy coincidence that one of the world’s experts on the role of EPO in erythropoiesis was Jerry Spivak (Figure 1), a Hopkins hematologist, whose office was just down the hall from mine in Johns Hopkins Hospital. Based on Chuck’s suggestion and Jerry’s encouragement, I decided to focus on *EPO* gene regulation and was fortunate that John Gearhart (Figure 1), who was a faculty member in the physiology department at Hopkins, agreed to collaborate with me to generate *EPO* transgenic mice. Stylianos Antonarakis served as my mentor on a daily basis in the lab and Haig Kazazian provided advice about the direction of the project and funding opportunities.  At this point I should emphasize how uncommon – if not inappropriate – it was for me, as a starting postdoc, to: (a) enter the Kazazian-Antonarakis lab, in which the investigators were establishing a paradigm for molecular dissection of human genetic disease, which subsequently served as the template for hundreds of investigators studying dozens of inherited disorders, and blithely assume that I would initiate a completely unrelated (and unfunded) research project; and (b) enlist the participation of a senior faculty member in another department as well. Such was the incredible generosity of my mentors.  My good fortune grew larger when John Gearhart called me up one day and asked me if I had seen the RFA on EPO. I replied, “What’s an RFA?” John told me that the National Institutes of Health (NIH) had released a Request for Proposals (a.k.a. RFA) to study the molecular mechanisms of *EPO* gene regulation. It seemed to be a tailor-made source of funding for my project. The only catch was that the RFA funded R01 grants, which are awarded to faculty members, not postdoctoral trainees. Stylianos agreed to serve as the principal investigator, with John as a co-investigator. I composed the application on a Macintosh SE computer in my apartment during a midwinter blizzard. The application scored in the fifth percentile and was funded for three years.  Around the same time, Haig Kazazian was on a flight back to Baltimore from California with Tom Pollard, a faculty colleague in Cell Biology who was an expert on the workings of actin and myosin in driving cell motility. Tom told Haig about his involvement with the Lucille P. Markey Charitable Trust, which was at that moment soliciting applications to fund research programs for young investigators as a bridge from postdoctoral to faculty positions. Mrs. Markey had been married to, and outlived, two wealthy men, including the owner of Calumet Farms in Lexington, Kentucky, a famous stable that had produced eight Kentucky Derby champions. She had several very enlightened advisors, who suggested that she use her considerable wealth to establish a trust to foster biomedical research. At its peak, the annual funding expenditures by the Markey Charitable Trust exceeded those of the Howard Hughes Medical Institute.  Although this grant application seemed like a great opportunity, there was a catch: the application was due the following week. I worked nonstop that weekend to prepare the application, secured letters of recommendation from Haig and Victor McKusick, and sent the application off to the Trust headquarters in Lexington. Incredibly, the application was funded for six years (one extra year as a postdoc and five years as an assistant professor). Although Tom Pollard was on the selection committee, he was no doubt recused when my application was considered, which was probably a good thing: several years later, when a faculty member in Tom’s department told him that she had discovered the *Drosophila* gene responsible for a developmental mutant, and that it encoded a transcription factor, he said to her, “Oh, I’m so sorry!”  The studies of *EPO* gene regulation in transgenic mice, and later in human cells, that were funded by these two grants led directly to the discovery of hypoxia-inducible factor 1 (HIF-1), as described in my [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2019/semenza/lecture/). One of the great benefits of receiving funding from the Lucille P.  Markey Charitable Trust was that the grantees met annually to present their research progress to the members of the selection committee, which was a Who’s Who of Science that included [Mike Brown](https://www.nobelprize.org/prizes/medicine/1985/brown/facts/), [Joe Goldstein](https://www.nobelprize.org/prizes/medicine/1985/goldstein/facts/), [George Palade](https://www.nobelprize.org/prizes/medicine/1974/palade/facts/), and [Torsten Wiesel](https://www.nobelprize.org/prizes/medicine/1981/wiesel/facts/). At the annual meeting in 1993 or 1994, Joe Goldstein, who was one of my personal scientific heroes, gave an after dinner speech that made a deep impression on me. He spoke of what he called “technical courage,” by which he meant a determination to follow the science wherever it led, rather than being limited by the particular experimental techniques that one was most comfortable using.  This advice was soon put to the test. We had attempted to identify cDNA sequences encoding HIF-1 using a bacteriophage expression library cloning approach without any success. In mulling over my options, I came up with three choices: (1) We could continue to use the same screening approach and hope that our luck would somehow change after screening millions of bacteriophages; this seemed very close to [Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/)’s definition of insanity. (2) We could give up and wait for someone else to do the job; that wasn’t an appealing option. (3) We could take an entirely different experimental approach, which was to perform a biochemical purification of the protein. This seemed improbable, given that I was trained in molecular biology and we did not even possess a fraction collector at the time. Fortunately, Tom Kelly (Figure 1), who was then the director of the department of molecular biology and genetics at Hopkins, was one of the pioneers of DNA affinity chromatography. Tom’s lab provided advice and assistance that was essential to our eventual success in purifying HIF-1 and isolating DNA sequences encoding the HIF-1α and HIF-1β subunits. This work was reported in papers published in 1995 in the *Journal of Biological Chemistry and the Proceedings of the National Academy of Sciences.* The latter manuscript, which was communicated by Victor McKusick, was submitted to and returned without review by the editors of *Cell, Science,* and *Nature*. This PNAS paper has now been cited over 6,000 times.  It is satisfying that the first translation of our discovery of hypoxia-inducible factors to the clinic has been the development of drugs that increase HIF activity as a means of stimulating red blood cell production in patients with chronic kidney disease. Unlike recombinant human EPO, which must be injected, these new HIF stabilizers are small molecules that can be taken by mouth. Four different drugs are currently in phase III clinical trials that have enrolled over 20,000 subjects and it seems likely that one or more of these will be approved by the FDA sometime in 2020, exactly 25 years after the publication of our papers reporting the purification, cloning and sequencing of HIF-1 of the HIF-1α and HIF-1β subunits. **Friends, collaborators, and trainees** By now, the reader is fully aware that our discovery of HIF-1 could not have been achieved without the mentoring that I received from Haig Kazazian, Stylianos Antonarakis, Victor McKusick, Jerry Spivak, John Gearhart, and Tom Kelly at Johns Hopkins. I have also been extremely fortunate to have an abundance of wonderful collaborators at Johns Hopkins and at other universities with whom I have investigated the role of HIF-1 in development, physiology, medicine, and evolution as described in my Nobel Lecture. Among the longest and most valued friendships, forged over decades of collaboration, have been those with Nanduri Prabhakar (University of Chicago) and Joe Prchal (University of Utah), and my Hopkins colleagues Chi Dang, Larissa Shimoda and Akrit Sodhi (Figure 1). I am honored to serve as the C. Michael Armstrong Professor at Johns Hopkins University. Mike Armstrong (Figure 1) has been a tremendous supporter of our work and with Mike’s help we hope to one day reach our goal of developing drugs that block HIF activity for the treatment of cancer.  I have had the distinct pleasure of training an extremely talented and hardworking group of 55 postdoctoral fellows, 30 graduate students, and 40 undergraduates. Since 1996, when I decided that I would not be able to adequately mentor the members of my lab unless I gave up my spot at the bench, all of our experimental data has been produced by these trainees and collaborators. Some, but by no means all of them, are mentioned in my Nobel Lecture.  Among my fondest memories of the whirlwind that occurred between the Nobel Prize announcement on October 10 and the Nobel Lectures on December 10, 2019, two stand out. The first of these was a lab reunion at our home in November, which was attended by over fifty present and former lab members from as far away as Hong Kong. The second was a private dinner, which Laura and I hosted for thirty of our closest family members and friends at the Gondolen restaurant, that lasted late into a snowy December night in Stockholm. **Saving the best for last** My fulfilling scientific career has been made possible by the love, understanding, and support of my wife Laura and my children Allie, Evan, and Gabe (Figure 2). They have transformed my pedestrian life into a fantastic journey and give meaning to every breath I take. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0513= GS  Gregg Semenza: Hello.  Adam Smith: Hello, my name is Adam Smith, calling from Nobelprize.org in Stockholm. Well, first of all, many, many congratulations on the award of the Nobel Prize.  GS: Thank you.  AS: Were you asleep when the call came?  GS: Most definitely. [Laughs]  AS: Nice way to be woken up.  GS: Yes, I think it took two calls. The first time I didn’t get there quite in time but managed on the second try.  AS: You must have … you must have had a nervous moment because I guess you may have had an inkling what the call was about, thinking you may have missed it.  GS: Yeah, either that or I thought someone had a very bad sense of humour.  AS: That could happen I suppose. What did you do upon hearing the news?  GS: Hugged my wife.  AS: So, this lovely combination of the three of you in the way your work intertwines, but you discovered the protein HIF-1. Were you amazed by how ubiquitous its involvement in pathophysiology and normal physiology seems to be?  GS: For sure. Yeah, we started studying a very specific and kind of limited question of how red blood cell production was regulated, and from there it expanded to so many areas of physiology and medicine. Quite amazing.  AS: Reading the story of how it all pieced together, it illustrates how much science research is about solving puzzles.  GS: Yes, and unexpected turns. That’s what makes science so exciting, you never quite know where your studies are going to lead you.  AS: It must be a little bit like being a detective.  GS: Yeah, it is. You have the added benefit that solving the puzzle may ultimately impact on people’s health, of course the most important part of the process.  AS: That’s an interesting point because all three of you have one foot in the research lab and one foot in clinical practice. Do you think that’s an important point?  GS: Yeah I do. I think it’s really important to have people who are kind of there at the boundary between research and medicine to facilitate the discovery of knowledge that will translate ultimately to improvements in clinical practice.  AS: It must be increasingly hard to keep both things going, with increasing clinical workloads and, I don’t know, more form filling if you’re a scientist.  GS: Yes, that’s right. In fact I stopped my clinical work about 20 years ago and focussed on the research at that time.  AS: I must say, you do sound … you sound quite knocked back by the news.  GS: Yeah, well certainly nobody expects that, that’s for sure. Even after people have been telling you for, you know, 20 years or more that it’s going to happen, no one expects it.  AS: That’s right, because the three of you got the Lasker Prize in 2016, which is sometimes an indicator isn’t it?  GS: Yeah, sure, but it’s still no guarantee and there’s certainly lots of deserving candidates, so I was certainly speechless when I received the news.  AS: Well, it’s going to be a day of conversations with journalists who are going to be landing on you. Will you find any respite before then, perhaps not?  GS: No, I don’t think so. [Laughs]  AS: We look forward enormously to welcoming you to Stockholm when you come in December to receive the Prize.  GS: I certainly look forward to it.  AS: Thank you very much indeed, and once again congratulations.  GS: Okay, take care.  AS: Thank you, bye bye. |
| Interview |  |
| Q40 | What was your childhood like? |
|  | Gregg Semenza: I have two brothers and two sisters, so we have a large family and especially when we were young of course that involved a lot of chaos, and we had a lot of freedom at that time. Children now seem to have very scripted lives and whereas we had a lot of freedom. Basically, we go out of the house in the morning, at say in the summertime and you come back in the evening for dinner and nobody is expecting to see you in between so, y it was a lot of fun to grow in that kind of an environment. |
| Q5 | Was there a particular teacher that inspired you? |
|  | Gregg Semenza: For my carrier inspiration, I was very fortunate to have a high school biology teacher, a Dr Rose Nelson and she was a PhD, so she had done research, she had done post-doctoral training and she taught us biology, not as a series of sort of facts but she would teach us about discoveries and about scientist who made discoveries and sort of the excitement of learning something new in science. And that really excited me. She also recommended to me a summer programme at a research institute where I was able to experience research firsthand. All those experiences really, really excited me and developed a passion in science that I have had ever since, so I really owe that to her. It’s one of my regrets that she passed away before this time because she was a very, very positive person and very abluent, joyful, she always had a beatific smile on her face and she would be teaching us something and she would say,:“Now, I want you to remember that when you win your Nobel Prize that you learned that here”. And she said this, not to me, but to the class and she would say this as a statement of fact, so I don’t know how she knew, but she was really a remarkable teacher. |
| Q1 | Why did you become interested in genetics? |
|  | Gregg Semenza: I guess the idea of hereditary passing down of traits and how this was determined by sequences within the DNA. It’s kind of a very amazing thing to go from these molecules to traits of living organisms and that really interested me. I was first interested in genetics, sort of basic genetics and thought I would do basic genetic research, but while I was in college, a family that we knew had a child born with Down syndrome and I became interested in medical genetics, and decided that I would try to get training both as a MD and a PhD, so that I could do both genetics research and medical genetics as a clinical specialty. |
| Q3 | How do you deal with failure? |
|  | Gregg Semenza: When I was a college student I worked in a lab in Boston and the leader of the lab, he would always say: “Search and research”, because that’s the nature of science. There are always obstacles to be overcome, experimentally, and that’s a challenge and if that isn’t something that is enjoyable to you then probably science is not a good line of work because we are constantly faced with those kinds of obstacles and challenges. And part of the fun of the work is using our creativity to come up with solutions to those kinds of problems when they arise.  Persistence is a very critical attribute, absolutely, and then the other part of it that is very helpful, is to have colleagues who take orthogonal approaches to the science. They may look at the science in a slightly different way and may provide an avenue for circumventing various obstacles. When we were trying to isolate the DNA sequences that coded for the subunits of hypoxia-inducible factors we took one approach because we thought that there was only one protein that was involved, and we took an approach that involved screening human DNA sequences in bacteriophage and we screened millions and millions of these clones, and we got negative results. As a leader of the research project, it’s sort of my role to decide what to do. We could continue doing what we were doing – that didn’t seem like a very good idea. We could give up and let someone else do it – that didn’t seem like a very good idea either. Or we could take a completely different approach which was rather than a molecular genetic approach to take a biochemical approach and try to purify the protein through biochemistry. And this was not exactly our foretake, we owned none of the equipment that was required for purify proteins, did not really have the expertise to do that, but fortunately, across the street at Johns Hopkins was the lab of Tom Kelly and his lab was one of the first labs to purify a protein based on its binding to DNA. With the assistance of his lab, we were able to do that, to purify the protein from a hundred leaders of cells, growing in culture and to get just enough of the protein that we could obtain some protein sequence and then use that protein sequence to identify the DNA sequences of what turned out to be the two subunits of the protein. So, in fact the approach that we had been taking would never have worked because that approach only works if the protein has the single subunit and because our protein turned out to have two different subunits only through the purification, the biochemical purification, would we have been able to succeed. |
| Q20 | How important in freedom in science? |
|  | Gregg Semenza: The freedom and the creativity, these are the really fun parts of the job that no one tells us how to do our work and as long as we are successful, we are left alone and we can do our thing. To have that freedom to, not only with regards to problem solving, but even more fundamentally, what questions do we ask, what are the really important questions that we would like to answer. That’s left entirely up to us and obviously that changes over time. So, we started with more basic, fundamental questions and then over time have shifted to more applied applications as the project has evolved. That’s been very satisfying over the course of thirty years, to be able to connect the dots to very molecular fundamental questions: how does the cell sense the oxygen concentration and respond to changes all the way to … can we develop new treatments for anaemia, for cancer, for cardiovascular disease. And as someone trained both in research and medicine, for me, I’ve always thought it’s my role to bridge between the basic science and the clinical translation and it has been very satisfying to reach that point where we see these translations occurring now as a result of these basic discoveries that were made 25 years ago. |
| Q38 | Have you ever doubted yourself? |
|  | Gregg Semenza: That’s a good question. I guess I doubt myself often. I often doubt, you know, am I taking the best approach? Am I running the lab most efficiently? Am I mentoring my students well enough, could I be doing a better job with that? I guess I have those kind of doubts or self-criticism on a fairy regular basis. |
| Q19 | How did you discover you had been awarded the Nobel Prize? |
|  | Gregg Semenza: I think the word is dumbfounded. It was of course in the US and it was in the middle of the night and I was sleeping very soundly, and the phone rang and when I finally was awoken out of the sleep and got to the phone in the hallway it had stopped ringing. I was not even really awake yet and I figured, well, maybe this is somebodies’ idea of a bad joke, because I did know what day it was. So I went back to sleep and actually quite a while later the phone rang again, I said: “Perhaps I‘d better be quicker this time”. So I got to the phone and Thomas Perlmann apologized for waking me up and then gave the good news and I was sort of on the phone and my jaw just dropped and I didn’t really … words weren’t coming out. Of course, my wife was there, and she could hear what was being said on the phone and her jaw dropped and she couldn’t say much either, we were just kind of mute. It was a very one-sided conversation. |
| Q23 | Can you explain your Nobel Prize-awarded discovery? |
|  | Gregg Semenza: Everybody appreciates the importance of oxygen. You just have to hold your breath and you’ll start feeling uncomfortable very soon, because you have a hundred trillion cells in your body, and they all need oxygen on a continuous basis. Principally to make energy, which allows us to … for this complex organism to function. The body uses glucose and oxygen in order to generate energy. By the same token, oxygen at too higher levels causes damage to cells, so there has to be a very tight coordination between supply and demand. The amount of oxygen that each cell requires, has to be matched by the delivery of oxygen which is of course carried by red blood cells through the blood vessels to each cell. There is a beautiful physiological system that maintains the balance between consumption and delivery of oxygen in every one of the hundred trillion cells in your body under normal healthy conditions and if that balance is disturbed by many common diseases, including cardiovascular diseases and cancer. |
| Q16 | What practical applications does your work have? |
|  | Gregg Semenza: The first translation of the discovery of this system to the clinic is the development of new drugs for the treatment of anemia. We started by studying the hormone that controls red blood cell production, called erythropoietin, or EPO. Patients who have a chronic kidney disease, their kidneys stop making EPO and they become anemic. The discovery of EPO was a revolution because it enabled the patients to receive a recombinant EPO protein as an injection, to stimulate red blood cell production. Of course it’s a recombinant protein and it has to be injected and now there are in development drugs that induce the activity of the factors that we identified, the hypoxia-inducible factors that control EPO production, and these drugs can be given as pills by mouth. The treatment of anemia can be made much more convenient for patients, both with kidney disease and other causes of anemia. And there are four different drugs that are all in advanced clinical trials now, over 25,000 patients are being studied in these trials and one of the drugs has already been proved for use in China and Japan and will probably be approved in the US and in Europe within the next year, if everything goes well. That will be the first application of our discoveries to the clinic.  Another area in that context, the hypoxia-inducible factors are, as I said, play an important role in physiology and when they are not produced in sufficient amounts, we want to stimulate that. But in cancer, the factors are produced at very high amounts because oxygen becomes very limiting in cancers because the cells grows so rapidly that they basically outgrow their blood supply and become very hypoxic. And this can lead in fact to the cancer cells dying because they don’t have enough oxygen, which, of course, you can say what is bad about that, that’s what we like cancer cells to do, to die, but of course, the cells that are very far away die, but those that are closer, they can survive but their exposure to low oxygen changes them, makes them more invasive and metastatic, more difficult to kill. We believe these cells are really cells that are very dangerous in terms of the risks of the cancer spreading through the body and resisting therapy and pretty much all of the cancer therapies are targeted to cells around blood vessels that have lots of oxygen that are rapidly dividing, whereas the hypoxic cells are not really targeted by any therapy and we think that if we can inhibit the activity of the hypoxic inducible factors in the hypoxic area of the cancers, that will complement the existing therapies and lead to a better outcome for patients with advanced cancer. There is a HIF inhibitor that is now on clinical trials for kidney cancer, so, we’ve already started down that road as well. When I say we I mean the scientific community, the pharmaceutical industry, recognizing the importance of this area for targeting in different diseases. |
| Q41 | Is there a good balance between basic and applied research in medicine today? |
|  | Gregg Semenza: Most applied research comes from a foundation of basic research and what I mean by that is that the basic studies are all often done just trying to understand the system and the properties of that system without directly saying, we want to target this particular disease, because that tends to be less effective than to say, let’s just learn about this system and by doing so, over time it will become apparent how we might target the system therapeutically. That’s how we started, just with very basic fundamental research, and it’s lead now, I think, to many applications. Being apparent that that again will take time to unfold but we’ll hopefully resolve in new treatments for a number of different diseases. |
| ID | 0514 |
| Biographical | As a basic scientist, I have been fortunate to see my research findings translate into a powerful new potentially curative treatment strategy for cancer. The first patient I met was Sharon Belvin. I met her in 2006 at Memorial Sloan-Kettering Cancer Center (MSKCC). Jedd Wolchok, an oncologist at MSKCC, called and asked me to meet him in his clinic. There, he introduced me to Sharon Belvin, who was 24 years old and had been battling metastatic melanoma. Melanoma had invaded her brain, lungs, and liver. She was diagnosed at the age of 22 and had received multiple prior therapies but her cancer continued to grow and, when she was 23, she was told that she only had a few months left to live. But, as a last-ditch effort, she participated in a clinical trial of a then experimental drug, anti-CTLA-4. Within 3 months of starting treatment, her tumors shrank in size and then disappeared. In 2006, when I met her, it was her one-year anniversary of having completed the treatment. Her disease had responded to the treatment and she was considered in remission and possibly cured.  Sharon and I have become good friends. When her first child was born a few years later, she sent me pictures. Then pictures of her second child. She is now 13 years out from her battle with cancer and enjoying life with a vibrant family. I can’t help but cry whenever I tell this story. My meeting with Sharon was my first experience of how years of research as a basic scientist could have an impact on patients. Her experience, and those of many other patients with many types of cancer who have benefitted from this work, has provided inspiration to work to continue improving this therapy for the benefit of many more patients. **Early life, South Texas** I was born in 1948 in Alice, a small farming and oil town in the brush country of the Rio Grande Valley in South Texas. Those early years in Alice shaped who I would later become. Being in Texas, the whole town, including my two older brothers, was obsessed with football. But, I learned from a young age that being crushed under a pile of big sweaty boys on a hot Texas afternoon was not my idea of fun. My interests lay more in knowledge and playing at chemical and biological experimentation. If you couldn’t find me curled up with a book, I was probably in the garage dissecting frogs or making homemade bombs to test in the nearby woods.  My Dad was the old-fashioned kind of doctor that made house calls, and I would sometimes accompany him on his rounds around town. I think he was the first immunologist I met because, in the days before vaccines for measles, mumps, and other childhood diseases, he would take me with him so that I could be exposed to the other children who had these illnesses. It was his way of exposing me to the infectious agents while I was young so that I could develop immunity against these infections and avoid the dangers of contracting these illnesses as an adult.  My Mom died when I was 11 years old. This was my first loss to cancer. At the time I didn’t know it was cancer because people simply did not speak of such things during those days. All I knew was that my Mom was getting sicker and spending increasing amounts of time in bed. She would go to the hospital for treatment and come back with burns on her neck. I later learned that she was suffering from lymphoma and was receiving radiation therapy, the standard-of-care treatment at the time. One morning in summer of 1960, as I was leaving with family friends to go swimming, I was told to go back inside and see my Mom. I sat at her bedside and held her hand as she died. That was a defining moment in my early life. And then, not long after my Mom died, my uncle died from melanoma and another uncle later died from lung cancer.  Cancer treatment has always been in the back of my mind. Still, I can’t really say that the impact of cancer on my family motivated all that I would later do, but years later I knew that should the opportunity ever arise I would do all that I could to apply my work to curing cancer.  In high school in Alice, I was fortunate to have a few great teachers who went the extra mile to encourage me to do my best and to take advantage of available resources, some outside the reach of the standard curriculum. A counselor arranged for me to participate in special summer programs for talented students at University High School in Austin after the 8th, 9th, and 10th grades. The topics for the programs varied, but all focused on individual or small team conducted projects. These summers were invaluable in immersing me in new situations and broadening my perspectives. The summer after my junior year, I participated in a biology course sponsored by the National Science Foundation at UT Austin. The mornings during that summer were spent in lectures presented by Irwin Spear, a truly exceptional teacher who taught freshman biology at the University of Texas at Austin (UT Austin) during the academic year. And the afternoons during that summer were spent working in research laboratories. This was a life changing experience, and I began to seriously consider a career in science.  I had an unusual experience when I returned to Alice for my final year in high school, when biology was typically taught. I knew of Darwin and the Origin of Species from my reading, and Dr. Spear’s lectures had made it clear how essential the ideas of selection were to the understanding of many aspects of biology. So, when I feared that biology as taught in Alice was going to be completely devoid of any mention of these ideas due to the religious beliefs of the faculty, I refused to take the class. I could see no value in such a course. I told the school officials that teaching biology without Darwin was like teaching physics without Newton and would be a waste of time, and I would not enroll in the course. The response was that it was a required course and, without it, I would not be allowed to graduate (among other threats). Finally, a wise counselor proposed that I fulfill the requirement by taking a correspondence course from UT Austin. I successfully completed it and graduated high school in 1965. **The University of Texas at Austin: undergraduate and graduate training** I enrolled at UT Austin in the summer session immediately after high school graduation. Due to my summers in Austin, I never thought of going anywhere else. In accordance with my father’s hopes, I began as a premed student. However, I became dissatisfied with the rote memorization required in some of the pre-med courses. At the beginning of my second year, in order to make a little money and hopefully gain entrance into a research lab, I became a dishwasher for G. Barrie Kitto, a new assistant professor of biochemistry at UT Austin. Over time I was allowed to help with experiments, then do my own, and eventually have my own projects as an undergraduate researcher.  I gradually learned of a key difference between medical practice and laboratory research. I realized that a physician must have a brain full of facts which can be accessed rapidly to deal with emergency situations that may arise during patient care. Physicians have to be able to quickly analyze symptoms and implement a treatment plan. And physicians cannot be wrong. They must be accurate in order to help patients or, at least, avoid harming them. A scientist’s job is very different. A scientist is usually focused on interesting, and hopefully important questions, and generating experiments to test hypotheses. As a scientist, it is equally valid to prove the hypothesis true or false. That’s fortunate, because many of our hypotheses are wrong; in fact, if you are asking interesting questions, most of them are wrong. Being wrong can actually be a good thing, because the answers generated in disproving an incorrect hypothesis will help you and others to propose alternate hypotheses. Then, you go back to the lab to do more – hopefully better – experiments. I did not have the discipline to be a physician, so I chose to be a scientist and have more fun. My initial projects involved the biochemical taxonomy of sea urchins, sea cucumbers and starfish. These studies were interesting and taught me the importance of precision and rigor. My next major project focused on biochemical and serological characterization of bacterial asparaginases, which at the time were showing promise in the treatment of childhood leukemias.  In addition to my courses and laboratory studies, I truly enjoyed the music scene in Austin. These were wonderful years in Austin, especially with respect to the great music from Jerry Jeff Walker, Willie Nelson, and many others as well as the eclectic venues for hearing live music such as the Broken Spoke, Soap Creek Saloon, and, of course, the Armadillo World headquarters. Life was good!  It was also during my time at UT Austin that I took an undergraduate course in immunology taught by the late Professor Bill Mandy. Professor Mandy gave one lecture on T cells and I was hooked. T cells travel throughout the body seeking out cells that shouldn’t be there, such as virus-infected cells or even tumor cells, and T cells then eradicate these aberrant cells. Nothing was known about how T cells recognized foreign cells, or what regulated their proliferation and function, or virtually anything else. I was fascinated, and decided to devote my career to solving their secrets. **Scripps Clinic and Research Foundation: 1974–77** Professors Mandy and Kitto helped me get a post-doctoral appointment in Ralph Reisfeld’s laboratory at Scripps Clinic in La Jolla, California. I felt that this was a great choice because Scripps was a hotbed of research in immunology, and because Reisfeld had recently reported the isolation and initial characterization of human histocompatibility (HLA) antigens.  These molecules had been shown to be important in rejection of allografts in humans, and the mouse homologs, MHC antigens, were suspected as having a more general role in T cell recognition of other antigens. I was reasonably productive, and succeeded in obtaining some of the very first primary amino acid sequence information from both HLA class I and class II antigens.  But, once again it was not all work. One day we met Clay and Ailene Blaker, two expatriate Texans who moved to San Diego to surf and start a band, “Clay Blaker and the Texas Honky Band.” Clay was a singer/songwriter who wrote much of his own material. (One of his songs, “Lonesome Rodeo Cowboy” later became a hit for the country superstar George Strait). The music filled a void and reminded me of Austin. I had been playing harmonica for years, either tooting by myself or trying to play along with records by blues masters like Muddy Waters and Jimmie Reed, or with county outlaws like Willie Nelson and Waylon Jennings. I started sitting in with Clay’s band occasionally, and ended up becoming a regular band member, playing with the band at a country dive bar called the Stingaree every Tuesday night for more than a year. At one point the band decided to move back to Texas to play in the dance halls around Gruene and New Braunfels in the hill country of central Texas. I decided to keep my day job as a post-doctoral fellow, but Clay and Aileen were very successful, earning a strong following. **The University of Texas System Cancer Center – Science Park, Smithville: 1977–1984** I heard from a friend that the M. D. Anderson Cancer Center in Houston was opening up a small research institute in Smithville, which was about an hour away from Austin, and I secured a position as Assistant Professor. It was my chance to seriously devote my efforts to immunology, and also to get back to Austin.  It was a wonderful situation. We were in a bucolic setting in the Lost Pines area of central Texas, in the midst of a state park complete with a lake and hiking paths. The lab was about 7 miles from town, and we regularly saw deer, armadillos, and other wildlife on the laboratory grounds. There were only six faculty members and perhaps 50 staff in all. There was a grand esprit de corps, and we were accustomed to working together when extra hands were needed. We worked very hard, but also enjoyed the Austin music, exciting as ever, with many of the original artists still there, but also many new faces, like Stevie Ray Vaughn, Beto and the Fairlanes, and too many others to name.  Nominally the theme of the lab was carcinogenesis research, and my main project was to make monoclonal antibodies and use them to detect cell surface changes as liver cells become neoplastic. My colleague Douglas Hixson and I made good progress, but I was also free to begin my own efforts in T cell biology.  It was during my time at Smithville that I heard a lecture that Irv Weissman presented at the main campus in Houston that gave me some ideas, and led me to think of a series of experiments that might lead to identification of the T cell antigen receptor (TCR). The TCR was considered the “holy grail” of immunology at the time. Many high-profile labs and scientists were feverishly trying to find the TCR as its identification was key to unlocking the mysteries of T cells. T cells recognized MHC plus antigen that was found on antigen presenting cells (APCs), but the question remained: what was the specific molecule on T cells that enabled this interaction? I made a series of monoclonal antibodies that recognized clonotypic antibodies on mouse T cell lymphomas and I designed a set of biochemical experiments that, with the help of graduate student Bradley McIntyre, led to the identification of the protein structure of the TCR. This discovery led to a lot of notoriety and invitations to high level conferences.  After that, the race was on to clone the genes encoding the TCR. I spent a sabbatical as a visiting scientist in Irv Weissman’s lab in order to conduct experiments aimed at finding the genes for the TCR but, other brilliant scientists, including Mark Davis and Steve Hedrick, as well as Tak Mak, were the first to identify the genes for the TCR.  Nonetheless, my time in Irv’s lab opened a whole new world to me. I was invited to the University of California Berkeley to give a seminar and eventually I was offered a tenured-track position as a full Professor. **The University of California, Berkeley: 1984–2004** UC Berkeley is a marvelous place, teeming with bright, inventive people seeking knowledge. My time at UC Berkeley was notable for my interactions with many wonderful colleagues and students. It was a time of discovery, collegiality, long days working in the lab, and long nights partying with everyone in the lab. Max Krummel described it best by saying that the lab was filled with many personalities who enjoyed each other’s company so much that they worked together and had fun together, like a family, or like a pirate ship filled with great people having a great time, even as they continued to steer the ship in the right direction. We all worked hard to understand fundamental aspects of T cell activation and its regulation. These were exciting and heady times. I remember many scientific meetings, especially conferences at Asilomar where my lab members would lead intense scientific discussions during the day, and then celebrate at night by building a bonfire on the beach and dancing and singing until sunrise.  I also took on leadership roles for the first time at UC Berkeley, including chairing a fledgling new Division of Immunology in the Department of Molecular and Cell Biology, recruiting faculty as the department continued to grow, and building a supportive environment for junior scientists to succeed. I should point out that my strategy for mentoring consisted of protecting faculty from bureaucracy, providing resources, such as lab space, funding, and collaborations, encouraging people to pursue their scientific passion, and basically leaving them alone to pursue their goals, with some guidance when needed. I am very proud of the outstanding faculty that I hired, most of whom quickly rose to the top ranks of their fields. It was a joy to share data and interpretations of our research finding.  I also tried to inspire a culture of “work hard, play hard” in my lab and the department. New ideas and projects were always encouraged and drinks after work were also encouraged to discuss successes and disappointments. The bonds that were formed with people at Berkeley are lifelong because they were forged with a sense of camaraderie and shared vision.  My own scientific vision was clear at Berkeley: decipher the way in which T cell responses are regulated. The entire process of T cell responses starts with the TCR. The TCR is signal one and can be compared to the ignition switch of a car. It is needed to turn the car on and start the process of T cell activation, but we knew that it was not enough to get it going. A second, costimulatory signal, which could only be provided by specialized APCs such as dendritic cells was required. Without the second signal, T cells failed to proliferate and failed to respond to antigen, a state defined as anergy. In 1992, Fiona Harding in my lab showed that CD28, another protein on the surface of T cells, was sufficient and necessary to provide the second signal for full activation of naïve T cells and to prevent induction of anergy in T cell clones. CD28 can be compared to the gas pedal in a car, which allows the car to start moving.  Still, there was another important piece of the puzzle that had yet to be solved. Another receptor on the surface of T cells, named CTLA-4, had been found that bore significant homology to CD28. There was no scientific consensus on the potential function of CTLA-4 as most thought it was another positive costimulator. In 1993 and 1994, studies from my lab and Jeff Bluestone’s conclusively demonstrated that CTLA-4 is a negative costimulator that directly opposes CD28. CTLA-4 can be compared to the brake in a car, which acts to stop responses before they cause any damage.  Max Krummel worked tirelessly to conduct experiments focused on defining the role of CTLA-4. After we showed that CTLA-4 acts as an inhibitory receptor to control T cell responses, I immediately designed the experiments to test the idea that antibody blockade of CTLA-4 would lead to tumor eradication. I outlined the experiments to Dana Leach and he injected mice with tumors and then treated them with anti-CTLA-4. He showed me results from the first experiment in 1994 and I was absolutely blown away. The treated mice had all rejected the tumors. It was astounding. By blocking a single molecule, CTLA-4, we had reversed tumor growth and death! I knew that we had to immediately confirm the data by repeating the experiment in a blind fashion.  But, Dana was leaving on Christmas vacation to visit his family, and he did not have time to repeat the experiment. We agreed to do a blinded experiment where he injected a new set of mice with tumors and to treat half of them with anti-CTLA-4 and leave the other half untreated, without my knowing which group was which. He set up the experiment and left on his trip. I monitored the mice daily and recorded tumor growth on all of them. Initially, I was disappointed, since all of the mice demonstrated tumor growth equally. But then, around day 14, I noticed that some of mice had tumors that appeared to have stopped growing. Over the next few days it became apparent that the tumors were shrinking, and eventually disappeared, from some of the mice. It, of course, turned out that all the mice that eventually rejected tumor had received the anti-CTLA-4 antibody. It was another eureka moment! I knew that we had just figured out a way to treat cancer in patients. We conducted many other experiments in mice and confirmed our data over and over again with a variety of tumor types. We did not find any tumors that we could not cure with CTLA-4 blockade as monotherapy, or in combination with other agents, such as chemotherapy, radiation, vaccines, or local ablation.  We clearly demonstrated that CTLA-4 was an inhibitory signal on T cells, which was the first time that an inhibitory pathway had been described for T cell responses, and we showed that blockade of CTLA-4 could lead to tumor eradication. We tried to convince many different pharmaceutical companies to work with us over the next 5 years but had little success due to skepticism in the field after many failed clinical trials with other immunotherapy agents such as vaccines and cytokine therapies. Many people did not believe that it was possible to treat cancer with a drug that did not target tumor cells but instead targeted T cells. The field of oncology was focused on identifying genetic mutations in cancer cells and then targeting these specific mutations with drugs, even though such studies indicated that tumor mutations would continuously change and accumulate, which would lead to escape from the genetically-targeted drugs. I argued that the mutations would elicit T cell responses; therefore, we needed to target T cells to improve their responses against these tumor mutations. I repeated my claims that the immune system was a living and evolving system and if we allowed T cells to do their job, by removing the brake with anti-CTLA-4, the T cells would keep up with the evolving mutations in tumors so that T cells would eradicate the tumors and cure patients. My claims were met with skepticism over and over again. Luckily, my friend Alan Korman, convinced Nils Lonberg at the biotech company Medarex that it was a worthwhile endeavor to help with our project. Medarex had a technology well-suited to the task: mice whose antibody genes had been replaced by human genes and could directly produce human antibodies. Alan joined Medarex and with Nils quickly produced an antibody (MDX-CTLA-4 or MDX-010), which was renamed ipilimumab by the US Food and Drug Administration when it entered clinical trials.  As the inventor of CTLA-4 blockade I was not, of course, involved in the trials, but was kept informed of the main efforts. The early trials were promising, with objective responses in a Phase I trial of ipilimumab in melanoma, and in some small trials in prostate, kidney, and a few other types of cancer. While this generated considerable excitement, I heard troubling reports that ipilimumab failed with more stringent trials with progression-free survival (PFS) as the endpoint. I began to worry that the clinical investigators might not fully appreciate the biology of CTLA-4 blockade, and were treating it as a conventional cancer drug that kills cancer cells, rather than a drug that activates immune responses by removing inhibitory signals.  As much as I loved UC Berkeley, I began to feel the need to learn more about cancer clinical trials, which was not possible there. In 2003 [Harold Varmus](https://www.nobelprize.org/prizes/medicine/1989/varmus/facts/) and Thomas Kelly offered me the opportunity to lead the Immunology program at the MSKCC in Manhattan, and I accepted, not only to develop a world-class immunology program, but also to be close to the anti-CTLA-4 trials, many of which were being conducted at MSKCC. **Memorial Sloan-Kettering Cancer Center: 2004–2012** I arrived in Manhattan during the summer of 2004 with most of my laboratory intact. Over the next 8 years, I did my best to help Thomas Kelly hire a cadre of the best immunologists that we could, and I feel that we succeeded in building a truly spectacular group of basic immunologists involved in a variety of studies relevant to the cancer problem. My own lab continued to study mechanisms of checkpoint blockade, new combinations that enhanced efficacy, and to identify and characterize new checkpoints that might also be targeted to improve the efficacy of checkpoint blockade.  One of the biggest pleasures of being at MSKCC was getting to know Dr. Lloyd Old, considered by many to be the father of modern tumor immunology and immunotherapy. I was very lucky to have him as a friend and mentor. One of Lloyd’s mantras that still resonates with me today: “We must learn from each and every patient!” Lloyd and Dr. Padmanee (Pam) Sharma, an oncologist who was near completion of her postdoctoral studies as an immunologist with Lloyd, had been consulting with the Medarex team in designing and conducting trials with ipilimumab.  Sharma’s experience in patient care, clinical trials, and immunology were impressive, and she left MSKCC to begin her independent career at the University of Texas MD Anderson Cancer Center in 2004. We agreed to stay in touch and try to work to better understand how CTLA-4 blockade impacted patients’ immune responses.  At MSKCC I worked closely with Dr. Jedd Wolchok, who was the clinical investigator leading the anti-CTLA-4 trials in patients with metastatic melanoma. Jedd and I worked with Bristol-Myers Squibb (BMS), including Dr. Rachel Humphrey, who was leading the clinical trial development of anti-CTLA-4 with the Medarex team. Rachel and I became colleagues and good friends, and even band members in a new band that we established with Tom Gakjewski (University of Chicago) and Patrick Hwu (MDACC), both of whom were working in the emerging field of immuno-oncology. Naturally we agreed to name the new band “The Checkpoints”. The band has grown to include a full horn section with Jedd on tuba and has a fairly large repertoire of rock and roll, blues and pop songs. We have entirely too much fun playing at scientific meetings! Again, the theme of “work hard, play hard” permeated my years at MSKCC.  During this time, BMS faced a critical decision that would determine the fate of immune checkpoint blockade as a strategy for cancer therapy. A Phase III registration trial of ipilimumab in metastatic melanoma with the endpoint of PFS had begun. While this endpoint was reasonable for cytotoxic drugs, it was not clear that it was appropriate for CTLA-4 blockade. Our work in mouse models indicated that anti-CTLA-4 works at the time of T cell priming, and allows the expansion of T cells to large numbers to deal with the tumor mass. In our preclinical studies in mice, the tumors almost always grew before they regressed. Of course there are many reasons why the details of mouse results might not reflect those of clinical studies. A more serious concern was that PFS had been one of the endpoints evaluated in many of the earlier trials, and many of the earlier trials had failed to identify clinical benefit using the PFS endpoint. Also, a trial by Pfizer with a different anti-CTLA-4 antibody had failed. The choice for BMS was to shut down their trial with anti-CTLA-4, or incur the tremendous additional costs of a trial with the endpoint of overall survival, which would likely take many more years to complete. The pressure to stop the BMS Phase III anti-CTLA-4 trial was tremendous, but clinical investigators, including Pam Sharma and Jedd Wolchok, and some of the BMS team members, including Rachel Humphrey and Elliott Sigal, championed keeping it open, and prevailed.  While waiting for the next few years for the outcome of the Phase III trial, we all continued our studies. We were invited to many scientific meetings where we would meet with other researchers in the field, including Pam, to share our data at podium presentations during the day and over drinks at the bar in the evenings. It was an exciting time as we all shared our experiences from different institutions and different clinical trials. Those involved in research related to CTLA-4 became a growing community of investigators. Anti-CTLA-4 was working for patients with metastatic melanoma in early clinical trials and, in 2006, Pam shared with us that she was conducting pre-surgical studies in patients with bladder cancer and she observed tumors disappearing in those patients as well.  She also performed novel immune monitoring studies on the tumor and blood samples that she took from patients and identified CD-4 T cells expressing inducible costimulator (ICOS) as a critical component of the anti-tumor responses. It was impressive to me that she could design studies that provided both significant clinical data and novel insights into the scientific mechanisms underlying responses with anti-CTLA-4. I asked her to collaborate with Jedd and myself on the involvement of the ICOS+ T cells in melanoma, and we found in those studies, and in others, that the novel ICOS+ T cells play a causal role in the therapeutic effect of antiCTLA-4 both in patients and animal models.  Our team of investigators expanded to include many more people over the years. The field of cancer immunotherapy exploded as a result of the clinical success of anti-CTLA-4, which opened a new field termed immune checkpoint therapy. Scientific meetings had more and more talks related to immune checkpoint therapy. Immunotherapy sessions at meetings, which previously had less than 50 people in attendance, required larger and larger rooms as hundreds and then thousands of people attended. Cancer immunotherapy went from a fringe science to events that were compared to sold-out rock concerts, which was fitting since our band played after some of the scientific meetings to an equally growing fan base.  The results of the Phase III trial of ipilimumab were finally presented in the Plenary Session of the annual meeting of the American Society of Clinical Oncology (ASCO) in June of 2010. The audience, used to many years of failure of immunotherapy trials presented to tiny audiences, was electrified: ipilimumab was successful in extending the median overall survival of melanoma patients. This had never before been reported in trials of melanoma patients for any other agent. Several years later, when sufficient data were available, a retrospective study showed that thousands of patients with metastatic melanoma who had undergone a single course of treatment, typically consisting of 4 doses of therapy over 3 months, were alive 10 years later.  In March of 2011, I was attending a small Banbury meeting on melanoma at the Cold Spring Harbor Laboratories and I was nervously checking my email because it was the day that the US Food and Drug Administration was scheduled to announce its decision on ipilimumab. At about 11:30AM I received an email from Alan Korman with a picture of of him and Nils Lonberg sharing celebratory drinks of whiskey! This was my first indication that the news from the FDA had been positive and anti-CTLA-4 had become an approved standard-of-care treatment for patients with melanoma.  I’ve met many patients who were successfully treated with anti-CTLA-4, including Sharon Belvin who became a close friend over the years. Unfortunately, during my time at MSKCC, I also experienced many losses, including the death of my brother Mike in 2005, and my friend, and mentor Lloyd Old in 2011, from metastatic prostate cancer. AntiCTLA-4 led to tumor eradication and even cures in some patients but not in all patients. And, for patients with certain tumor types, such as prostate cancer and pancreatic cancer, anti-CTLA-4 did not seem to work at all. I was familiar with Pam’s work focused on evaluating patients’ samples from clinical trials to identify mechanisms of response and resistance to anti-CTLA-4 therapy, including a trial in prostate cancer patients that she designed in 2009, and I was convinced that we needed to expand these studies to build a larger program.  It is safe for me to say that the collaborations with Pam and I had over the years had clearly become a highlight in both my scientific career and my personal life. With time we developed a remarkable level of mutual respect and admiration and love. Eventually we became partners not just in science, but also in life. **University of Texas MD Anderson Cancer Center: 2012–present** At MSKCC, my lab had continued exploring ways in which to improve anti-tumor responses with anti-CTLA-4 treatment. We performed many experiments including combinations with chemotherapy, radiation therapy, cryoablation and with other immune checkpoint agents. After anti-CTLA-4 was shown to have some clinical success in the early clinical trials, many investigators searched for other potential inhibitory molecules. These studies led to identification of the PD-1/PD-L1 pathway as another inhibitory pathway that regulated T cell responses. Clinical trials also led to FDA-approval of anti-PD-1 and anti-PD-L1 antibodies as treatments for patients with cancer. Our lab also showed that combination therapy with anti-CTLA-4 plus anti-PD-1 improved anti-tumor responses in mice.  These data were also translated to the clinic and the US FDA approved combination therapy with anti-CTLA-4 plus anti-PD-1 for patients with melanoma and patients with kidney cancer. Again, these studies demonstrated that some patients responded to therapy but, some patients did not. I knew that we were at the tip of the iceberg in terms of unleashing the full power of the immune system to treat cancer and I wanted to delve deeper by building a translational research program to quickly move between the lab and the large number of clinical trials with immune checkpoint therapy that had emerged as a result of the success with anti-CTLA-4. I decided to move to MDACC to build the Immunotherapy Platform with Pam.  In 2013, I left MSKCC to partner with Pam, who was already conducting mechanism-based clinical trials to study immune responses in patients who receive the immune checkpoint agents. I am Chair of Immunology at MDACC. I’m also continuing to work on fundamental immunologic mechanisms in my lab and we recently demonstrated significant differences between CTLA-4 blockade and PD-1 blockade. In addition, based on Pam’s clinical and laboratory studies, which had already established a translational research program for genitourinary malignancies, I worked with institutional leadership to expand this translational model to the entire institution, encompassing 18 different departments and multiple tumor types. Pam and I established and lead the Immunotherapy Platform. Partnering with physicians from around the institution, we obtain and analyze tumor samples from patients on treatment in clinical trials with immune checkpoint inhibitors or other combination immunotherapy studies. We’re currently involved with immune monitoring studies from over 100 clinical trials. Our goal is to gain mechanistic insight into the therapies that will allow us to develop rationally based combination therapies to bring the benefits of immuno-oncology to more patients with more types of cancer with the goal of obtaining cures.  Of course, my time at MDACC also reverberates with my motto, “work hard, play hard”. I have a second band in Houston called The CheckMates. I continue to play harmonica at events with both The Checkpoints and The CheckMates. I’ve also had the privilege to play with Willie Nelson and Mickey Raphael, who I consider to be the greatest harmonica player on the planet. I continue to follow my passion for science and for life, and I’m truly grateful for the privilege of having a lifetime spent studying fundamental issues of biology that interested me, and that turned out to be of benefit to people with cancer. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0514=JA  James Allison: Hello.  Adam Smith: Hello. This is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize in Stockholm. Is this Professor Allison?  JA: Yes it is. Yes it is. Sorry you guys had so much trouble to get hold of me.  AS: Many, many congratulations on the award of the Nobel Prize.  JA: Oh, well thank you, thank you so much. It’s, as you might imagine, the dream of a lifetime. I don’t know what to say – I’m just stunned.  AS: How did the news actually reach you?  JA: Some reporter called round about 5:30 or so, from Sweden, and then my son called. Saw it on TV!  AS: Your son must be pretty happy too.  JA: Yep. It’s amazing. I’m still in shock. I don’t know what to say.  AS: It’s the first prize awarded specifically for a cancer therapy for many years, and that’s a nice hopeful thing for everybody, that it’s something to reward.  JA: Yes, I think that’s correct, yes. Really hopeful, getting it to work, to try to get everything to work better for patients.  AS: You didn’t actually set out to find a cure for cancer – this was basic research?  JA: No, no, no, I was trying to understand how T cells work. We figured out this one thing about this negative regulator. Had this idea that if we just took that off, you know, maybe it would do a better job of killing cancer cells, and sure enough it works!  AS: Yet again an example of not knowing which way research is going to take you?  JA: Yep, I always consider myself a basic scientist, but not any more I suppose!  AS: I have to say you do sound excited. It’s nice.  JA: Well speechless. It’s kind of sinking in.  AS: Yeah, yeah.  JA: [Inaudible] found out, came to their hotel room. I’m at an immunology conference in New York city.  AS: So people are joining you in your hotel room?  JA: Yes, yes.  AS: You’re assembling a party around you.  JA: Some people heard about it, been showing up, spontaneous celebration going on, a little champagne.  AS: That sounds pretty good. And I have to mention that I’ve actually heard you playing the harmonica at an immunotherapy conference before.  JA: Oh really? With The Checkpoints, yeah.  AS: I do hope you plan to bring your harmonica to Stockholm when you come in December?  JA: I’ll bring it. [Laughs]. I don’t know if I’ll play but I’ll bring it.  AS: I was wondering whether I was brave enough to ask you to play on the telephone now.  JA: Oh I don’t have one with me now, I’m sorry.  AS: I think you should play, you’re good at it if I remember right.  JA: Oh, thank you.  AS: It’s a pleasure to speak to you, and we greatly look forward to welcoming you to Stockholm when you come.  JA: OK, well thank you so much.  AS: Congratulations again.  JA: Thanks, thank you so much.  AS: Bye bye.  JA: Bye bye. |
| Interview |  |
| Q2 | What triggered your interest in researching a new cancer therapy? |
|  | My personal experience with cancer did indeed get my attention, let’s put it that way. My mother died when I was about ten years old of lymphoma. I was with her when she passed away and shortly after two of her brothers died of cancer, one of melanoma, the other of lung cancer, so I got to see the ravages of conventional therapies. So I always wanted to do something about cancer, I didn’t really know how. I would say I went into immunology because I was fascinated by immunology, these T cells, they were just discovered when I was in college and these cells grow all over your body and go through tissues and they can detect when something there is not meant to be there. And then they eliminate it. And how do they do that?  At the time there was nothing known about it. I’ve spent the last almost forty years now trying to figure that out. But my approach was that if I can figure that out maybe we can use the knowledge somewhere along the way to think about cancer, going back and treating cancer. That’s the way I approached it. In a way I was doing the work but the idea of ultimately treating cancer… but I was really doing because I wanted to know how T cells work. So it was fundamental research I was interested in, not necessarily the cancer aspect but I was aware, always aware that it was *there*, you know, if I could just figure out enough, to be smart enough to come up with a new way to do it. |
| Q17 | How does it feel to do work that saves lives? |
|  | After we first got into clinical trials, I had cured a lot of mice in my laboratory, of my own hands. When you cure mice, they bite you and I will stop there, they are not grateful at all, let’s put it that way. Of course we gave them the cancer in the first place so I guess that’s not wrong. But to me, after we started, I could sort of figure out what was going on, sort of understand that it was a good thing but it was mostly numbers to me at first. And then when I had the chance to meet the first patient which was about 2006, actually it was 2004, anyways in that era, it really changed everything. It was a patient named Sharon Belvin. She was 22 years old when she was diagnosed with metastatic melanoma, which is basically a death sentence in that time. She had just finished college, gotten engaged, you know, and wanted to start her life and Bam! she gets this diagnosis. So she started on ipilimumab and in a few months her tumours were completely gone. I met her when her doctor called me in New York and called me and said that I’ve got a patient who wants to meet you. She told her “The guy who invented this is here – do you want to meet him?” So she did.  I went over to our patient clinic and walked into this room with her doctor, she and her husband and her parents and it was just … Let’s put it this way; it was a life changing moment. That’s when it first really became clear to me exactly what was going on and I have followed her since then. She’s fourteen years out now, almost 15 years, and has two beautiful children and she told me several years ago, you know she said “They tell me I have this chronic disease that I have to keep an eye on but I say to hell with melanoma, I am done with melanoma. I am cured and I will live my life like I am cured.” And that’s when it really caused me to think about this. It isn’t just a cancer therapy, this is a way of liberating people from the burden of always every day having to be thinking about the fact that you have this disease that can come back and kill you. You are always looking over your shoulder and that’s what she taught me, that takes a bigger tool and patience than I had imagined. A lot of people don’t like to, a lot of conditions don’t want to say that and I do think you ought to be careful because you don’t want an optimism about what is happening, but the statistics on thousands of patients say that if you make it in four years … and this is just metastatic melanoma, you are probably going be good for 10 or more. So people ought to just quit worrying about it and get on with their lives. |
| Q16 | What is the main impact of your discovery? |
|  | The main impact of our work is to show that you can effectively get your own immune system to attack cancer. It is a very radical departure from the conventional types of cancer therapies, which are radiation, surgery and chemotherapy. All of which is either to remove or kill the cancer cells. What we do has really very little to do with the cancer cell. What I figured out was a molecule that is involved in stopping T cells responses. When you respond to bacteria or cancer you’ve got to generate a huge amount of T cells. So we worked out this pathways by which they get started, but then you’ve got to stop them at some point, or they can damage your body. We had the idea maybe that is why we don’t deal well with cancer, why the immune system doesn’t deal well with cancer. It’s one particular molecule, I thought, if we can pick and inactivate it that is kind of you disable the breaks and you just let the thing keep going for a while but it has nothing to do with cancer. We are not treating the cancer.  So it has really revolutionized how you go about treating cancer where you go in with chemicals or radiation trying to kill every last tumour cell and you know that’s all you can do. But the immune system gives you a way of getting your own T cells to attack the cancer and again, the kind of cancer … You don’t need to design a different thing for every cancer, let’s just put it that way. And once you got the T cells, you got them for the rest of your life, so if the cancer comes back it can immediately rejuvenate and this memory cells can then go after the cancer. So fundamentally it is completely different than conventional therapies. The great thing about it is that it has now become clear that immunotherapy is the fourth pillar of cancer therapy but I like the other three, it can work with them, you can combine it.  And what it is going to do in the next few years, it is starting now so this is going to happen pretty rapidly, as people begin to reevaluate radiation, reevaluate genomically targeted therapies and radiation, and realise that you don’t have to kill every cancer cell. You can just give enough to kill some cancer cells whatever the treatment is and maybe get away from all the adverse events that are associated with those kinds of therapy and give them the benefits, such as memory, of immunotherapy. I would say that is beginning to happen in lung cancers, best examples so far, I think that is going to be happening more and more and I think there are going to be rapid developments pretty soon. But the main thing is again to get durable responses instead of just giving somebody several months, several years or switching drugs or approaches. That is not to say that nothing worked at all until this came along, that is not true. Even if drugs didn’t work by themselves, many types of cancer you can just keep changing them and still keep people alive for long periods of time. But that is not the same as actually curing them. |
| Q1 | Where does your passion for science come from? |
|  | I became committed to science, although it was before I was in the eight grade, because I always liked to have my microscope, chemistry set and just mess around and I liked figuring out things. My dad was a doctor so I was on the way for a while, a little tour, but basically assuming that I was going to be a doctor. I started college as a pre-med major but I had this experience after my junior year in high school, I participated in a science program at the University of Texas at Austin where you as a high school student had lectures in the mornings, which was fantastic, biology teachers, and then worked in labs in the afternoons. For me, it was just like heaven. It was just so much fun. I said this is what I want to do.  I was thinking about it after I matured a little bit and we thought as a doctor you have to, as you are treating people you have to fill your head with facts, just an incredible number of facts and have them in there so when a patient presents to you with a particular set of symptoms you develop an algorithm to treat them and you better be right. Because if you are wrong at the very least you don’t hurt anybody. But as a scientist you are supposed to be wrong, you are supposed to be testing and questioning, saying how does this work? Does it work this way? And if you can figure it out easily and you are right every time you are probably working on boring stuff. If you are right in a big way a few times a year or a few times a decade with really big stuff that’s enough. And so that is the key to be able to identify anything important, questions and follow the experiments down the road. If you are wrong you just keep going. You just learn something. Learn more, every experiment teaches you something. So hopefully you get to the point where you have got something that you can’t prove it is wrong. |
| Q40 | What kind of a student were you? |
|  | As a student I think I had a pretty strong will. Not that I was studious or particularly disciplined in my approach to my studies. But I think I was inquisitive and creative enough … I mean I got in trouble a lot at school and one big one was when after my experience at the University of Texas in summer working in a laboratory taking biology, I came back and I had known about evolution but I really hadn’t been exposed to this class. I realized how fundamental the ideas of Darwin about selection was fundamental to understanding biology, otherwise it is just a bunch of trees, flowers, species all these stuff, family kingdom and all this. That is a way of organizing it, but it is not a way that helps you understand. But the principals of selection can help you understand how things work and how things got to where they are going and better yet give you a worldview where you can begin to predict what is going to happen in the future. I refused to take the high school course because it didn’t have evolution in it. For religious reasons they didn’t teach it, and I said Well, I am not going to take the course and anyways it was quite a … playing chicken with the school because they said you have to take it because you need it to graduate and I said Well, I am not going to waste my time on memorizing kingdom phylum and all that stuff. And so they finally let me take biology from the University of Texas again by correspondence. I fought my way into getting proper training. |
| Q5 | Who has influenced you? |
|  | One would be Barrie Kitto. I worked with him as an undergraduate and graduate student getting my bachelor’s degree and my PhD. He taught me something about how to do science and sort of instilled in me that we do science because we have to and we should do things that benefit mankind to pay back for allowing us to have all this fun. And then I guess the other would be Lloyd Old again for giving me insights into how you really connect laboratory science with treating people and how you need to view every patient as a source of information. They shouldn’t be wasted by not doing everything you can to understand why a drug worked or why a drug didn’t work. And that patient … something that Pam Sharma has the same feelings about which is why I think we work so good together as we really are after the same thing eventually.  One of the things that we both believed in was that it is not enough just to do a clinical trial and look at clinical signals, you need to do science, dissect what is going on, tissue specimens of the cancer and blood and just look at what is happening in respect to immune cells and so you know what the mechanisms of what you are doing is because we know that only a fraction of patients actually respond to these things, at least when you give them one at a time, and so she worked very clever way called pre-surgical therapy. Pre-surgical trials where patients that have local disease are getting the drugs before they go to surgery. Then you get the whole organ to dissect and study and just start generating amazing data from it. We started collaborating on some of that work and I just started writing grants together, sort of grew out of that, so now we work together. We each got our own labs, but we are on a big operation called immunotherapy platform at MD Anderson where we got about almost 70 people that work for us in that group.  The whole goal of it is to study what is going on in patients, right now we are involved in about 115 trials of very diverse types of cancer. Very diverse immunological drugs and also working with pharmaceutical companies to bring us the newest drugs and work with us maybe from steps that haven’t been in humans yet, mice experiments to learn about it and I think it is unique in the world actually. We are generating what I think could be just very important data and have made some progress on enhancing the effectiveness of immunotherapeutic approaches for example in kidney cancer and pretty soon perhaps in prostate cancer where it hasn’t really worked up until now. |
| Q19 | How did you react to being awarded the Nobel Prize? |
|  | Found out, got word of the award in a pretty strange way, for some reason the committee didn’t know how to get a hold of me so about 5.30 New York time the phone rang and I went Wow! but it was my son and he was watching the press conference broadcast and said ‘Dad, you won it, you won it!’ and that was how I found out. It was actually about an hour and a half later before I got the official word. Some people realized what was going on and heard on television that they had trouble locating me so one of the public relations guys from where I work called them and said Hey, this is his cell phone number so … But that was a pleasure getting word from my son. Several of my friends and we had a meeting of cancer immunotherapy people, there were 2-3,000 people there, so really a lot of my very closest friends and people I have worked with for three or four decades were there and so the word begins to spread even at that early hour in the morning. And people somehow got their hands on bottles of champagne and so about 6.30 there’re about 15 people in our hotel room celebrating. |
| Q38 | How do you stay focused when people question your research? |
|  | There are a lot of points when people question your research. I have been through several episodes of that and the first is, before you say anything, you should be pretty sure you are right, you shouldn’t just go out there on a limb unless you want to. If you are wrong someone is going to prove you are wrong sooner or later, you should be the first one to do that. But I think that I have gotten into controversies before and if I am convinced enough that I am on the right track I pretty much ignore them. I’ll argue about it at meetings and stuff enough, but I just keep going and go to the next tap and just keep building up. I don’t get hung up and worrying. Try to do it so that when you get in a position with an argument you are confident enough that you are correct, you have done that experiment that tells you that there is no other explanation except the one you got. And if anybody challenges you they better have that one too. |
| Q23 | What is your greatest achievement in science? |
|  | better I guess my greatest achievement in science so far would be I think … There has been a number of them and figuring out how details work but I think it is the realization that what this molecule CTLA4 did. You know, I didn’t discover the molecule, it was discovered by others but its function was unknown for a long time and the first function that was proposed, we showed was incorrect. In simple terms it was thought to be another positive, you know like another gas pedal that we showed acknowledges the breaks. And we had to take that and say ‘Okay, now we can treat cancer’. |
| Q7 | Tell us about your passion for music. |
|  | I am a musician, but I don’t know about highly accomplished. I have fun at it. Ever since I was kid I loved music. I tried to learn the guitar and piano and stuff like that but it was always beyond me, I just couldn’t. But at some point I picked up the harmonica which is very easy to play, very visceral instrument. I started playing for fun and then teamed up when I was doing my post-doc studies in San Diego. I teamed up with some Texas ex-pats who were there and played honky-tonk music at country-western bars around San Diego County, California. Then they went professional. I still played for fun and listened to records. And then at an immunology meeting, maybe 12 years ago, somebody spread the word to this conference that anybody who has a musical instrument bring them and we will get together and just play. It was an odd assortment of musics, a couple of guitars and keyboards, my harmonica and a trombone and lots of other things.  Anyway we just had lot of fun, but three of us, a keyboard player, a guitar player, just had a particular good time playing, and so after a few years we started to put together a band fairly serious and I called it *Checkpoints* after the immune checkpoint blockade. Everybody in the band is either a physician or a scientist working in that field. We have been playing ever since. Mostly plain sort of advanced amateurs, mostly at conferences, when people are there we do fund raises for cancer charities, and things like that. I have played with Billy Nelson several times, he has been one of my favourite musicians and just people you know for a long time for forty years or more and now I have had a chance to play with him several times. The most notable was sitting in with him briefly at the Austin City Limits Festival a few years ago when there was 70,000 people in the audience. It was pretty remarkable walking out in front of that many people. |
| Q14 | Are there similarities between scientific research and playing music? |
|  | I think there are similarities between science and music. I mean, in both you try to build a team that works. Each person has its own contribution and their own part of the overall work to do. And hopefully all of them see the big picture as well but people take care of their own individual thing. When a good science team is working it is kind of like a good band where you can communicate just with a gesture of a head or a wink or something. The other person knows exactly what is going on. So there is the communication and every now and then my lab has been so well tuned it feels like a really good band, where it’s just going to go where it’s going to go without any conscious leadership. Everybody is just doing what they are supposed to do. |
| Q26 | What qualities are necessary to be a successful scientist? |
|  | I think to be a successful scientist, of course you need to have a high degree of intelligence and discipline. After all, science involves making hypotheses and testing them, as I said, most of the time you are wrong and one thing that a lot of people miss too and you have to … especially young people, you have to really get the /- – -/ and to do that is kind of tedious because you finally get it all together then you got to do it all again at least twice more to make sure it is reproducible. You can’t skip that step, just because something happens once, you know you got to do it all. So you just have to be able to persevere but in the same time know when you are going down the wrong track.  It takes discipline but creativity, you have got to learn how to view your datas or crystal or something, you know when you look at every facet of it, get to know it from every direction. Look at what it tells you beyond the reason you did the experiment and figure it out. And so I think that’s pretty much it; it is the ability to really study the data and really learn what it is telling you. In order to avoid to keep doing experiments that are just going to give you results that are consistent with what you thought you think you should get, your job is really to turn that on its head and say I want to design an experiment that it can’t, that there is no other explanation, except one from this experiment and then decide to try to prove yourself wrong. And try hard, not just the easy ones you know that are consistent but I think the killer experiment. And I think it is the ability to recognize those and seek those rather than just the easy stuff. |
| Q37 | What do you hope the future holds for cancer research? |
|  | The word cancer became very shortly after it was conceived of was to really do basic science and understanding what causes cancer, what are the lesions, the genetic lesions and what are the circuits and everything. The ultimate goal was to design drugs to hit those things. The one thing that came out of that is that you can’t cure cancer doing that, because cancer cells are inherently unstable in their genomes. You can come up with a drug that treats one of those lesions but there will already be another one there that your drug doesn’t hit. But I think now where there are cases where the tumour will almost disappear, they never really or very very rarely with the drugs that came out of the official war on cancer, it will never kill all the cancer cells but then again you don’t need to kill all of them when you are treating with immunotherapy. You can use them like vaccines to kill the drugs that have the right lesion. They can be used to form a basis of a really more individualized approach to cancer therapy where you study what is going and treat them with the right drug, be it chemotherapy or the genomically targeted drugs and then come in with immunotherapy. |
| Q34 | What’s next for you? |
|  | What’s next is working with Pam Sharma. Right now in some cancers like metastatic melanoma combinations of checkpoint blockers we give long-lived, pretty durable responses. We don’t know how long because it hasn’t been enough time yet but it looks like about 60% which is pretty good because when we started on this if you were diagnosed with metastatic melanoma the immediate life expectancy was 11 months. And no drug had ever lengthened that, so now 60% of people are going to get four years. And we will see, it may be more. We need to get that to a 100%. In other cancers maybe 30% or something so we need to just, what I call ‘raise the tail’.  If you look at a survival curve in something like melanoma or other lethal cancers, we started at 100% and with time it drops down to some level. It used to go to zero at some point and you could just move the median over with treatments but now we know that the survival curve flattens out at some level at some point. But we need to get that as high by doing the right combinations as close to 100% as we can. And in other cancers, notably pancreatic cancer and glioblastoma really haven’t responded at all, and so we need to keep working very hard with those again not by just throwing random combinations of things but by doing the science, treat them with something, if it fails it fails, but look and see why it fails, what didn’t happen. It is easy if it works to figure out why it works, it is not so easy if it didn’t work. But by figuring out why it didn’t work can help you make it work, that something is being missed so that’s our passion. That is our goal right now. We know we can benefit a lot of patients. I think overall it is 20-25 % of all cancer patients, we would like to get that up as high as we can get it. |
| ID | 0515 |
| Biographical | **Prologue** Burning wooden walls collapsed in front of us. I was on the back of my mother, who was running away from our burning house, gasping for air. Although I was just three and a half years old, I vividly remember this scene that seems to be engraved forever in my memory. It was one of the most devastating American bombing raids targeting civilians, which took place in Toyama City on August 1, 1945, just two weeks before the end of the war. We escaped the fire by jumping into a ditch beside a rice field to avoid the heat from the nearby burning houses. Just minutes before, an incendiary bomb had hit the bomb shelter in our garden where we had been hiding. Luckily, that bomb did not explode. I believe I was extremely fortunate from this early stage of my life.  I was born in Kyoto on January 27, 1942, less than two months after World War II started in the Pacific region. My family traces its ancestry back to a priest from a temple called Honjo-san Sensho-ji. Many years ago, when visiting the temple for the first time, I immediately recognized my relatives among others without any introduction. Their familiar eyes, eyebrows, noses and cheeks resembled those of my immediate family members.  We were welcomed by the head priest, Kuniyuki Honjo, who showed us the Sensho-ji Temple and writings about its origins. We were told that the Temple had been established sometime between 1077 to 1080 by Goromaru Fujiwara, a guard who helped the third son of the Emperor Go-Sanjo escape fighting in Kyoto, then Japan’s capital.  My father worked as a surgeon at the Kyoto University Hospital. He later became the head of the Otorhinolaryngology Department in the Yamaguchi University Medical School in Ube City, where he served until his retirement in 1976. Having spent several years in Montreal’s McGill University and Northwestern University in Chicago learning advanced surgical operations, he was fluent in English and perceived it was the new *lingua franca* one needed to master. Thus, my father introduced me to Ms. Kato, a Japanese woman born in Hawaii who taught me English two years ahead of my classmates, which helped my communication skills later in my career. My father enjoyed painting and was also an excellent golf player. I seem to have inherited his athletic but not artistic traits, although I do appreciate and enjoy paintings and music. While my father educated me rather strictly, my mother was protective and warm, forever my guardian goddess. She not only saved my life but shaped the person I was to become with her love (Fig. 1).  My first moment of enchantment with the natural sciences took place when I observed the tiny rings around Saturn in a clear sky using a portable telescope in the playground of Kamihara Elementary School in Ube during a summer vacation. Afterwards, I began to read many astronomy books and was determined to be an astronomer. My passion for astronomy continued for a few years until my mother gave me the biography of Hideyo Noguchi, a world-famous yet unconventional Japanese microbiologist. Noguchi obtained his medical doctor’s license while struggling with incredible poverty and also a physical handicap after seriously burning his hand. He went to Philadelphia at the age of 24 to meet the great pioneer in the infectious disease research Simon Flexner, who later hired Noguchi at the Rockefeller Medical Institute. Noguchi is mostly known for his finding that progressive paralytic disease is caused by infection of the brain with syphilis, and for his pursuit of the cause of yellow fever. Ironically, the latter was to cause his sudden death in Ghana.  When I first had to make decisions about my future path at the end of senior high school, I was still uncertain. I knew I did not want to be a clerk or a civil servant, because I wanted to do something I was passionate about. I considered becoming a lawyer or embracing a diplomatic career, because I thought I could communicate effectively. However, the medical profession was very attractive to me, as not only my father but many of our relatives were clinical doctors. In the end, I chose to continue this legacy and applied for entry to the Kyoto University Medical School.  During the years around 1960, as I entered medical school, I felt I was witnessing a revolution in biology, with discoveries such as the double helix structure of DNA in 1953 and the decoding of the triplet nature of the genetic code in 1964 by [Marshall Nirenberg](https://www.nobelprize.org/prizes/medicine/1968/nirenberg/facts/) and Philip Leder. I recall being extremely impressed by a Japanese book called *Revolution in Biology* by Atsuhiro Shibatani, who happened to be a colleague of my father at Yamaguchi University. Published in 1960, the book contained amazing speculations: that cancer is a manifestation of mutations in our DNA; that automated DNA sequencing will enable us to define these mutations; that the development of ‘molecular surgery’ will allow us to repair defects in DNA and may ultimately cure cancer. The night after I was exposed to Shibatani’s extraordinary imagination, I could not sleep. I was totally immersed and fascinated by biochemistry and molecular biology, which I believed would lead to a better understanding of what life is. **Early training** Fortunately for my scientific career, I became bored with memorizing Latin names for anatomy and the symptoms of many diseases with unknown causes in medical school and began to spend most of my time in the laboratory of Professor Osamu Hayaishi. Hayaishi was a great biochemist – the discoverer of oxygenase enzymes – who had just returned to Kyoto University from a nine-year stint at the National Institutes of Health (NIH) and Washington University in St. Louis. He worked with the biochemist and Nobel Laureate [Arthur Kornberg](https://www.nobelprize.org/prizes/medicine/1959/kornberg/facts/), with whom he kept a close friendship throughout his life. I eagerly joined Hayaishi’s department for graduate studies between 1967–1971. During this time, and also later in my life, I learned much from Hayaishi – not only about science but also other enjoyable pastimes like golf and wine tasting, which later gave me much pleasure. In Hayaishi’s lab, I was mentored by Yasutomi Nishizuka, who was then famous for elucidating how the molecule NAD, essential for energy production in all living cells, is synthesized from the amino acid tryptophan, and later discovered protein kinase C and its regulation by phorbol ester.  I believe it was in the summer of 1967 when I found a very interesting paper by John Collier demonstrating the requirement for NAD by diphtheria toxin for inactivation of protein synthesis enzyme EF-2. This work was striking, as at that time toxins were thought to function by directly binding components of cellular machinery to block their activity. I had a strong desire to find out why NAD is essential for diphtheria toxin’s function. I was, fortunately in the best place to answer this question, due to the availability of labeled forms of NAD generated by Nishizuka’s research on the NAD pathway. I quickly established that diphtheria toxin is an enzyme that catalyzes transfer of the ADP-ribose moiety of NAD to EF-2 and published this finding in the prestigious *Journal of Biological Chemistry* (Honjo et al., 1968). Publishing this work while still a graduate student gave me a boost of confidence. The remaining two years of my graduate course were, sadly, scientifically lost, as student riots forced the closure of the university campus. I was already thinking of the next step. Following the example of my mentors and my father before me, I was determined to challenge myself in an international scientific environment.  I was fortunate to be hired as a postdoctoral fellow at the Carnegie Institution of Washington in Baltimore. The beautiful Carnegie building was located next to the northwest corner of the Homewood campus of Johns Hopkins University. Retrospectively, an incident which changed my life occurred about one year after my arrival. Donald Brown gave a seminar in Carnegie about the organization of the immunoglobulin (Ig) gene. At that time, not only immunologists but all biologists were keen to find how animals generate specific antibodies against almost every foreign antigen they encounter. Two major hypotheses were put forward to explain the enormous diversity of antibodies produced by B lymphocytes. The first so-called ‘germline’ hypothesis claimed that we may have as many as one thousand genes responsible for the antibody diversity phenomenon. The second theory, called ‘somatic hypermutation’ originally proposed by [Sir Frank Macfarlane Burnet](https://www.nobelprize.org/prizes/medicine/1960/burnet/facts/), claimed that DNA mutations in immune cells could generate enormous lymphocyte diversification from a limited number of inherited genes. A major problem with the germline hypothesis was explaining how individual copies of the Ig variable (V) gene could differ so greatly while maintaining the important structural information contained in the Ig constant (C) region gene. Based on his studies on the organization of ribosomal RNA genes, Don proposed that multiple copies of the C gene might be conserved by frequent homologous recombination between other copies of C genes to repair errors and suggested that this long-standing mystery of biology could be approached with modern molecular biological technology. I could not stop asking Don where the best place to tackle this fundamental problem was. He suggested Philip Leder, whom I met three months later when he gave a seminar in Carnegie. My long journey in molecular immunology began when Phil accepted me to his lab at NIH.  The work in Phil’s lab was exciting every day. There was a movable arrow on the wall pointing either to the germline or somatic hypermutation theory. The strategy Phil proposed was to count the number of the light (L)-chain C genes by hybridization kinetics, using radiolabeled cDNA derived from purified Ig L chain messenger RNA. The speed with which these labeled genetic probes were reannealed after denaturation, together with total cellular DNA, would reflect the number of L-chain C genes present in the genome. Our conclusion was that there is only one copy or very few copies of the Ig Lk or Ll chain gene. Ironically, these results ran contrary to Don’s preferred germline theory of diversity. **Back to Japan** With this result, after almost four years in America I felt drawn back to Japan. Phil advised me to stay, as in 1974, it was apparent that the Japanese universities had neither money nor the sophisticated facilities to carry out advanced molecular biological studies. I faced the second big choice in my life. I finally made up my mind to go back to Japan. Firstly, I wanted my small children (my daughter, Yasuko who had recently been born in Baltimore, and my five-year-old son, Hajime) to experience aspects of Japanese culture that might be lost to them if we continued to live abroad, and secondly, I wanted to nurture a strong culture of molecular biology research into Japan, as my mentor Hayaishi had done for biochemistry. I am happy to have seen my children thrive back in Japan, Hajime as a gastroenterologist and Yasuko as an embryologist, although for their success I owe a debt of gratitude to my wife Shigeko as I was a typical, workaholic Japanese husband. Phil accepted my decision and kindly recommended me for a small grant from the Jane Coffin Childs Memorial Fund, which was instrumental in launching my career at the University of Tokyo. He also generously sent precious RNA reverse transcriptase, an essential reagent to generate cDNA that was then difficult to obtain.  The University of Tokyo was considered the best university in Japan. However, I found that not only the infrastructure but also the spirit of science was far behind what I had experienced in Hayaishi’s laboratory. To avoid direct competition with Phil, I decided to reorient my work on the Ig heavy (H)-chain gene structures that had their own unique biological question, i.e., how different classes of antibody like IgG, IgE or IgA were made during immune responses. Although the question was clear, I faced many technical hurdles as even a basic piece of equipment like a gel dryer was difficult to find. I remember going down to the Akihabara area – where many shops sell electronic components – to buy thick rubber plates, hose and mesh to build my own vacuum drying apparatus for electrophoresis gels, which were essential for visualizing proteins. A few brilliant medical students – who later took the graduate course in my lab – voluntarily worked after classes with me.  It took almost three years until we began to obtain interesting data. Surprisingly, we found that the gamma chain constant (Cγ) gene was deleted from DNA in myelomas. To examine whether CH gene deletion was an artifact of the myeloma cancer we were studying, I asked Michael Potter – an expert in plasma cell cancers working at NIH – to send more myeloma cells producing different Ig classes. Tohru Kataoka and I carried out extensive Cot Curve analyses of many myeloma DNAs (Fig. 2). At that time, I was commuting from Yokohama to Tokyo, which took 90 minutes each way. One night, while poring over results on the train on my way back home, I found that the CH gene deletion always takes place upstream the CH gene expressed in that particular myeloma, assuming a specific order of CH genes on the chromosome. That was the moment when I reached the DNA deletion hypothesis model for class switch recombination (CSR) (Honjo and Kataoka, 1978). I was extremely delighted when our research was highlighted by the *Nature* editor Miranda Robertson, in that journal’s News and Views.  In 1977, I returned to Phil’s lab for three months when they restarted experiments after the lifting of a long, frustrating moratorium on gene cloning technology. I quickly succeeded in isolating Cγ1 cDNA, starting from purified mRNA using molecular cloning techniques, with the help of John Seitman. I was fascinated when we established the sequence of the Cγ1 gene, and finally discovered that each domain of the Cγ1 chain is separated by noncoding spacers. Akira Shimizu and others went on to map all the CH genes on the mouse chromosome (Fig. 2). We were very much delighted to prove that the proposed DNA deletion model of antibody diversity was absolutely correct. The next clear goal was to elucidate the mechanism in detail, and especially to identify the enzyme(s) that catalyze(s) CSR. **Journey to aid** In 1979, five years after I came back from Phil’s laboratory, I was invited to become the head of the Department of Genetics at Osaka University School of Medicine. Elevating a relatively early-stage researcher to such a prominent position was something unprecedented in Japan. However, my stay in Osaka was short, as in 1984 I was invited back to Kyoto University to succeed Hayaishi after his retirement. A highlight during my time in Osaka was being invited to the Nobel symposium organized by Erna Möller and Göran Möller in 1982. There I met Eva Severinson, who later proposed a collaboration to clone cytokines which could enhance class switching, as she had established a mouse helper T cell line and a sensitive experimental assay system for class switching. By expressing a fulllength cDNA library in amphibian oocytes, we discovered IL-4 and IL-5, which turned out to be critical for not only CSR but also T cell differentiation.  In 1991, I was invited to NIH as a Fogarty Scholar, a very valuable sabbatical opportunity. It provided me with a year’s salary and residence within the NIH campus, to encourage interactions with its many scientists. I enjoyed staying at the NIH campus and talking with many immunologists, including William Paul, who provided an education in cellular immunology, especially regulation of the immune response. One day I met Warren Strober and his associate Yoshio Wakatsuki from Kyoto University, who told me they had a cell line that could be stimulated to switch from producing IgM to IgA antibodies *in vitro.* Instantly, I realized this cell line could be what I was looking for in order to identify the enzyme(s) responsible for induction of CSR. After repeatedly selecting efficiently switching clones for two years, we finally isolated a cell line (CH12F3) that robustly expressed IgA after 48-hour stimulation with CD40 ligand, IL-4 and TGF-β1.  Masamichi Muramatsu began looking for differences in cDNAs expressed by CH12F3 cells before and after stimulation (Fig. 3). One gene that caught his attention was expressed only in activated B cells but not T cells. In addition, the gene was turned on in germinal centers, the active sites in the lymphoid tissues where CSR was known to take place. Surprisingly, the clone closely resembled genes in the cytidine deaminase family, including RNA editing enzyme APOBEC-1. Indeed, Muramatsu could show it had noticeable if weak cytidine deaminase activity on free cytidine. We published a paper on the isolation of the activation induced cytidine deaminase (AID) gene in 1999 in the *Journal of Biological Chemistry.* Privately, I had chosen to name the gene AID because both aid and Tasuku can mean “help”, which I did not tell Masamichi. We continued to investigate the AID function by knocking out the gene in mice. By the end of January 2000, we could show that AID-deficient animals lacked both CSR and SHM (Muramatsu *et al,* 2000).  We had been asked for collaboration by Anne Durandy and Alain Fischer from Hôpital Necker-Enfants Malades in Paris, who were trying to identify the gene responsible for a severe immune deficiency in patients with hyper-IgM syndrome type 2 (HIGM II). These patients had very high concentrations of IgM in their blood, strongly suggesting a genetic defect in class switching. We sent primers to Paris to detect the AID gene, which their group used to identify AID mutations in all HIGM II patients. They also found HIGM II patients were defective in SHM. We quickly confirmed that this process was also lacking in AID-deficient animals. The result was completely unexpected, as the scientific consensus at the time was that SHM and CSR were completely different modifications carried out by different genes. However, these findings showed that the AID protein alone was responsible for these two critical genetic alterations in Ab genes during immune responses. It was a eureka moment for me and the entire group working on AID. At this time, serving as a dean of the Medical School of Kyoto University, I was afflicted with very severe back pain, to the point of not being able to walk or sit comfortably. I worked on the AID paper lying on the floor in my office while colleagues kneeled next to me to discuss plans and ongoing experiments. I remember the year 2000 for both the physical challenge and some of the most exciting scientific breakthroughs in my life.  I presented this result at the Annual Meeting of the American Association of Immunologists in Seattle in May 2000, after we sent the two manuscripts to *Cell* describing AID deficiency in mice and humans. The lecture was well accepted by a large audience. Although it was clear that the game was over in the hunt for the enzymes responsible for CSR and SHM, for us this was the beginning of another journey to find out how such a small protein can mediate two complicated genetic changes in immune cells. **Discovery of PD-1, its function and application** The mechanisms of clonal selection, namely, how immature T cells are selected during development in the thymus, was another big question in immunology. In my lab, Yasumasa Ishida was striving to identify the molecule(s) responsible for the thymic T cells selection, and proposed comparing the gene expression of growing and dying cells from the thymus (Fig. 4). In May 1991, he used this technique to identify a gene expressed during this process which we named PD(programmed cell death)-1 (Ishida *et al*., 1992). The structure predicted from the gene sequence indicated that PD-1 is a surface receptor protein, related to but distinct from known receptor molecules involved in lymphocyte activation. Therefore, I thought we should focus on finding the function of this protein in immune cells. Hiroyuki Nishimura generated knock-out (KO) mice on a mixed genetic background in June 1994, but to our disappointment the KO mice were identical to controls (Fig. 4). Fortunately, Nagahiro Minato, a very knowledgeable and experienced tumor immunologist in our faculty, suggested that we should breed the PD-KO mice to create an inbred strain and continue to monitor the mice before drawing any conclusion (Fig. 5). Thanks to Minato’s guidance, by November 1997, we observed that when introduced to the autoimmune-prone lpr/lpr strain, PD-1 deficiency led to arthritis and nephritis at five months of age. Continuing our patient monitoring, we found that PD-1 deficiency on the C57BL/6N background caused mice to develop similar autoimmune symptoms at 14 months of age. These findings convinced us that PD-1 is a negative regulator of the immune system (Nishimura *et al,* 1999). Disease manifestation in PD-1 KO mice was milder than that of CTLA-4 KO mice, all of which were reported to die within 4–5 weeks. The CTLA-4 gene, originally discovered by Pierre Golstein, was shown to encode a negative immune-receptor by Jeff Bluestone, Craig Thomson, Jim Allison, Tak Mak and Arlene Sharpe. The comparatively mild and chronic symptoms in PD-1 KO mice suggested to us that PD-1 could safely be targeted to treat diseases. Around March 1998, we began a series of experiments targeting PD-1 as a therapy for various disorders characterized by defects in immune regulations, such as cancer, infection, autoimmunity, and rejection of transplanted organs. Reasoning that blocking PD-1 would be simpler than enhancing its function, boosting the immune response against cancer became our first goal. Yoshiko Iwai began work looking ways to use PD-1 in therapeutic applications and generated many reagents and experimental systems (Fig. 4).  Ever since discovering PD-1, we had predicted the presence of a specific binding partner or ligand (Ishida *et a*l., 1992). On September 17, 1998, we spoke with Steve Clark, the head of the Genetic Institute, about our problem with identification of ligands for PD-1. He proposed using their Biacore instrument to screen for PD-1 ligands in the supernatants from a variety of cultured cells. I agreed to collaborate and provided not only the reagents but all our knowledge about PD-1 because this molecule was completely unknown to them. Meantime, we tried to identify the PD-1 ligand by fishing for molecules which bound to an engineered PD-1-Ig fusion protein. Although we clearly detected binding of PD-1-Ig protein to various cell types, including some tumor cells, we were unable to purify or identify the miniscule amount of binding proteins. After a year of silence, on October 5, 1999, Clive Wood, who was responsible for this project under Steve, sent word out of the blue that they might have identified the PD-1 ligand. On October 25, 1999, in Boston, Clive explained that their collaborator Gordon Freeman at Dana Farber identified several B7 family cDNA in a deposited data base and the Clive group found the protein encoded by one of them (clone 292) had bound to the PD-1 expressing cells we had sent from our laboratory. In Japan, we confirmed binding of the 292 protein to PD-1, and performed experiments showing its immune inhibitory function. Together, we published our identification of a PD-1 ligand (PD-L1) (Freeman *et al.*, 2000). Just before the submission of our paper, I learned that Lieping Chen had published a paper describing the identical cDNA as a B7 family member with costimulatory activity, without knowing its receptor (Dong *et al*., 1999).  Meanwhile, we continued our studies aimed at treating cancer by PD-1 blockade. By September 2000, Iwai had found that myeloma expressing the PD-L1 grew more slowly in PD-1 deficient mice compared with wildtype mice. I was very excited and convinced that PD-1 would make an excellent target for cancer treatment. As I needed good blocking antibodies against PD-1 or PD-L1, I talked with Minato and urged him to hurry in our collaborative work towards this goal. Minato’s group had already started searching for antibodies which could effectively block either PD-1 or PD-L1. Yoshimasa Tanaka in Minato’s laboratory worked diligently on the project, and by the end of 2001 we had gathered enough data to demonstrate that PD-1 blockade by PD-L1 antibodies can prevent different types of tumor in mouse models (Iwai *et al*., 2002) (Fig. 5). In my own group, Iwai showed that the spread of B16 melanoma cancer from spleen to liver could also be prevented by anti-PD-1 antibody treatment (Iwai *et al.,* 2005).  As we prepared our publication about PD-L1 isolation, I asked Wood how we might approach patent applications, and was informed that Wood and Gordon had already applied for a patent covering PD-L1 and its usage in November 1999 without informing me. I was surprised and registered a complaint through a lawyer, but to no avail. However, Wood’s patent was declined, perhaps lacking sufficient data to support its usage. More unpleasant surprises were to come, as more than 10 years after our PD-1 blockade paper was published, Freeman and Wood sued me by claiming co-inventorship of the PD-1 cancer immunotherapy patent. The precise timelines in my story thus arise from a desire to publicly clarify how we came to discover the therapeutic value of PD-1, due to my draining and still unresolved legal battle regarding the intellectual property rights. **Clinical application** As I anticipated the clinical application of our finding on tumor treatment by PD-1 blockade, I approached Kyoto University to apply for the intellectual property right for usage of PD-1 blockade for cancer treatment. Frustratingly, they lacked the human and financial resources to support my application. At this point I turned to a small Japanese company, Ono Pharmaceutical, because we had been involved in other collaborations.  Unfortunately, Ono also had no capacity to organize clinical trials for cancer drug development and searched for a bigger partner. They spent almost a year visiting more than a dozen companies without success. It was obvious that, at this time, neither the pharmaceutical industry, clinicians, nor even many biologists believed that trying to enhance the immune system could help cure cancer. I was terribly disappointed when Ono officials told me they had decided to abandon the project. I decided to turn to my network of friends in the USA, many of whom had started their own companies.  I visited one such venture capital company in Seattle and they surprisingly agreed to invest in my proposal almost instantly, on the condition that Ono would be excluded from future developments. I waited for several months for Ono to confirm they had no intention to use our patent independently before committing to the Seattle partner. Ono then stunned me with the news that they now had the resources to invest in developing a PD-1 treatment. Later, I learned that Medarex, the biopharmaceutical company led by Nils Lonberg had found our published PCT patent application and directly approached Ono with a collaboration proposal. I was extremely lucky again. Without this chance encounter, the PD-1 cancer drug development might have been delayed by many years.  The paper summarizing the first clinical trial (Phase I) on PD-1 antibody published by Suzanne Topalian’s group in 2012, showed very promising complete or partial responses in roughly 20 to 30 percent of patients with terminal melanoma, lung, or renal cancer. In addition, patients continued in unprecedented good health for more than a year and, half after treatment. In Japan, we carried out a smaller clinical trial on drug-resistant ovarian cancer patients in collaboration with the Gynecology Department at Kyoto University. I was immensely pleased to hear about a patient whose large tumor had been completely cured by PD-1 blockade therapy, and to watch her enjoying a round of golf on a TV program about the breakthrough drug. Two patients treated for a year with PD-1 antibody are still free from tumors almost five years later. The PD-1 antibody was approved for melanoma treatment by PMDA in Japan in 2014, quickly followed by the FDA in the USA. **Science media** In 2013, *Science* magazine selected cancer immunotherapy as the number one scientific breakthrough of the year. The author of that article described the development of therapy targeting CTLA-4 by Jim Allison in detail. However, I was shocked as the article continued: “In the early 1990s, a biologist in Japan discovered a molecule expressed in dying T cells, which he called programmed death 1, or PD-1, and which he recognized as another brake on T cells. *He wasn’t thinking of cancer, but others did*.” I was speechless! Clearly, this *Science* editor reporting cancer immunotherapy had either not read our papers describing cancer therapy by PD-1 blockade, or had intentionally neglected them (Iwai *et al.*, 2002, 2005).  This article was a symbol to me of deficits in our current system of science journalism. Scientists are eager to publish their papers in the so-called top journals like *Science, Nature* or *Cell*, as they are judged by their peers and funders based on such publications. When I first became a researcher, editors of these journals such as Miranda Robertson, Peter Newmark, Ben Lewin and Linda Miller, were very knowledgeable, reliable and sincerely interested in research. I was happy to send my manuscripts to their journals as I felt confident these editors had the knowledge and training to allow them to perceive the importance of our science. However, more recently, perhaps due to the enormous expansion in the number of journals, this no longer seems to be the case. When in-house editors rely on the majority vote of outside reviewers with different opinions rather than their own judgment, paradigm-shifting papers have difficulty being published, as by definition they run against the concepts held by the majority. It is notable that none of my papers cited by the Nobel Committee were published in these so-called top journals. The current peer review system tends to reject newly emerging concepts or new findings running against the established dogma in the scientific community. Since scientists feel they have at some point received unfair statements from our colleagues, I believe revealing the names of peer reviewers is one way we might mitigate some of these problems. Certainly the *status quo* needs to change to make our current peer review system more constructive and efficient. **Six “*C*”s in science** To carry out science, I always say to my students; if they do not have *C*uriosity, then they should not choose a career in science. There are many types of scientists. It is always important to find out what you really want to know. Imagine research as a journey deep into mountains to find the origin of the mysterious river. Sometimes on the path you may discover an interesting stone which you bring back and find it very precious upon careful examination. My style of doing science is to find something totally unknown, or to map a totally new route to an unknown cave from which water is coming out. You should keep asking what you wish to know rather than what you can do. You need to embrace *C*hallenge and have the *C*ourage to invest your effort and time. These three “*C*”s were the basis of my research career. Once you fix on a project, three more “*C*”s are required. Of course, you have to *C*ontinue your research with lots of *C*oncentration. *C*oncentration means placing research as a central activity in your life, sometimes sacrificing other important calls on your time to focus on your goal. To *C*ontinue and *C*oncentrate, you may need *C*onfidence that you can do it. Or it could be the other way around. Concentration and *C*ontinuation may eventually build up *C*onfidence. The last three “C”s are as important as the first. **Dreams** Aside from scientific activities, I still have two dreams at the age of 76. As I have watched younger generations struggling for support, I have long thought Japanese universities should create their own funds to support young scientists. Compared to American universities with large endowments, Japanese universities rely more on government funds. Since the future prospects of the science budget from the Japanese government are not so promising, I have proposed that Kyoto University set up a fund using royalties from our PD-1 patent. Fortunately, this fund has already started accepting donations. I sincerely hope others will join this initiative to help instill scientific enthusiasm in the next generations of researchers. This is especially critical in Japan, where human creativity is our most important natural resource.  Another dream of mine is age-shoot. I started playing golf while living in the United States. Over there, the green fee was only five dollars, which even an impoverished post-doc could easily afford. Perhaps I love golf for its similarities to science. For every shot, the given conditions are never the same. You have to think how far you are going to hit, in which direction and whether to add spin to stop on the green and so on. Most importantly, one must avoid big mistakes. It is totally different from team sports or those where you must score points. In golf, you have to always choose from many ways to approach a shot and this decision lies with you alone. Probably, this challenging game sparked my curiosity to which I am so attached. I dream of achieving a score equal to my age before I turn 80. **Coda** The curiosity surrounding my two favorite molecules, PD-1 and AID, will continue thanks to my long-time collaborator, the Romanian scientist Sidonia Fagarasan (Fig. 3). Her work in my lab and beyond revealed that PD-1 and AID are essential molecules for the generation and selection of intestinal IgA that regulates our microbiota. Microbiota, in turn, control the immune system by promoting expression of AID, PD-1 and IgA, which are essential for maintaining immune tolerance to microbiota and self, metabolic balance and even brain function. Using AID-deficient mice, Sidonia was the first scientist to show that dysregulated gut microbiota greatly change the host immune system (Fragasan *et al.* 2002). How serendipitous that my two favorite molecules should collaborate in such a fascinating way to control the immune system, the microbiome and to fine-tune anti-tumor activity! It feels impossible to learn everything even just about these two molecules, as they have a far-reaching impact on other major physiological systems of the body. Indeed, despite so much progress, I believe we are just beginning our exploration of life sciences, because we understand so little about biology and physiology. After all, medicine has made great leaps in fixing acute problems, but when it comes to physiology we are humbled by the body’s complexity, as we are decoding the continuous evolutionary experiments of the past four hundred and sixty million years. Every day I come to the lab enthusiastic to learn more about immune regulation in the context of physiological systems, still dreaming that curing cancer patients everywhere on this planet by immunotherapy will become possible someday. **Acknowledgements** I am deeply grateful for the precious support for the preparation of this article by Sidonia Fagarasan, Alexis Vogelzang, Blake Thompson and Maki Kobayashi. **References****Dong, H., Zhu, G., Tamada, K., and Chen, L. (1999) B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nature Medicine* 5, 1365–1369.****Fagarasan, S., Muramatsu, M., Suzuki, K., Nagaoka, H., Hiai, H., and Honjo, T. (2002) Critical roles of activation-induced cytidine deaminase in the homeostasis of gut flora. *Science* 298, 1424–1427.****Freeman, G. J., Long, A. J., Iwai, Y., Bourque, K., Chernova, T., Nishimura, H., Fitz, J., Malenkovich, N., Okazaki, T., Byrne, M. C., Horton, H. F., Fouser, L., Carter, L., Ling, V., Bowman, M. R., Carreno, B. M., Collins, M., Wood, C. R., and Honjo, T. (2000) Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *The Journal of Experimental Medicine* 192, 1027–1034.****Honjo, T., Nishizuka, Y., Hayaishi, O., and Kato, I. (1968) Diphtheria toxin-dependent adenosine diphosphate ribosylation of aminoacyl transferase II and inhibition of protein synthesis. *Journal of Biological Chemistry* 243, 3553–3555.****Honjo, T., and Kataoka, T. (1978) Organization of immunoglobulin heavy chain genes and allelic deletion model. *Proceedings of National Academy of Sciences of the United States of America* 75, 2140–2144.****Ishida, Y., Agata, Y., Shibahara, K., and Honjo, T. (1992) Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *The EMBO Journal* 11, 3887–3895.****Iwai, Y., Ishida, M., Tanaka, Y., Okazaki, T., Honjo, T., and Minato, N. (2002) Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proceedings of National Academy of Sciences of the United States of America* 99, 12293–12297.****Iwai, Y., Terawaki, S., and Honjo, T. (2005) PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *International Immunology* 17, 133–144.****Muramatsu, M., Kinoshita, K., Fagarasan, S., Yamada, S., Shinkai, Y., and Honjo, T. (2000) Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. *Cell* 102, 553–563.****Nishimura, H., Nose, M., Hiai, H., Minato, N., and Honjo, T. (1999) Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity* 11, 141–151.** |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0515=TH  Tasuko Honjo: Hello.  Adam Smith: Oh hello, am I speaking to Professor Honjo?  TH: This is he.  AS: Hello, my name is Adam Smith, calling from Nobelprize.org, the official website of the Nobel Prize. First of all, congratulations on the award of the Nobel Prize.  TH: Thank you very much. It’s a great honour.  AS: What was your first reaction on hearing the news?  TH: Oh, well, certainly I am very much pleased and very much honoured.  AS: It’s the first Nobel Prize awarded for cancer therapy for many years. What message do you think this sends?  TH: As you say, for treatment certainly this is the first time, and I think that many people tried very hard to cure the cancer but fortunately we, Jim Allison and myself, studied this checkpoint inhibitor therapy. I mean, we discovered the principle, and this is really working. So for me it’s more than happy to see many patients – often I can see them telling me, “You saved my life”. This is my most enjoyable and, I would say, I’m very pleased to hear what I have done is really meaningful.  AS: It shows that you never really know which way things will go in research, because you didn’t set out to discover a cure.  TH: No, no. Well, you know, biology is such a complex system. It’s totally different from the engineering. We cannot design. Many people tried to find the therapy for cancer, but all failed. And myself, I never expected my research, working on the immune system, would lead to the cancer therapy. But, in a sense, I’m very fortunate that I also thought about it. You know, you have to try many things and if you’re lucky you can hit, but you have to pursue. That’s my feeling.  AS: And what is your hope for the future of immune checkpoint inhibitors?  TH: Well there are still several problems, but two are most important. One is, still only 30% of patients are responding, so we wish to have some biomarkers to predict whether he or she is responsive or not. Secondly, definitely we wish to improve the efficacy of this treatment, and I’m sure this is a target of many, many scientists in the companies. So I believe these two problems will be solved in the near future.  AS: That’s a very hopeful message, and indeed I think the award of the prize is a very hopeful sign for a very large number of people around the world today.  TH: I think so. It’s encouraging, and we need the power of many, many people to push this therapy in a really satisfactory level. This is just the beginning of the whole story.  AS: Thank you very much indeed. We greatly look forward to welcoming you to Stockholm in December.  TH: Oh, yes, yes, I’m looking forward to that.  AS: It’s very exciting to talk to you, and once again, many, many congratulations.  TH: Thank you very much. I really appreciate. |
| Interview |  |
| Q19 | How did you receive the news that you had been awarded the Nobel Prize? |
|  | The first message I received from another foundation was by a telephone call. It was around 5 p.m. of October 1st. Actually people told me that something happened maybe before 4 o’clock se we are completely free out of these things. We were concentrating with my colleague about our paper in the manuscript editing and suddenly my secretary came with some stiff face and knocked and opened the door and: “You have to take the phone!”, so I was not so sure what was going on, something bad or good. I took the phone and the person calling was Dr Perlmann so I made it to catch the point and then I had a very nice and pleasant conversation. But often I heard there is a fake call. And so of course he also mentioned I asked him to send an e-mail to just confirm. Once I received the e-mail, it was real and so we told everybody in the lab and of course my family and other kind of the good exciting celebration – I mean the nice picture. The picture we took then was posted on the website of the Nobel Foundation so it was a very exciting and pleasant and unforgettable incidence in my life. |
| Q1 | Why did you decide to become a scientist? |
|  | There are several reasons, first I had to decide whether go to medical school or the law school or several other choices. Of course I went to medical school strongly influenced by my father, I mean the family reason, and secondly I read the biography of Hideyo Noguchi who was the very interesting doctor, who went to the United States in his 20s and become professor in the Rockefeller Institute. He found the syphilis as a cause of the paralysis. He died in Ghana during his study on the yellow fever pathogen so that was very striking, and I went to medical school. And the other reason I had a friend, only a father and a son and he died of this stomach cancer, very acute and I was very sad and I thought can I do anything for this type of disease. |
| Q16 | Can you describe the main impact of your discovery? |
|  | Cancer immunotherapy has been, I mean the idea, has been around many decades before Jim Allison and myself demonstrated in the above system. The reason why many people failed one after another is they didn’t realise that the immune system is already suppressed by the tumor growth. If we push the accelerator of the immune system while the immune system is under the strong brake, there is no way they can drive the immune system forward. And only the people find the major immune negative regulator means a break, that was CTLA-4 and PD-1. Jim Allison first showed say CTLA-4 blockade can cure the cancer in animal model and soon after we found a PD-1, I mean we found the PD-1 before, but we demonstrated the PD-1 blockade can also cure the cancer. Unfortunately, the PD-1 one is less toxic, PD-1 blockade I mean, and has chronic and now it is used in a wide spectrum of tumor starting from melanoma, lung cancer, renal cancer, stomach cancer, many. That is slightly advantage of the PD-1 over CTLA-4. CTLA-4 has a very strong activity and sometimes too strong, also a bit side effect is strong. |
| Q17 | How does it feel to do work that saves lives? |
|  | I received many prizes of course before the Nobel Prize and this is probably the last prize I get. But I felt when I see the patient and saying they were saved by the therapy we developed, that is the most moving, and also the time I feel my life has some meaning. So that was the very very, you know, unforgettable and also very touching. And I feel awarded. |
| Q4 | Can you tell us about some of the cancer patients you’ve met? |
|  | I am not a clinician but I have been involved in some clinical trials and the one lady who had a big tumour, this is a ovarian tumour, and doctor of course thought hopeless but she recovered and that was almost five years ago and treatment lasted one year and she is still tumourfree and enjoying her life. One time I saw she was playing golf so it was really amazing. A similar story; I play golf myself and I have a friend who told me: “This is my last round in my life because I have lung cancer”. But about half a year or so later he came back and had just started the treatment we developed, and he was just completely cured. It was fantastic. |
| Q41 | Do you have a message for those who are fighting cancer today? |
|  | Unfortunately our treatment is still not complete, only 20-30% are responders and we have a long way to go, but now this is just the beginning and many many scientists and the industry jumped in. I hope this therapy will be widely used and reach almost everybody in the world hopefully by the end of the century just like the infectious diseases almost completely eradicated during the last century. I hope this century will be remembered as the century of the cancer treatment. That’s my hope. |
| Q13 | Do you think that diversity is important for fruitful research? |
|  | Yes, I think so. Always, especially in the life science. We don’t exactly where is the best target. Nobody knows which mountain we should climb. We have to try many things, so for that purpose everybody has to think different ideas and have to discuss, so diversity is including everything; gender, nationality, different culture, maybe age. You have some brave young people, very brave, that’s good and aged people has more experience and that’s very important. |
| Q26 | What qualities do you need to be a successful scientist? |
|  | To make yourself a good scientist I would say first, you have to have curiosity. If you don’t have any curiosity you better choose something else. To be good scientists we have to solve something new. Something new usually is not easy because it is difficult, that is why it remains unknown. You need enough courage to tackle this difficult problems and you need courage and that is a challenge. Challenge with courage. I call this three primary C’s. And then once you decide to tackle, you have to concentrate and continue and eventually you build up confidence. So this is another three C’s. That is what I tell my students. |
| Q38 | How have you maintained your curiosity? |
|  | I never tried to keep my curiosity, it comes from inside. When I learn something new I always: Oh, this is quite interesting but why? Curiosity is just endless; it just comes from inside. |
| Q5 | Who has most inspired you? |
|  | There are several levels. As general science the first incident I was enchanted or charmed by the natural science is the very tiny tiny ring around the Saturn which I watched through the telescope at the elementary school. That was the first. I got very much interested, I wanted to be an astronomer and I read many books. But then later switched to medicine because I read the biography of Hideyo Noguchi. And the second very critical moment, maybe the time to come back to Japan, so it was another big choice in my life whether I stay in United Stated, keep going and many people advised to stay, but I decide to go back to Japan. That was -74, another type of turning point. Both cases I was fortunate that my decision was correct or correct because I made something, retrospective. |
| Q2 | Was there a specific moment that sparked your interest in science? |
|  | For my science I have so many important mentors or advisors. The first mentor was Osamu Hayaishi, who discovered oxygen, gas oxygen directing cooperation into the organic compounds, gave my solid background in science and also international theory. Science has to be international, it is not a local thing. And the next person who opened my eye to the molecular immunology is Donald Brown of Carnegie Institution of Washington. Without him I never go into this particular field and then I went to Philip Leder’s laboratory where I actually started this antibody diversification. So those three are very important during my scientific career. |
| Q3 | How did you stay focused on your research for all these years? |
|  | I didn’t have any resistance, fortunately my parents very supportive, psychologically and financially they supported and my family, wife and children – I was kind of workaholic. I don’t spend much time with my family, I feel sorry for them, but they just allowed me to concentrate on my research, so I am very fortunate. |
| Q7 | You’re a keen golfer – do you do your best thinking on the golf course? |
|  | Playing golf I completely forget about science and I concentrate. But the reason why I like golf game it’s not the competition, it is kind of the fight against yourself. For example if you hit a bad shot you get angry but you get angry against yourself and always you have to think very carefully because every time you hit, the ball run into different conditions sometimes grass thick sometimes different weather and you always have to think. But it is a different type of challenge. I can completely forget about my science. It is also very enjoyable. |
| Q34 | What do you consider to be your greatest achievement? |
|  | For scientific career I think I made two major contributions. One is I found the molecular mechanism for the antibody diversity, namely antigen induced antibody diversity class switch recombination and somatic mutation and this PD-1 break discovery and its application to cancer immunotherapy. But these days, I am still working, I am very much pleased that my two lines are now coming very close. Because cancer immunotherapy depends lots on your gut microbiota. And gut microbiota regulation depends on IgA secretion and the molecule I discovered for antigen induced memory, AID, I found another important molecule. And the two molecules collaborate to maintain our gut microbiota and this is important for homeostasis and also anti-tumour immunity. So that is my scientific contribution, but for the personal life I have a family and two children, fortunately both are doing well. Our son is the medical doctor, physician, and daughter is the embryologist working in science field and what’s rest? I also served at the administration in the medical school and I also served as the scientific advisor to the Prime Minister almost ten years ago. And I don’t know whether I made something through this type of administrative work but at least I tried to improve scientific environment. |
| ID | 0516 |
| Biographical | Jeffrey C. Hall was born in Brooklyn, New York, near the end of World War II (in Europe). His parents, fortunately for him, were among rare young adults in the U.S. who achieved college educations during the Depression. Hall’s father used his higher education credentials to become a journalist, his mother a school teacher. These are arguably mindful vocations, and they promoted a mindful atmosphere in Hall’s home when he was growing up, without there being any indoctrination and probably without Hall himself necessarily being aware of this salutary environment.  Eventually, what Hall’s father achieved vocationally caused him to work in Washington, D.C., covering the United States Senate along with presidential campaigns. Thus his offspring were raised mostly in a Maryland suburb of Washington. The aforementioned intra-home atmosphere (enhanced by how interesting it was for Hall to absorb information from his father about politics, society, and their historical contexts) made it axiomatic that he and his two siblings would attend college. Hall did so, beginning in 1963, and became a Biology major at Amherst College (Amherst, Massachusetts). A key element of this experience stemmed from his desire to do “Senior Honors” research. This caused Hall to be assigned, as his Honors supervisor, Dr. Phillip T. Ives. The latter had, by then (mid1960s), been a longstanding *Drosophila* geneticist. Though Hall was unaware of the following during his college stint: Ives was a distinguished such geneticist then and later, as Hall learned during his post-undergraduate time.  In any event, Ives was an excellent mentor, who not only instructed his small number of undergrad supervisees superbly, but also imbued them with a fervent interest in basic research generally and *Drosophila* genetics in particular. As Hall was performing a low-level genetics project at that college, his Biology Department superiors (including Ives) recommended that he try to become a graduate student at the University of Washington in Seattle. This advice came Hall’s way in the context of an incipiently well-regarded Genetics Department having been established at “U-Dub” (W = double U). Hall took heed of those college-based recommendations and enrolled at U-Dub in 1967. Soon after joining the Genetics Department there, he joined (in turn) the laboratory of Prof. Larry Sandler. The latter was an excellent *Drosophila* geneticist, who like Ives happened to be a direct descendant of [Thomas Hunt Morgan](https://www.nobelprize.org/prizes/medicine/1933/morgan/facts/). Morgan, along with his students at Columbia University in New York, were pioneers who founded, sustained, and expanded the fruit-fly genetics “system,” during the 19-teens and subsequent decades.  Within U-Dub’s Genetics Department, Sandler’s – and Hall’s – leader was Professor Herschel Roman, founder and longstanding Chair of that department (1959–1980). Roman fostered departmental norms that promoted high-quality instruction, training, and mentoring. In this regard, “Hersch” was well acquainted, professionally and personally, with almost all members of his department. The interest he took accordingly caused him to pull Hall aside, albeit not by singling him out. In any case, Hersch recommend that Hall try for a postdoctoral position in the laboratory of Seymour Benzer, California Institute of Technology (CalTech, a.k.a. CIT) in Pasadena where, more than incidentally, Morgan’s lab had moved from New York in the late 1920s. For Benzer’s part, by the early 1970s, he had established a second career, after initiating his genetically-based vocation via “pure” genetic studies of microbes. Along with Seymour *also* moving to CalTech in the mid-1960s, he shifted his interests and activities into the nascent sub-field of behavioral-cum-neuro-genetics. Benzer chose *Drosophila*, possibly influenced by the famed “fly group” that had long been ensconced there. Morgan was dead – as was one of his famed students, Calvin Bridges (Columbia -> CalTech) – but the equally famed Alfred Sturtevant remained alive, as was the latter’s student (then CIT Professor) [Edward Lewis](https://www.nobelprize.org/prizes/medicine/1995/lewis/facts/).  Back to Roman’s intra-departmental office at U-Dub: That Chair’s recommendation – in person to Hall *and* on the telephone to Benzer – about the former doing a postdoc in the latter’s lab led to Hall joining that CIT group during the late summer of 1971.  For a few months thereafter, Hall was fortunate to overlap with one of Benzer’s senior grad students, Ronald (Ron) J. Konopka. That investigator had made himself into a “chrono-geneticist,” taking a genetic approach to study biological timing, viz. daily rhythms. Thus, as Konopka was completing his thesis project (PhD, 1972), Hall became vividly aware of what Ron had been doing and spectacularly accomplishing: Induce from scratch, via application of a chemical mutagen, novel mutants in *Drosophila melanogaster* that would potentially manifest abnormalities or anomalies of such rhythmicity (including that which is exhibited at the level of fruit-fly adult behavior: rest/activity cycles, normally manifested via ca. 24-hour cycle durations). Ron’s mutant hunting, followed by high-quality analysis of the rhythm-based phenotypes *and* mutational genotypes, was stunningly successful. This was based in large part upon Konopka inducing and identifying a magnificent trio of novel mutants: one that displayed only 19-h daily cycles (in constant darkness), a 29-h mutant, and a third (the original) that was arrhythmic, a.k.a. aperiodic. Ron named these variants *period* mutants, formally justified, for he demonstrated that each of the three mutations involved newly induced changes within *one D.* melanogaster *gene* (famously abbreviated *per* and pronounced “purr” as opposed to “peer”).  During these heady days of the early 1970s, Hall could not help become a fan of Konopka’s research, owing to the findings themselves, and against a recent background that caused him previously to become aware of daily rhythmicity in *Drosophila*. Exposure to the relevant phenomena – including that fly cultures maintain daily rhythms in constant darkness, in which condition they display what are known as a “circadian” rhythm” – occurred when Hall was a student in a college course; its instructor happened to include a module about circadian rhythms manifested by “emerging flies” (metamorphosis -> adulthood = “eclosion”). That Assistant Professor at Amherst College had recently completed his PhD thesis research in the laboratory of Colin Pittendrigh (Princeton University, New Jersey), whereby the latter was becoming one of the “grand old men” of rhythm-related research. However, neither Pittendrigh nor anyone else had brought any definitive *Drosophila* genetics to bear on studies of these eclosion rhythms. At all events Hall was fortunate, by coincidence, to be attuned to the way that Ron Konopka pioneered a genetic approach to asking “what is a circadian clock?” That quoted phrase alludes to the notion that Konopka’s novel variants seemed for all-the-world to be *clock* mutants, as the relevant publication, co-authored by Benzer, was entitled. Implicitly, if a mutation (actually two) can change the circadian-cycle duration in a constant environmental condition, that smacks of a “pacemaker” problem. The noun just quoted had been invoked in context of organisms of all kinds displaying daily rhythmicities of all kinds, including behavioral; and that such biological (physiological, biochemical, etc.) cycling persists in the absence of daily earth cycles, notably light:dark ones. Implication: Central pacemakers harbored *within organisms* underlie such rhythmicity. This kind of pacemaker can be regarded as synonymous with “the circadian clock,” as it was initially inferred to exist via a plant experiment (-> animal studies, including of invertebrates and mammals, -> microbes as well).  Aside from the rhythm-related sub-enterprise extant within Benzer’s lab, Hall’s own research there from fall 1971 to the end of 1973 did not involve time-based phenomena. Instead: neurochemical ones as well as a project involving genetic “mosaics.” The latter genotype entailed *Drosophila* that were each part-male (one X chromosome)//part-female (XX) and with the two kinds of chromosomal genotype marked phenotypically via “histochemical” genetic marking (one-X cells, including CNS neurons, unstained for an enzyme reaction; 2X ones stained). Hall’s mentor, trainer, and co-worker for these projects was a fellow postdoc in the laboratory of Benzer, whose supervisory actions tended toward *laissez-faire,* named Douglas Kankel (Brown University, Providence, Rhode Island -> CIT, -> Yale University, New Haven, Connecticut). Doug taught his labmate a whole lot about *Drosophila* biology, including neurobiology, against a background of Hall having previously done genetic (qua genetic) studies alone. The latter did manage to bring to his pair of Benzer-lab projects genetic expertise, involving a heavy dose of *chromosome manipulations* in the context of many types of such being afforded by the “lore of *Drosophila*,” harking back to Morgan and his students.  Shortly after Hall’s postdoc stint entered its third year, by which time his co-worker Kankel had moved to Yale as noted above, he received invitations to interview for Assistant Professorships at two U.S. universities: U. Missouri (Columbia) and Brandeis U. (Waltham, MA). These invites were promoted by none-other-than Herschel Roman, who had recently visited those two institutions and recommended that his former mentee be considered for faculty-level jobs. So Hall can never forget nor fail to appreciate how meaningful to him was Prof. Roman’s career-sponsoring support (1967–1971; then intra-1973).  After traveling for the interviews just referred to, Hall received job offers from both of the universities in question, initially from Brandeis. That offer led him to begin an Assistant Professorship there, winter 1974. Hoping to get some research going there – at this near-Boston locale – he continued the pair of projects that had been maturing at CalTech around the time when Kankel and then Hall moved across the United States from Southern California (U.S.). This collaborative association continued for a while, “Back East,” facilitated by both fledgling faculty members being located in New England. These two former Benzer lab members put forth publications presenting the neurochemical-genetic and nervous-system mosaic findings in 1976. Yet Hall and Kankel had published zero primary papers during their postdoc stints, during an era when that kind of ostensible non-productivity could nonetheless lead to faculty jobs; nowadays, applications for such must be accompanied by massive publication-ridden CVs.  One aspect of Hall’s lab studies at Brandeis University involved *courtship* behavior in *Drosophila*. The starting point was to observe and quantify courtship capacities of the aforementioned sex mosaics: Which portions of the neuro-histochemically marked CNSs had to be genetically male (or female) if a given mosaic would perform one or more elements of the sex-specific, courtship-behavioral sequence? This category of behavioro-neuro analysis proceeded to a merger of genetic-mosaic principles and practices with neurochemically *disrupting* mutations, stemming from the other project Hall and Kankel had performed, starting at CalTech. The rather complex “mosaic dissection” experiment in question, based at Brandeis, was initiated in Hall’s lab by him and a postdoc who joined it during the late 1970s: C.P. (Bambos) Kyriacou. A key reproductive-behavioral phenotype recorded during this study was a male-like courtship song (normally produced by a standard XY fly’s wing vibrations, put forth when he follows a female, ramping up toward eventually attempting to mate with her). Bambos’s and Hall’s question: Which types of mosaics − set up to be each all-male, but with some tissues neurochemically mutated, others normal − might sing abnormally, putatively correlated within intra-CNS locations of the neurochemical deficit? But this project ended up dying on the vine, because of the following: Kyriacou and Hall also recorded (with microphones and magnetic tape) the singing behavior of *control* males: siblings of the mosaics, whereby such XY controls were uniformly normal for their neurochemistry. Analyzing visually appreciable renditions of the auditory recordings led to their inability to discern supposedly canonical “song parameters,” previously but cavalierly reported by the early song recorders, who had been working mostly in the U.K.  By virtue of enhanced labor, Bambos broke down and analyzed the entirely of each several-minute recording; thus he pulled-out long series of relevant computations, concentrating on a key song parameter: rate of tone-pulse production (per series of 10-second bins). He therefore discerned that that singing element seemed to be fluctuating systematically. Further analyses revealed, indeed, that the rate in question oscillated rhythmically: speeding up, slowing down, speeding up again; with a cycle duration of about one minute for *D. melanogaster* free of behavioral/neural mutations. Next step, during the micro-era in question (late 1970s): Kyriacou and Hall wondered whether the only known rhythm-affecting mutations in “our” species might by-some-chance alter song rhythmicity. Hall, especially, knew that those variants were Ron Konopka’s *circadian* mutants (n=3, harking back to the latter’s PhD thesis project). So Hall wrote Dr. Konopka, asking for culture copies of Ron’s mutants, even though the Brandeis researchers were aware that circadian rhythmicity and song such are defined by cycle durations three orders of magnitude different from each other. Yet, Konopka’s *per* mutations – two of which caused altered cycle durations, the third causing arrhythmicity – were found to alter courtship-song cycling in ways paralleling effects of these genetic variants on daily rhythms.  So Hall’s admiration for Konopka’s chrono-genetic accomplishments and a coincidental matter of the former being instructed in a college course about biological rhythms in *Drosophila*, prompted that lab head at Brandeis, and others there, to enter an arena defined by actual chronobiological lab work. Meanwhile, a close colleague of Hall in Waltham, MA – then Associate Professor Michael Rosbash – had previously become aware of the Konopka mutants. After Hall and Rosbash met during 1974, the former could not help mention that banner study (emanating from his former postdoc lab) and speak highly of it; even though neither Hall nor Rosbash had any mid-’70s interest in doing anything about *per* mutants or the gene defined by them. Nonetheless, Rosbash also became well acquainted with Bambos Kyriacou, as the second half of the 1970s unfolded, enhancing the former’s appreciation for the *period* gene’s existence.  A few years later in the early 1980s, an experimental question suggested itself, whereby the *per* gene would have to be identified and isolated at the DNA level.  To make a medium-length story short as to how that question arose: We fantasized about “cloning *per*” from *D*. *melanogaster* (*mel*), using that DNA readily to do the same for *per* in the close interspecific relative *D. simulans* (*sim*), then transferring the latter into *mel* to ask whether such a single-gene infusion would bring with it regulation of *sim*-like singing rhythmicity. As of the early ’80s, Kyraicou and Hall had found that *sim* and *mel* males generate species-specific song-cycle durations *and* that the genetic etiology of this difference mapped to the same chromosome on which *per* is located.  Therefore, and initially *not* based on a specific interest in *circadian* rhythmicity in *Drosophila*, the researchers at Brandeis with material help from Kyriacou and from Konopka himself, set out to isolate *period*-locus DNA and identify it via behavioral bioassays: introduction of putative *per* DNA into *per*-mutant “hosts” carrying the arrhythmia-inducing mutation. This new project was rooted in an incipient, close collaboration between the laboratories of Hall and of Rosbash at Brandeis, augmented by the two sending behaviorally-pertinent strains to professional locations where the “two K” guys had ended up as of the mid-’80s.  This multi-lab effort eventually ballooned *as* its interests shifted mainly into the *daily*-rhythm arena. The researchers began to so study via multi-pronged approaches: behavioral genetics, cyto-genetics (application of chromosome aberrations), molecular genetics, and neuro-genetics. For Hall’s and Rosbash’s part, it was meaningful that they had become close not only professionally but also personally: respectively, related to co-awareness that Hall was a generic fruit-fly geneticist; and Rosbash was a generic molecular biologist, initially studying vertebrates and yeast from the mid-’70s into the ’80s. In addition, these two faculty members shared various personal interests, mostly revolving round low-culture stuff. Might their association – including separate, seemingly complementary, scientific backgrounds − promote a fruitful joining of forces: chrono-genetics deepening into the molecular-genetic area?  As this bi-lab collaboration at Brandeis got started and proceeded, the two were operating in competitive parallel with *per*-molecular studies performed in the lab of Mike Young (Rockefeller University, New York). Mike had become at least marginally interested in circadian rhythms affected by *period* mutations back when he was a graduate student in the 1970s, mainly studying other bio-genetic phenomena in *Drosophila*.  The *tri*-lab deal − a pair of collaborating groups plus one competing with the former two − began to work out. As of approximately the mid’80s, a quartet of publications (two from Massachusetts, two from New York) reported *probable* cloning of *per*, followed by nailing that matter via DNA-mediated “rescue” of the relevant *per*-mutational effects, as alluded to above. Hall maintains that a companion piece in this volume, based on his [Nobel Prize lecture](https://www.nobelprize.org/prizes/medicine/2017/hall/lecture/) in late 2017, usefully recounts sufficient additional features of these early-days stories, along with presenting the requisite background information from the 1970s and earlier.  No doubt the lecture-based articles by Profs. Rosbash and Young will flesh out all additionally relevant aspects of this history. Meanwhile, some quasi-editorial remarks, partly coming under the header of Hall tooting his own biographical horn; as well, what follows may usefully divulge some historical stuff, referring to the post-’80s era: In this respect, and in Hall’s experience plus opinion, it is possible to get carried away with “the primacy of *per*”: yes, the first clock gene cloned in any organism. Gene #2 of this type was identified at that level in *Neurospora* five years later. Could one clock factor, the PER protein, tell the whole fruit-fly story insofar as the circadian-pacemaker mechanism was concerned? A priori, no. Realizing this, Hall and associates such as Rosbash and Young “did Konopka’s” of their own, spearheading renewed searches for rhythm-related genes in *Drosophila*, whose products could be gleaned to contribute materially to said mechanism. Such mutant hunting was set-up to involve chromosomes extending beyond the one where *period* is located.  As elaborated citationally within Hall’s “lecture article,” this tri-lab endeavor led to identification of Young’s *timeless* (*tim*) gene, which encodes a PER companion; and *doubletime* (*dbt*), whose encoded enzyme influences the dynamics of PER protein “cycling.” Now *per* and *tim* must be transcriptionally activated, of course, before their first-stage products (mRNAs) can go up and down each day. Indeed, although perhaps anti-climactically, the Hall/Rosbash crew – including several valued co-workers (grad students, post docs, and others) – induced behavior-arrhythmia-inducing mutations at loci named *Clock* (*Clk*) and *cycle* (*cyc*), which also lead to very low levels of *period* and *timeless* products. Neither *Clk* nor *cyc* mutations (loss-of-function “alleles”) kill developing *Drosophila*; same for *per* or *tim* “nulls,” but unlike *dbt* ones, the latter gene being a developmentally vital one with pleiotropic effects. Thus, *Clk* and *cyc* – whose transcrioton-factor products co-associate to turn-on both *per* and *tim* transcription – can be regarded as semi-dedicated to rhythm-regulating processes.  Discovery of all these core clock factors in *Drosophila* was rooted in mutant hunting. Yet, extending beyond that core, circadian clocks must also receive inputs from the environment, e.g., so that these only *circa*-dian pacemakers can be subjected to daily re-sets, thus underpinning 24.0-hour cycle durations in natural conditions. One conspicuously acting input factor in *Drosophila* came to the fore thanks to yet another hunt for mutants performed by Hall and co-workers, which resulted in identification of a light-absorbing molecule called CRY. It is encoded by the mutationally defined *cry* gene, whose encoded protein − when activated by photic stimuli − “touches” TIM to promote the latter’s degradation during the falling phase of *tim*-product cycling. Now the core clock also has to do more than spin its internal wheels, plus be sensitive to external stimuli. Therefore *output pathways* must project from central-pacemaking functions, ultimately to mediate revealed rhythmicity (behavior, physiology, and much more overall). Starting with performance of *molecular*-genetic tactics, many output-gene candidates in *Drosophila* were uncovered at Brandeis and Rockefeller, plus within farther-flung research groups. One such gene, which encodes a brain neuropeptide, comprised a fruit of such searching at Brandeis; contributed to gaining insights about “outputs from the clock;” then was exploited molecular-genetically, neuro-genetically, and behaviorally by Hall’s research group and several others. The latter came to be composed of an ever-expanding venture, extending well beyond investigative activities occurring originally at only a small number of institutions. This swelling phenomenon included a variety of “other-directed” investigators, referring to how their careers started, dropping much of what they had been doing in order to start studying *Drosophila* chronobiology and that of other-organismal rhythms.  Hall could not help summarize elements of this post-*per* research, although the meaning of that seminal gene continued to be elucidated well past the mid-1980s. At a minimum, successful searching for further factors – notably at Brandeis and Rockefeller during the 1990s – signifies that these (dare we say) molecularly pioneering labs were serious about their hope to flesh-out rather robust understandings of the overall rhythm-related deal.  By analogy to entering what he just did, Hall comes near the end of this biog by inserting a partly personal coda: He has long regarded the *genetic* side of the overall enterprise to be extremely consequential, exemplified by what was just outlined within recent passages: so many “clock players” found in *Drosophila* via pheno-genetic screenings. So the attack on fruitfly chronobiology has had a lot to do with variant genotypes and associated *pheno-genetics* (to re-invoke an arcane term, meaning rhythm-related effects of genic variants, chromosomally based ones, and molecular “clones”). Conversations between Hall and Rosbash, and among other associates, have stimulated Rosbash to say that “the molecular biology made all the difference.”  Fair enough: Truly no one could have anticipated, for example, what *period*-gene products are about, absent “cloning *per*” then empirically analyzing the encoded RNA & protein (involving way more than sequencing the gene and describing PER protein on paper, hoping forlornly that that description alone would divulge much at first-blush). *In addition*, genotypic and phenotypic elements of the eventual extravaganza (momentarily factoring out molecular matters as a *gedanken* consideration) have been rate-limiting investigatively, in Hall’s opinion. For his part, and in order potentially to “do anything” chrono-wise, he relentlessly sensed appreciation for genetically based interactions with and mentoring by his early-career associates: Ives, Sandler, Roman, Lewis, Kankel, and Konopka.  If Hall had not been fortunate enough to come straight out of the T.H. Morgan tradition of *Drosophila* genetics, he wonders in retrospect whether he could have contributed to the overall behavioral/neurobiological/chronobiological enterprise in some sort of meaningful manner. Prof. Young *might* sense something similar. Although he was not a molecular-geneticist in his early pre-postdoc days, he too is a direct descendant of Morgan, via Young’s PhD research in a laboratory headed by an academic great-grandson of a fruit-fly-genetics pioneer. Hall has noticed, for instance, that Young merged with élan his molecular-genetic expertise with *Drosophila* cyto-genetics (matters revolving round the latter having been absorbed by that student of the fruit-fly in advance of Young beginning to focus heavily on biological rhythms and circadian clocks). Maybe Hall, as well, was able to tap into the aforementioned “lore of *Drosophila*,” influencing ways that he helped sustain the chronobiological endeavor at hand, in part via some sort of genetic diligence. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0516=JH  [Jeffrey C. Hall]: Hello.  [Adam Smith]: Hello, my name’s Adam Smith. I’m calling from Nobelprize.org, the website of the Nobel Prize in Stockholm. Many congratulations on the award of the Nobel Prize.  JH: Well thank you.  AS: Where am I calling you? You’re in Maine, is that …  JH: You’ve reached me where I’ve lived for many years in the middle of nowhere, Maine, rural Maine. Also known as Central Maine. In the extreme north east of this great country of ours.  AS: Sounds a beautiful place to be located.  JH: It is physically beautiful, including, I’m looking out the window, it’s a very beautiful day today, which is often is.  AS: Fall colours and the like I guess.  JH: Not quite yet but it’s still green as can be but it’s, because Maine is not like Arizona.  AS: You’re being awarded today for unravelling the mechanisms of the circadian rhythm.  JH: Yes, correct. That was about half of our work, during my time when I was employed, had to do with circadian rhythms, indeed. That became amongst our most well-known research achievements, if any. Usually, and, relentlessly co-authored with Rosbash with whom you’ve already spoken. So he and I joined forces in the early mid-eighties and imagined that we might, or we might not as the case may be, go onward and upward doing research together in that arena. Which often involved crucially, what I call AIs – actual investigators – like students, post-doctoral supervisees, from the two labs working very closely together, even day by day. So that was enjoyable, it wasn’t that either lab was way out on its own limb. We had a lot of mutual support, I think it’s fair to say.  AS: You obviously had a very special working relationship, there was something magical about the team.  JH: This was based in large part on becoming close personally at the beginning where our research interests in very general terms were in genetics, writ large. It was only after six, seven, or eight years that we started to work things together and imagine that possibly our backgrounds and our skills, if any, might be complementary. The key reason that we got into that kind of relationship was because we were personally close. We had mutual interest in low culture stuff like sports and rock and roll music and abusable substances and stuff. And so we spent a lot of time just carousing or sitting together in misery at local sports stadiums. We have also certain, many similar interests, even in the pre-rhythm research days. He as a molecular geneticist, I as a straight up fruit fly geneticist.  AS: And that brings us onto flies. We should say a word for flies on this day of all days because once again the power of the fly as a model organism has been demonstrated.  JH: That’s right, this is something I’ve always … I was taught when I was a graduate student about a phrase, it’s known as the lore of *Drosophila*. To know about the deep history going all the way back to the 1920s, and the 40s and the 90s and now the second decade of the current century. It’s just one of a zillion examples of how basic research on a supposedly irrelevant organism can have broader significance than, with regard to what’s going on in terms of that organism itself. And this has been true of fruit fly research, which has been a major contributor for decades. For well over a century actually.  AS: Well let’s dedicate this day to the fly.  JH: Yeah, the key fourth awardee here is, as some of us call them, the little fly. So the little flies deserve another tip of the hat, I think, in terms of what has happened today.  AS: That’s lovely. Indeed they do. And it’s been such a pleasure speaking to you. I’m very much looking forward to meeting you. Will you be coming to Stockholm in December?  JH: Yes I will, I think I almost have to. But I’m willing to.  AS: Good.  JH: I was in Sweden once in my time, back in the time when Swedish folk drove on the left-hand side of the roadway. So I’m looking forward to going back to Stockholm where I once was, in 1967.  AS: We very much look forward to meeting you, thank you. Bye.  JH: Bye. |
| Interview |  |
| Q1 | How did your upbringing influence your path to science? |
|  |  |
| Q25 | Do you think it’s important to have a mentor? |
|  |  |
| Q22 | What sparked your curiosity about our daily biological clocks? |
|  |  |
| Q23 | Is circadian rhythm a sort of sixth sense for living on earth? |
|  |  |
| Q36 | Did the universality of clock genes pave the way to the discovery? |
|  |  |
| Q11 | How would you describe your collaboration with Michael Rosbash? |
|  |  |
| ID | 0517 |
| Biographical | **My parents and Germany: tough times** My parents were born and raised in Germany. My mother Hilda was born in 1914 and came from a secular, quite comfortable family in Berlin. Her father, my grandfather, Magnus Sonntag had a pharmacy, which still exists today with the same name and in the same location (Marien-Apotheke, Wilhelmsaue 110, 10715 Berlin). As the story was told to me, Magnus was a soldier in WWI and home on weekend leave when he discovered his wife, my biological grandmother, with another man. Magnus kicked her out, she moved to Holland, which left her 3-year-old daughter with a father at the front and no other parent in Berlin. My mother was sent to live with her grandparents for a few years and never saw her biological mother again – although there were some subsequent communications (see below). My grandfather remarried, and my mother thankfully adored her step-mother. There were two much younger children from this marriage, and all 3 siblings have now passed away.  My father Alfred was born in 1912 and raised in Baden-Baden. My grandfather Joel Rosbasch (my parents dropped the c upon arriving in the US) went to Germany as a young man sometime around 1907 to escape from difficult economic times in the Ukraine. He left his family including 3 young children behind in Kremenchuk and got a job in a cigarette factory in Stuttgart, not very far from Baden-Baden. Cigarettes were rolled by hand in those days. My grandfather was skilled in the art and so had no problem securing a job in early 20th century Germany. He sent for his family, including my father’s 3 older siblings, who were all then raised in Germany. According to my father’s one younger sibling, my Aunt Lotte (she passed away at the age of 98 in 2013), my grandfather saw the handwriting on the wall and left cigarette-making shortly before that industry was mechanized. He moved his family to Baden-Baden and ran a small grocery-dry goods store there, together with my grandmother; they lived above the store. Although the Rosbasch family was quite religious and kept kosher, the children – my father and his siblings – were educated in the secular German system. My father was a top student at Gymnasium and was asked to tutor those fellow-students who were struggling with math − again according to my Aunt Lotte.  Both of my parents were in university, my father studying law and my mother medicine, until Jews were no longer allowed to pursue these professions – in about 1933 I believe it was. They then both turned to Jewish professions. My mother studied some aspect of Jewish education, and my father – who had an excellent voice as well as a religious background – became a cantor. My parents were married in 1937 and in that same year my father got his first real job as a cantor in a synagogue in Breslau, which is now Wroclaw in Poland. According to my mother and my Aunt, my dad loved that job as well as the Germany of his youth (see below). He didn’t want to leave; like many German Jews he found it incomprehensible that the madness of the mid-late 30s would not somehow dissipate and then evaporate. My mother was more pessimistic, realistic one can say in hindsight, and insisted on going to the US – where there was some distant family who helped with visas. I vaguely recall that her biological mother sent her from Holland the money for passage. My mother was never one for negotiating or discussing something that she felt strongly about, and so just said to my father that she was going to the USA either with or without him. Being besotted about my mother (yes – story from Aunt Lotte once again), he left for the States with my mother in 1938 a few months before Kristallnacht. The next morning after this wicked night, the local Baden-Baden Gestapo came to my grandmother’s home for my father, demanding “the tall one,” to which she defiantly responded, “You’re too late; he’s gone to America.”  At the risk of a tangent, it is interesting to note that this one year as a cantor was sufficient to make my father “beamte” or tenured in the German civil service. This status entitled my father to a pension, and my mother collected a widow’s pension for decades based on this one year of service; this had nothing to do with being Jewish or restitution. Few people in the United States know that all clergy in Germany are state employees and receive their salary from the federal government. This is true for rabbis, priests, imams as well as protestant ministers, and it was true in the 30s and is still true today. What is remarkable, and a testament to German bureaucracy, that all of this continued to function like clockwork (pun intended) – even for Jews − at the same time as another wing of the German government was gearing up to efficiently carry out the final solution. As Dave Barry would say, “I am not making this up.” **Moving to the US and my childhood** My parents arrived in New York with few resources and no job. While my father searched for a job, my mother cleaned hotel rooms – a fact she bitterly recounted to me for the rest of her life as if it were my doing. (I had/ have lots of Jewish guilt but this was too much even for me.) My father joined the myriad of rabbis and cantors from Europe pounding the New York pavement and looking for work, to no avail. At this time my mother was looking through some National Jewish newspaper, the Forward perhaps, formerly the Jewish Daily Forward, and saw an advertisement for a cantor’s job in a reform congregation in Kansas City Missouri. She suggested my dad apply, who said “But we’re not Reform Jews.” (To more religious Jews, Reform Judiasm at that time was an anathema, essentially indistinguishable from Christianity.) My mother was not to be deterred. “We are now; making a living comes before some ridiculous religious division,” she replied. My dad went to Kansas City, interviewed for and was offered the job, and my parents moved there in late 1938. So my mother once again came to the rescue.  My parents loved Kansas City and had nothing but good things to say about their 8 years there. They made wonderful friends, learned lots about America including how to drive (taught by some of those friends) and had their first child; I was born there in 1944.  I have two family anecdotes about Kansas City. The first concerns a seminar that I gave perhaps 15 years ago in the Stowers Institute for Medical Research in that city. I was in the office of the Director Rob Krumlauf, when he told me that the Institute had been Menorah Hospital, a famous Kansas City hospital before the hospital building was gutted and turned into the Stowers. I vaguely recalled the name of the hospital where I was born; sure enough, the Stowers seminar room is at or very near the precise location of the Menorah Hospital maternity ward where I had been born.  The second anecdote comes from my Aunt Lotte, my father’s younger sister whom I have already introduced. She was a 29 year old single woman when I was born and came to Kansas City in 1945 to help out my mother with her young child. One day in May during that stay, Aunt Lotte went to the cinema with my father. This was before TV and the only place where one could see a recent newsreel, which happened to show that day the surrender of the German generals. My father said to his sister after watching, “I am surprised to discover how sad I am, how ambivalent I apparently am about this allied victory.” He was of course glad that the war had come to an end and with a victory for the US. Nonetheless and despite his religion and negative experiences in Germany during the 30s, he had been educated as a German patriot and to have respect for the German military; those sentiments had not entirely disappeared. The moral lesson: life is not simple.  My parents moved to Boston in the summer of 1946 when I was two and a half years old. Moving between synagogues is not unlike moving between academic institutions. A bigger, more prestigious synagogue offers a rabbi or cantor a job with better conditions and more salary, perhaps in a more interesting city. The offer was successful in moving my family.  We lived in an apartment in Brookline until 1950 at which point we moved to our own home in Newton, all part of the American dream. I was six at the time and began second grade at the Cabot School. As I have recently described in some detail (“Life is an N of 1”), I had some behavioral issues throughout school – probably throughout life. In hindsight, it is likely I had ADHD or some variant thereof, but the worlds of education and psychology were too naïve to treat these kinds of problems in the 50s. Perhaps this was a good thing, at least for the kids who were problematic but not too disruptive. Meds today may be given too liberally and too quickly, perhaps as much to help teachers and parents as to help the troubled kids. Certainly, I turned out OK without any meds or treatment.  My dad died of a heart attack in the fall of 1954 at the age of 42. He died in the synagogue on Yom Kippur eve, shortly after singing Kol Nidre, the liturgical chant which is sung by the cantor at the beginning of this most sacred holiday. It is said that only the holiest of men die on Yom Kippur; I would like to believe this is true. I should avoid any confusion at this point and state unequivocally that I am a devout atheist and quite anti-religion. Nonetheless, I do have an irrational connection to this event and to my family history, which is now obvious even to the most casual reader. Emotional issues are not easily dismissed, and my own health history is not unrelated. I had a heart attack at the age of 38 and am still here and in decent shape at the age of 74.  My father had had an initial heart attack a few weeks prior, for which he had been hospitalized. There was apparently a big family brouhaha that ensued over whether he should return to singing, which is physically quite stressful. My mother told him that he had to decide himself, and so with his physician’s OK, he went back to his normal job. If hindsight is 20:20, foresight in this case was blind.  Our small nuclear family was destroyed by my father’s death. My fragile mother, just 40 years old, never fully recovered; my brother and I – ten and six at the time – were left to fend for ourselves, at least emotionally. In this case perhaps and in contrast to my possible childhood behavioral issue mentioned above (ADHD), some professional intervention might have been a good thing, for my mother as well as for me and my brother.  My father’s death was an additional blow for my mother in an entirely different way. She had matriculated at BU Medical School and was slated to begin classes in the fall of 1954. This was when my brother began first grade, when both of us would finally be in school full-time. This was therefore the first opportunity in more than 20 years that she had to fulfill her dream of becoming a physician, the path she had been on in 1933 when the Nazis had forced her to leave university. BU had even fast tracked her path by giving her two years of credit for her time in a German university studying medicine. However, we had no financial resources and so my mother had to go to work to support her two children. She took a six-month course at the Massachusetts General Hospital (MGH) and then went to work at the Beth Israel (BI) Hospital as a cytologist. Within a few years, she became the head of this new subdivision of the BI Pathology Department. She supervised a team of cytologists and ran this well-known and profitable department for many years. After being a widow and working at the BI for 20 years, she married another German Jew, a widower from Pittsburgh. She moved there in 1974, at about the same time I came to Brandeis, and lived in Pittsburgh for the last 34 years of her life, until she died in 2008 at the age of 94.  Although painful, this history still does not do justice to the difficult life my mother had. I have already described the extent to which her education and secure world as a comfortable Berlinerin were destroyed by the Nazis. She then had to begin life anew in the United States at the age of 24. In addition, however, her own Sonntag family was divided by thousands of miles; her parents and brothers went to Brazil in the late 30s when my mother and father emigrated to the US. My mother only saw her parents once after 1938, a visit she made alone to Brazil fourteen years later in 1952. Thank goodness she made that trip, because my grandparents both died one year later in 1953, a year before the death of my father. They never managed to see their daughter’s children, and my brother and I never met our maternal grandparents. In addition to all this history, can you imagine losing both your parents and your husband within one year at the age of 40, and then having to go to work to support your two young children?  This short ode therefore serves to put into perspective some less than admirable personality features of my mother: she was emotionally distant, not very empathetic and also quite selfish. I do prefer nature (hard-wiring) over nurture (environment) as the principal explanation for personality, but the hard road my mother had to travel has made her family more forgiving about her shortcomings. Lastly, she was unbelievably proud of her children, including my academic accomplishments. She would always ask my wife, “Do you think he will win the big one?” What a shame that she died 9 years too early and did not live to see my Nobel Prize. **High school and college (Caltech)** I was a rather indifferent high school student and went to Caltech to escape the unhappy home life briefly described above. Caltech was a good school and also as far away as I could get from Boston in the early 1960s. Going to college there was a stroke of good fortune, because it was academically very challenging. My fellow undergraduates were really smart, and most of them were also hard-working – a combination of diligence and fear of failure. I in contrast had no study habits from high school, a combination of the likely ADHD I referred to above and the fact that I could succeed reasonably well without any effort. This was impossible at Caltech, and after a year or 18 months of trying to succeed without working like in high school, I finally succumbed to the old adage, “If you can’t beat ’em, join ’em.” So I buckled down, started to study and did well academically.  I remember that the Caltech Dean of Students Paul Eaton told me at graduation in 1965 that I had the very lowest projected GPA of all the students in my class. (In those days before computers, Caltech had some primitive system for projecting the academic performance of their applicants.) He told me this to emphasize how proud he was of my performance, which had dramatically exceeded expectations. In hindsight, I had been accepted to Caltech almost certainly because of “geographical distribution;” west coast schools wanted east coast students as well as west coast students. My good academic performance at Caltech is an important lesson I try to remember: statistics are important, especially for making policy, but there are always individual outliers.  Not only did I do well academically, but the course material had also become MUCH more interesting. Skating along the surface, studying only just before exams, doesn’t provide the positive feedback that comes with real learning, with thinking often about academic material. Once the old habits were broken, they were replaced by the positive feedback loops of understanding.  I was aided in this transition by a wonderful advisor and mentor, Norman Davidson. ND as he was called was a fantastic chemist, who was just transitioning in the early 60s from physical chemistry and statistical mechanics to nucleic acids. He was a no-nonsense guy, who challenged me to do well. He was also a fantastic role model with his complete joy in doing research and running a lab. I had never met a grown-up who loved his work so thoroughly. I remember the day I decided to do research for a living. ND was walking down the hall away from me and was wearing a t-shirt. On the back it said on top, “I’d rather be in the lab,” and then on the bottom, “Or maybe playing tennis.” (He really liked sports, skiing as well as tennis, and had been a basketball player as an undergraduate at the University of Chicago.). I didn’t know what it was really like to run a lab, but I said to myself, “this has to be a good thing if it can bring such unbridled joy.” **Paris** I went to Paris for year after Caltech. It was highly unusual in the 60s to take time off, to not go directly to graduate or professional school, but I had a desire to see the world. (My mother was an inveterate traveler, so perhaps my wanderlust was inherited or perhaps culturally transmitted.) I had been working and saving money during my junior and senior years of college to travel for a year, when I decided on a lark to apply for a Fulbright Scholarship. I knew some French from high school and even one semester in college, and Paris was a romantic destination. I also had learned in a Caltech class about [Jacob](https://www.nobelprize.org/prizes/medicine/1965/jacob/facts/) and [Monod](https://www.nobelprize.org/prizes/medicine/1965/monod/facts/) (the lac operon, gene regulation and allostery), and so Paris even seemed like a good scientific destination. My choice was prescient, because these two gentlemen – along with their French/Pasteur colleague [André Lwoff](https://www.nobelprize.org/prizes/medicine/1965/lwoff/facts/) – won the 1965 Nobel Prize in Physiology or Medicine, which was awarded a month or so after I arrived in Paris.  To my surprise, I was awarded that Fulbright Scholarship and was off to Paris by boat from New York together with the rest of my fellow Scholars in the late summer of 1965. The Fulbright organization used that trip and the first two weeks of our time in Paris for group bonding and orientation. My recollection is that I was the only scientist in the group, which was great for my general education. Most of my colleagues were Ph.D. students in French literature, from prestigious US universities. They were therefore not only older but also wiser than I was, especially in matters that concerned France, French language and French culture; my fellow Scholars therefore helped me acclimate to my new circumstances.  Despite my genuine praise above for Caltech, it was at the time an institution with no female undergraduates and more generally a rather narrow cultural bandwidth. It turned out that I was desperate for a different experience and so fully embraced what Paris had to offer. This was just about everything: in addition to the obvious − women, cuisine and wine − about which I knew virtually nothing at the age of 21, there was the remarkable cultural and political heterogeneity of mid 1960s Paris. I was stunned by all the refugees and students from all over the world, which reflected the genuinely cosmopolitan nature of the city as well as the influence of colonial France and the French language in the Middle East, Africa and Asia. It also reflected the parochial nature of my life in the US in the 50s and 60s; I don’t think I had ever met an Arab before Paris, and I didn’t know where the Maghreb was or what the word meant. (It is a major region of North Africa, including Morocco, Algeria, Tunisia and Libya; I also just learned from Wikipedia that it includes Mauritania.) There were also tons of Lebanese in Paris; I did know where Beirut and Lebanon were only because − like most Jews at the time − I knew they were just north of Israel.  1965 was at the end of France’s colonial era, 9 years after Dien Bien Phu and only 3 years after the end of the Algerian war. This recent history explained many of the refugees and the left-wing politics that were thriving in the Paris streets. However, I also met charming and generous rightwing people. Most memorable were the Pieds-Noirs. (The term refers to Europeans, mostly French people like [Albert Camus](https://www.nobelprize.org/prizes/literature/1957/camus/facts/), who had lived in Algeria for generations and had now “returned” to France.) Their politics was understandably colored by their experience of having been uprooted from their homes and adopted land by revolution. I learned a lot from all of these people, from their politics, their languages, their experiences, their stories, their families, and even their home-made couscous.  You might be wondering: how did a young scientist have time for this cultural accretion? The short answer is that I didn’t work much that year. The longer answer is as follows: I was assigned by the Fulbright organization to the lab of Marianne Grunberg Manago at the Institut de Biologie Physico Chimique. Marianne was a very famous 44-year-old scientist in 1965. She had been a post-doc of [Severo Ochoa](https://www.nobelprize.org/prizes/medicine/1959/ochoa/facts/) at NYU and famous for having done the work for which he won the Nobel Prize in 1959. In fact Marianne’s enzyme, polynucleotide phosphorylase, won two Nobel Prizes as it was used to synthesize the oligonucleotides used by [Marshall Nirenberg](https://www.nobelprize.org/prizes/medicine/1968/nirenberg/facts/) to crack the genetic code (1968 Nobel Prize).  Marianne was a very nice but somewhat imperious European professor and totally dumfounded by the assignment of a very assertive 21-year-old Caltech undergraduate to her laboratory. She put me to work with her wonderful technician Jacques Dondon to help make the stock of charged tRNAs for the lab. This preparative work took a full week and was interesting the first week, tolerable for the second but quite boring by the third. Every week I would ask Marianne to give me a proper research project, and she kept responding by saying she would do it “next week.” So after 4-5 weeks of this back and forth, I changed my tack. I said, “Marianne, I am going back to graduate school in the United States without question, but I am now having the time of my life here in Paris in other ways. I am seeing and learning things I never imagined existed. I like the lab here and will work if I have a research project but not without one. So if you still don’t give me a research project next week as I have been asking, I will stop coming to the lab except once a week to collect my paycheck and to peruse the journals.” She never gave me a project, and I stopped working in the lab as previewed. I spent the year doing all these other things in Paris, including learning to speak French well, and I also traveled all across Europe. In the decades that passed, Marianne never mentioned this conflict to me – if I can call it that. She followed my career and proudly saw me as one of her scientific progeny.  In the immortal words of Edith Piaf, “I regret nothing” about my year in Paris. I made dear friends and acquired a life-long appreciation for French culture and the French language. I even benefited professionally because I had a long string of outstanding French students and post-docs who came to Brandeis years later and had a huge, positive impact on my career; it all began I believe with that year in France at the tender age of 21 and with my subsequent quite fluent facility with French. Moreover, I was offered big director jobs 20–25 years later. The offers were flattering and I was tempted, but I was recently married with my current wife, a Chilean who adored the States and was reluctant to change countries once again. Moreover, she convinced me – correctly in hindsight – that I would never be able to navigate institutional politics in a foreign culture like France. There is too much important that is left unsaid, in conversation and negotiation, that only a native can glean, despite excellent language skills. My wife said, “Let me put it this way; if you have had trouble at Brandeis, imagine what this would be like in France.” **MIT** I went to graduate school at MIT, which was a great place for me. I decided to work on eukaryotic gene expression in the lab of Sheldon Penman. He was very smart, committed to the lab and a caring mentor. There was also a wonderful collection of students and post-docs in his lab. Notable from that period of time were Bob Weinberg, Hung Fang and Rob Singer. My work went well. I gained confidence and experience, and generated first-rate publications.  MIT was a much bigger, more cosmopolitan place than Caltech, and the late 60s was a more interesting period of time in the United States than the early 60s. Vietnam had polarized the country, MIT was a center of political activity, and marijuana had gone mainstream. I was very engaged in the anti-war movement and considered devoting more time to this political work. I spoke to Sheldon about it, and he told me I would have to change advisors if I wanted to do politics in a way that would interfere with my lab work. Moreover, he said that there were MIT faculty members who would be OK with a less than complete effort to the lab, who were themselves committing considerable time to anti-war activities. Because Sheldon was quite right-wing and in favor of the US military effort in Vietnam, I thought this might have contributed to his inflexibility. So I went to Sheldon’s younger colleague [David Baltimore](https://www.nobelprize.org/prizes/medicine/1975/baltimore/facts/) for advice. David was anti-war and only six years older than I was, i.e., in some ways my peer. To my surprise at the time, he endorsed Sheldon’s viewpoint by agreeing that a PI can insist on the effort that a graduate student should make in his/her lab. And he too suggested I switch labs or agree to pare down my political activities if I wanted to stay working for Sheldon. I respected and was grateful for David’s candid opinion, which had a big influence on my decision to remain in Sheldon’s lab. My scientific career has almost certainly had more influence than any political contribution I might have made, and I would not be writing this Nobel biography had I not made the decision to remain with Sheldon.  Two anecdotes stick in my mind from my 5 years at MIT; they are both illuminating I suspect. Sheldon and I had the identical old car. When he decided to upgrade and buy a new car, he generously offered me his old one for parts. He knew I had some experience fixing cars from my Caltech years and so might make use of the gift. I accepted but had another idea in mind. I spent an entire Sunday trying to remove intact his faculty parking sticker so I could affix it to my driver’s side window. Failing that, I tried removing his window to replace mine, but that too was problematic. I finally settled on removing my driver’s door and replacing it with his door. The only minor problem was that his car was blue and mine was white, so I drove for the next year a two tone car, white with a blue door. (No way was I going to pay to have my car painted to address this minor issue.) To my delight, the parking garage guards at MIT paid no attention to my new two-tone car, and so I parked in the close and prestigious faculty lot for a year. As a testament to habituation, I became more and more bold over the next year and was eventually caught by the police for parking illegally in that lot. Sheldon was ticketed because the sticker was registered to him. He read me the riot act but was secretly amused, I always thought, admiring perhaps of my chutzpa.  The second anecdote was when I – a graduate student − fired one of the technicians in Sheldon’s lab while he was out of town. I was working at the hood (fume cupboard) and jostling for space with a technician, who had admittedly been there first. I was in a rush and told her in a rude way that my work was more important. She took offense, not unreasonably, and said something like “I can’t work here any longer,” to which I responded with an even more offensive remark. She then stormed out and did not return for the rest of the day. It took an hour or two for the reality to hit me, including the fact that Sheldon was due back at MIT the next morning. I had to drive to the technician’s apartment that evening and beg forgiveness. She wouldn’t open her door for me, and it took 30 minutes of pleading and throwing pebbles against her window to get her to let me in, finally accept my apology and promise not to tell Sheldon the next morning.  A simple, polite summary of both anecdotes is that I had a difficult character. Thank goodness for the permissive, tolerant environments of Caltech and MIT. **Post-doc and Edinburgh** I had planned to go for my post-doc to the wonderful Hogness lab at Stanford, to study *Drosophila* chromosomes, and I wrote and received a Helen Hay Whitney Fellowship to do that. A few short months before leaving MIT however, I had a change of heart. It was catalyzed by meeting a couple of chromosome-nucleic acid researchers from Scotland, Mick Callan and John Bishop, both of whom spent some time in 1970–1971 in Boston. There was also my wanderlust; I thought this might be the last time I would be able to live in Europe, an opportunity I should not pass up. So I inquired about going to Callan’s lab in St. Andrews and planned to collaborate with Bishop in Edinburgh at the same time. I wrote the Whitney foundation, which gave me permission to switch. I then wrote to Hogness and honestly explained my decision, including my desire to live for a while in Europe. He wrote me back a handwritten note and was a complete gentleman about the situation. After I became a PI myself, I appreciated even more his graciousness. Not going to his lab had multiple layers of irony: Mike Young went there a few years later, and many of my colleagues and friends were trained in the Hogness lab at the same time as I would have been there, e.g., Ray White, Gerry Rubin and Michael Grunstein to name just a few.  I was not very happy in St. Andrews. It was a lovely town but a bit sleepy after Boston and MIT, culturally as well as scientifically. Callan was an excellent scientist but not very communicative; he did his own work and kept to himself. So, I transferred to the Bishop lab in Edinburgh, which was a more dynamic city and scientific environment. John’s lab was an excellent place, and I learned a lot from him as well as from my colleagues in his lab, for example Nick Hastie, Saveria Campo, and Stanley Perlman. There was the Birnstiel lab next door, which had Peter Ford as a post-doc and Adrian Bird and Michael Grunstein as students. I collaborated with Ford during my time in Edinburgh. A couple of hundred meters or so down the road was the Zoology Department with Ed Southern and his laboratory.  Edinburgh and the UK will always have a special place in my heart, and I have life-long friends from my time there, especially Michael Grunstein and his family. The Brits also have a special place in my head. Their educational system and general approach to science was not identical to the way things were done in the US. Simply put, the UK approach was more cerebral whereas Americans are more pragmatic. I would like to think my exposure to the UK way of doing science complemented my American education and natural instincts, which are almost pathologically pragmatic. **Recruitment to Brandeis** I was only about 15 months into my post-doc when Brandeis called me up and asked me to apply for a faculty position. I said it was too early and I wasn’t interested, but Harlyn Halvorson, the Director of the Rosenstiel Center at Brandeis persisted. “Just come give us a seminar.” Since my mother lived only a few miles from Brandeis, it was an opportunity to visit her too, so I left Edinburgh for a long weekend. I gave a seminar, met with faculty, and they ended up offering me the job I had said I didn’t want. It turned out that they had a blue ribbon committee to recommend people for the two molecular biologists they wanted to hire. The chair of that committee was Jim Darnell. He was the mentor of my MIT mentor Sheldon, had known me since the beginning of my Ph.D. there and had kept his eye on me.  The upshot was that Brandeis leaned over backwards to get me to accept the job. They let me stay in Edinburgh for more than 18 months to complete my post-doc. The space, set-up money and teaching conditions were generous. And then to top it off, they offered to pay me my Brandeis salary for the year before I would arrive on campus. Although this turned out to be complicated (I couldn’t keep my fellowship while keeping my salary), Brandeis supplemented my salary to bring my total compensation to match an assistant professor salary. This effectively doubled my 1973 salary, from about $10K to $20K. My post-doc salary of 10K was already extraordinarily generous by UK standards, especially with the then current dollar to pound exchange rate. To put my 1973 salary in perspective, it was considerably higher than that of my PI Bishop. Moreover, he was a Reader, the equivalent of an Associate Professor, with a mortgage and 3 children, and I was single. One important outcome of all this was that I banked the extra 10K, which was exactly the 25% down payment for the house I purchased in 1975–76 more than 40 years ago. We raised our children in that house and still live there. I therefore owe Brandeis the roof over my head in addition to the shirt off my back and a good fraction of my Nobel Prize.  There is of course more to say, but I am ending this brief biography to coincide with my arrival at Brandeis, when the Brandeis circadian rhythm story began. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0517=MR  [Michael Rosbash]: Hello  [Adam Smith]: Hello may I speak to Michael Rosbash please?  MR: You’re speaking to him.  AS: Thank you very much. My name is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize. So I suppose it’s funny in a way that a prize for working out the molecular mechanisms of the circadian rhythms is announced in a way that disrupts your own sleep cycle.  MR: Indeed. [Laughs] Ironic, yes. I hadn’t thought about that, I must confess, but absolutely, yes.  AS: How did you hear the news?  MR: The phone on the night table by my bed woke me out of a deep sleep. And the gentleman Thomas Perlmann, yes, he told me the news. And I was shocked, breathless really. Literally. My wife said, “Start breathing.”  AS: In a way this is something that everyone takes for granted, their adaptation to night and day. But it’s sort of the original adaptation to environmental influence, isn’t it?  MR: It is, it is. Before the atmosphere has its current constitution and before nutrition was anything like it is today, the earth rotated on its axis and the light dark cycle impinged on the beginnings of life, yes.  AS: And I suppose it’s hard for people to imagine how different it was 30 years ago when you were starting this work, that you were real pioneers in linking genes to behaviour.  MR: Right, it’s true, it’s true. We didn’t think of ourselves as that, you know everybody … There’s an element of craft in the work, you know, we’re putting one foot in front of the other. Trying to get more experiments to work than fail but in hindsight, yes, there’s some truth in that.  AS: And the prize is also a celebration, I suppose, of your close working relationship with Jeffrey Hall.  MR: It is, it is. Yes. Long, long, long partnership.  AS: What made you such a strong team?  MR: We were very, we had very … Two things, we were very good friends personally, before in fact we started to work together. And secondly we had complimentary skillsets.  AS: I gather he’s a bit of a maverick, riding Harley-Davidsons and the like.  MR: That sort of thing yes. And the like. Yes, that’s a good way to put it. Very British and very appropriate.  AS: Will we look forward to welcoming you to Stockholm in December?  MR: Of course you will.  AS: Great, well enjoy your day and thank you for speaking to us.  MR: Thank you very much.  AS: Thank you.  MR: Bye bye. |
| Interview |  |
| Q1 | What was the moment you decided to pursue science? |
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| Q6 | What effect did your upbringing have on you? |
|  |  |
| Q42 | Are you more of a morning person or a night owl? |
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| Q11 | Do you remember first meeting Jeffrey Hall? |
|  |  |
| Q11 | How did you and Jeffrey Hall complement one another? |
|  |  |
| Q20 | What drove you from competition to collaboration in your field? |
|  |  |
| Q41 | Can we control the biological clock, possibly prolonging human life? |
|  |  |
| Q40 | What are your tips for handling jet lag? |
|  |  |
| Q23 | Is our circadian rhythm like a sixth sense? |
|  |  |
| Q25 | Is it important to have a mentor? |
|  |  |
| Q12 | What’s your advice for young people? |
|  |  |
| Q42 | Where do you do your best thinking? |
|  |  |
| Q18 | How has your family supported your work? |
|  |  |
| Q7 | How do you spend your free time? |
|  |  |
| Q14 | What sports learnings also apply in science? |
|  |  |
| Q37 | What research are you pursuing right now? |
|  |  |
| Q17 | How has your research benefitted humankind? |
|  |  |
| ID | 0518 |
| Biographical | I remember reading this big book, *The Wonders of Life on Earth*, when I was eleven or twelve. It said bird migration was controlled by some kind of internal timer, some kind of clock. Some birds, it explained, use the position of the sun to orient their migration, and the clocks in their heads are able to track time in order to assume the same direction of flight even as the position of the sun moves throughout the day. I thought that was both mysterious and fascinating. It was my first exposure to the notion of biological clocks.  I was born in Miami, Florida on March 28, 1949, into an environment where biology was all around. The neighborhood kids spent a lot of time running around each other’s backyards together. Many of the families had greenhouses with an array of exotic plants that always interested me. We were close to tourist attractions: the Parrot Jungle, the Monkey Jungle, the Serpentarium, the Orchid Jungle. The Parrot Jungle was especially close and a lot of the birds weren’t caged, so toucans and parrots would sometimes arrive in our yard. You’d see native wildlife, too. One time, my sister, Denise, and I caught a small alligator in the creek behind our grandmother’s house. The local newspaper published a photograph. But my favorite place was the “Rockpit”. This covered an area of about 50 acres and was the source of the landfill under our elementary school, David Fairchild. The excavations left scattered hills of coral rock that we would climb to survey the ponds below. The place had plenty of reptiles and the ponds were full of tadpoles. There was a “No Trespassing” sign next to the narrow gravel road into the Rockpit that said “Violators will be Prosecuted”, which to my eight year old mind meant electrocuted.  At the local hobby shop they sold models of all sorts of things. You could build model airplanes or cars, but you could also build model biological systems, like of the brain or something called the Visible Man. These were a mix of colored and transparent plastic that came in boxes just like those for model cars and airplanes and with similar price tags. You’d get these things and put them together, and they were a pretty reasonable representation of real anatomy. The other kids, especially my sister’s friends, thought I was really weird for putting people together, taking them apart, and have them sitting on the desk. But for me, although inert representations, the models were ways I could explore biology a bit more formally, beyond just observing nature as it was around me.  I was interested in chemistry, too. I got a chemistry set at one point and set up a lab in the back room of our house. We had this beautiful terracotta tile floor. You’d do things like use potassium chlorate to generate some oxygen and hold a match to it and get it to explode. But I also would just mix and match things kind of carelessly. I never blew myself up, but I did create something that bubbled over and shot small droplets onto the floor that left lots of little white stains. After that, my parents confined my chemistry lab to the garage.  There was a kid down the street whose father worked at Porsche, and he was always bringing home these sports cars and dissecting them while the neighborhood kids watched. Mechanics interested me and we started building our own vehicles – the most typical starting point was a lawnmower engine – for running around in the neighborhood. I built a go-kart. It’s amazing that I survived that, but it taught me a lot about the way things can be put together to work. Biology and motorized machinery are obviously not equivalent, but it was useful to think about what makes something work and to see what vehicles look like on the inside.  When I was in the fourth or fifth grade, I remember putting my books together in my desk with the science book on top and thinking somehow, I’m going to do something that involves the sciences. That evolved over the next couple of years into medicine. I had no idea how you could become a scientist. That was something else completely. But if you had an interest in the sciences, then becoming a doctor seemed like a reasonable path.  No one in my family shared my interest in science, but my parents, each with a high school education, were very supportive of my interests. My father was a bomber pilot in World War II. His plane was shot down in 1944 (he crash-landed in a potato field in Holland) and he was in a prisoner-of-war camp for the rest of the war. I have a copy of a letter a woman in the mid-west sent to my grandmother, saying that she had heard my father on a short-wave radio, asking that someone contact his mother to say he was alive and ok.  My parents met when my father came home to Knoxville, Tennessee. I think because of his war experience, he was not averse to taking risks, so when they went to Miami for their honeymoon in 1946, they just decided to stay. We went to church until I was about 10, but it was a very soft touch. And I don’t remember a particular political bent to any of the discussions in our family. I think an advantage of this was that I didn’t come out of a mold with a set of ideas that I’d eventually have to undo, because I became very irreligious in high school. I was much more enchanted by what you could prove to yourself than by having to put your faith into something.  In 1966 my father’s job changed and we moved to Euless, Texas, a small town near Dallas. I went to LD Bell, the local public high school, and later to the University of Texas at Austin, where the tuition was $50 a semester, still expecting to study medicine eventually. Having grown up in the Great Depression, my father was always concerned that I needed to work at developing a career, by which he meant something tangible, a well-established profession. Medical doctor was something he understood.  But my path quickly took a lasting turn, first with my father’s sudden death (he had a heart attack on a business trip during my first year of college) and then when I took a course in genetics with Burke Judd in my senior year. Burke was very contemporary in the way he thought about genetics – his course looked ahead to the questions on the horizon – and I went to speak with him on several occasions because I really liked the class. I learned from him that I could sign up to do a summer research project in his lab and see how I liked research. I hadn’t even known that this kind of thing was possible. That’s when I first began to realize how you could train to be a scientist.  It’s also how I ended up with my first mentor. Until then, the notion of having an advisor was foreign to me. Neither of my parents had gone to college, so although I took a lot of interesting courses, I didn’t have a way of thinking about how to make decisions about the future. Burke’s support and positive feedback very early on were very important in showing me this whole new world.  And I met my wife, Laurel Eckhardt, in Burke’s course. I had tried to introduce myself to her, but she paid no attention to me at all. Later, when we met again in Burke’s office I guess she realized maybe I was legitimate. I later learned that Burke and his course had also introduced her to the idea of a scientific research career. Like me, she was clueless about where scientific discoveries were made.  So I did spend that summer in the lab and it was a great time. The lab was a classical genetics lab and was focused on cytogenetics, that is, looking at chromosomes. There were two postdocs in the lab, Lenny Robbins and Ron Woodruff, who took me under their wings and seemed to think that I was serious enough to invest some time in. Lenny, especially, helped me learn more about biology, particularly molecular biology.  This was the early 1970s, and everybody was thinking about the new molecular biology. Burke’s lab was very interested in understanding the genetic complexity of eukaryotes using *Drosophila*, the fruit fly, as a model. Fruit flies have these enormous chromosomes in their salivary glands and it’s very easy to tell one chromosome from the other and even to tell specific regions apart. They have these striations that were thought at the time to be visible markings of the genes. You could count off the striations and you were just counting genes. But the tools were still too dull to go much further, to bring that down to a real understanding of the organization of these genes or other information in the chromosomes.  That summer, my project was to use genetic screens to look for sterile mutations in the X chromosome region on which Burke’s lab was focusing. But I could do other things. If I wanted to use the microscope to look at my own chromosome preparations, I could do that. It was like stepping all the way back to my chemistry and biology sets, but here was a real laboratory at my disposal. I’d spend hours talking with the postdocs in the lab and those in adjoining laboratories, just dreaming up experiments that we might want to do. I began pushing to introduce molecular biology into Burke’s lab so we could do some of the experiments that might get us to a better understanding of how eukaryotic genes and chromosomes are put together. By the end of the summer of 1971, I had made a career choice – to pursue genetics – and I had decided to stay on as a graduate student in Burke’s lab.  The lab was focused on a short part of the X chromosome and how many genes there were in that region, which included enough DNA to include about 400–500 genes the size of those in a bacterium like E. coli. The first sweep through had given us something like twenty genes, so what’s all the rest of that DNA doing? If knocking a gene out resulted in lethality, you wouldn’t miss that gene. But how do you know what you’ve missed? We knew that knocking some genes out led to a much more subtle phenotype, so that was a real question.  I was in the process of mapping mutations I had found that affected female fertility when Burke came in waving around a paper from Ron Konopka and Seymour Benzer, published in *Proceedings of the National Academy of Sciences (PNAS)* in September 1971, describing *Drosophila* circadian clock mutants that they had discovered. The gene they had found, which they named *period*, was in an area that seemed to be within, or very close to, the region we were studying in Burke’s lab. I thought these were pretty interesting mutations: in addition to their relevance to the general question Burke’s lab had about how many genes there were in the region, they affected wake-sleep behavior, a behavior with very solid properties.  So, I wrote to Ron and Seymour to ask for the mutations. One of the things about the *Drosophila* community is the unspoken agreement that if you discover something, once you publish it, you should give any mutations, any materials that you’ve produced, freely to anyone who asks for them. Ron sent the mutants right away.  I did experiments that proved that *period* was, in fact, a new gene and that it lived between two genes we already knew about. Missing *period* raised big questions about how we were counting genes, but there was only so far anyone could push with the tools we had. We needed to be able to really look at a gene, to actually have the DNA corresponding to a gene and map the mutations affecting that gene so we could understand how those mutations affected the gene’s activity and/or the gene’s protein product.  We weren’t in a position to do that work yet, but it was thinking ahead – where will this field be in five or ten years – that was exciting to me. That’s what you want to be thinking about, those are the questions you want to have in mind.  While I was working on locating *period*, I found two deficiencies that seemed to overlap, each of which eliminated the *period* gene and appeared to be missing only the *period* gene. That was a lucky find. But an even luckier find was a translocation – an inter-chromosomal exchange – that occurred right in the *period* gene, knocking out some of the gene’s activity. Because deleting *period* eliminated circadian rhythmicity without producing any other visible consequences, I began to think *period* was central to whatever larger process was involved in biological timekeeping. It could be a mainspring or a gear, by analogy, to a mechanical clock.  The question of the relationship between genes and behavior was completely unresolved at the time, and I saw that *Drosophila’s* clock and the *period* gene would be in many ways an ideal starting point to study that relationship. I saw that a periodic, quantifiable behavior like the circadian wake-sleep cycle would be a great starting point to begin digging into the genetic mechanisms that make a behavior work.  As I was finishing my graduate work in 1975 and thinking about where to do my postdoc, I learned from Burke that David Hogness at Stanford was going to use *Drosophila* to isolate pieces of cloned DNA and study single genes from all over the genome, in detail, at the molecular level. I realized that if I ever wanted to come back to the circadian problem, the translocation I had found would be a very powerful entry point to find the *period* gene within cloned DNA. But no matter what my questions were going to be, I knew I was going to have unsatisfying answers without the ability to isolate a gene and map mutations along that gene. With that, you could define everything: phenotype and genotype, chromosomes and DNA. This was only going on at Stanford and only in Dave’s lab. The big questions, as far as I was concerned, could only be answered by going there. Dave was a little bit like Benzer in the sense that he wanted to ask new questions and set off on a new frontier that presented risks, but also opportunities for some real excitement. I thought his taste in problems was fantastic.  Laurel was ready for graduate school at the same time that I was ready to begin my postdoc. She had been accepted into a Ph.D. program at Stanford and was looking forward to studying with Len Herzenberg in the Genetics Department. This meant I would be right around the corner from her in the Biochemistry Department. We packed up her car and a U-Haul truck and drove to California. We remember coming into San Francisco at night and all of a sudden seeing these lights up on the hills. We both thought it is like going to Mars or something. It was so different from anyplace we’d been before.  The big breakthrough that had happened at Stanford was the development of a method for cloning DNA – what we call recombinant DNA – in order to isolate large amounts of a single gene, or even a single segment of a gene. They had protocols for assembling these DNAs, for propagating them in bacteria or viruses, and for making maps of these isolated DNAs once they were present. And all of these things were very new at the time. Dave’s project was really the first genome project, although it wasn’t called that. It was an attempt to use *Drosophila* to fully define what the flies’ chromosomes carried. There was a chromosome map outside Dave’s office with tacks pressed into place everywhere a cloned piece of DNA had been located. Eventually these landmark DNAs would begin connecting with their neighbors. We all were enchanted by the tools and by the possibilities they represented. My first project was to isolate breaks in the DNA, using a method that I’d come up with at Texas, so I would have the complete picture of what a gene was doing and what phenotypes it was affecting.  I never lost my love for the outdoors and got pretty deeply invested in technical rock-climbing with a group of biologists at Stanford. We used to set up our experiments on a Friday night, knowing that they would have to incubate through the weekend, and we’d then take off for Yosemite with ropes and pitons and carabiners and all this equipment to climb rocks. We’d talk about work when we were out together, things that we wanted to find out, but there also was this excitement and terror of being on a big rock face. While I don’t climb rocks anymore, I remember those times as great fun that rounded out our experience in California.  When it came time to look for a faculty position, Laurel and I realized that I had to go to a metropolitan area with more than one academic institution, so she would not be limited when looking for post-doctoral positions once she finished her Ph.D. We settled pretty quickly on Rockefeller. It had tremendous advantages and was just very different from all the other institutions I had considered. I remember my first visit and talking with Norton Zinder. He was in Smith Hall – where I would soon have my first lab next to his. It was a dusty, dark, cavernous building, but there was a charm to the classical laboratories because of the deep history they held.  When I came to Rockefeller in 1978, I had a series of things I thought I could accomplish in five or six years. I was still asking, what’s odd or interesting and new about a gene from a multicellular animal? My thought was to isolate one or more genes from a genetically well-defined region and to see if we could hammer at them at the genetic and the physical levels to bring the functional and physical maps together and produce a complete picture of a piece of a chromosome. We had the new technology, recombinant DNA. We had libraries of cloned DNAs. That should mean that every gene in the fly was somewhere in that library; it was just a matter of fishing the right ones out.  And pretty quickly, we isolated two genes – *period* and *Notch*, a developmental gene – that we worked on in parallel for several years.  With *period*, the goal was to try to understand why or how it was making a contribution to behavior, to the flies’ sleep-wake rhythm. Laboratories had been studying circadian biology for decades, but they were really just guessing, hypothesizing, about what the underlying mechanisms might be.  But what *Drosophila* had were mutations in these genes, like those that Ron Konopka and Seymour Benzer had found, that suggested you didn’t have to rely on hypotheses and you didn’t have to guess about the basis for the biology. You could use the fly and find out answers. You could create mutants that have an interesting change in behavior and then ask what the underlying gene looked like. By exploring the genes that were critical to behavior, you could go in without the baggage of a model. You could simply let the fly and its genetics tell you what path to take. Before molecular approaches were in place, naming the *period* gene and having mutations that could be mapped by classical genetics to a given location on a chromosome provided no clear path for learning more about circadian biology.  So, we thought we had a great problem to work on and that we could attack it on our own. Initially, it was just a postdoc, Ted Bargiello, and I who started a “chromosomal walk” to get to the *period* gene. From my graduate school days in Texas, I had the translocation that broke the gene and told us where in this chromosomal walk it could be found. So, we were able to take a series of cloned DNAs to make a map, to put them together, and then to see where this break was. Then we asked which parts of the chromosomal walk were transcribed to make an RNA. When we discovered an RNA that was broken by this translocation, we knew this must be the *period* gene.  It was an interesting and stressful time because we started this work in the early 1980s without knowing anyone else was interested enough to invest time and energy in it. Ron and Seymour’s paper was not heavily cited. But as we were somewhere approaching this level of analysis, we learned that Jeff Hall and Michael Rosbash were on a similar mission to try to isolate the *period* gene and that they also had made some pretty good progress.  When we finished the first round of work, we had very good genetic and molecular evidence that we had found a single transcription unit that was *period*. We didn’t know any more about it. We didn’t have a gene sequence, but we could say that it was about 7,000 base pairs long. We published that in *PNAS* in April of 1984. It was the first publication to come out on the isolation of *period*, and the first molecular study to address circadian rhythms in any organism.  The next step, we realized, was to see if we could confirm that everything was limited to that one transcription unit. We needed a device that could record the sleep-wake activity of individual flies, so the in-house shop at Rockefeller made it for us. It was a combination of old microscope slide boxes, some sheet metal, and some primitive electronics. We generated DNA composed of just the wild type version of our transcription unit and we microinjected it back into embryos that were *period* null mutants, that is, they were arrhythmic. Then we put the flies in the machine, five flies at a time. The event recorder wiggled when a fly moved up or down. Ted, Rob Jackson (another postdoc who had joined the lab), and I camped out most of the time in the lab just to see what would happen. A few feet of chart paper would come out every day and after a few days, we could see that putting the transgene back into the null mutants had restored the flies’ rhythms!  That was exciting because it confirmed that we had the gene. It also had another level of import because this was the first time anyone had transplanted a gene to generate behavior. We had a simple animal and an easily measured, ubiquitous behavior that was well-understood but only at the level of phenomenology. The fly went from having none of that behavior to having the full range of that behavior just because this one gene was put back into it.  We published the report, which confirmed that the gene was the only thing that was necessary to restore the behavior, in the 1984 year-end issue of *Nature*. Hall and Rosbash published in 1984, too, and we could all see that *period* was the gene to move in on. A couple of years later we reported the sequence of the gene and the changes associated with Konopka and Benzer’s long-period, short-period and arrhythmic mutations. All three were single nucleotide changes, and the two that adjusted period length each changed a single amino acid.  Because we had competition, we thought carefully about how we might carry the project in a new direction, and give ourselves more room to operate independently. We wanted to avoid having two groups just doing the same things. And that’s when we decided to initiate a big screening effort to find additional genes involved in the clock. We thought we could learn more about the sleep-wake rhythm by looking for other genes that affected it. Meanwhile, Hall and Rosbash continued to work exclusively on the molecular biology of *period*. And I think both plans worked well because it kept us from making duplicative discoveries.  Initially our genetic screen went on and on without giving us anything meaningful, until finally, in the early 1990s, after seven thousand assays, two postdocs in the lab, Amita Sehgal and Jeff Price, found a new mutation. We named the gene *timeless*, and it had many of the same behavioral properties as *period*. Most importantly, in 1995 we discovered it encoded a protein that was a physical partner for the Period protein.  What excited us most is that we’d taken an agnostic approach to how circadian rhythms worked. We weren’t asking for genes that work with *period*. We weren’t saying let’s collect the things with which *period* interacts. We just said let’s find another gene that affects circadian rhythms. Incredibly, that took us to another piece of the same molecular system that depended on *period*. This was our first hint that there would be a single mechanism for keeping time in the fly.  Isolating *timeless* and unpacking its relationship to *period* made us realize that following the genetics could perhaps take us to the heart of what was controlling circadian rhythms. It was a huge boost – and it convinced us that we should keep screening and get every mutation in every gene that we could to see if we could repeat our success. Would every new gene that we isolated point us back to the same system, to a single machine responsible for circadian biology? In fact, it did, and that was extremely gratifying.  When we found *timeless*, Jeff and Michael immediately saw the benefits of driving genetics of the fly forward – that is, searching for all genes relevant to the clock system – as rapidly as possible. Our labs began a joint screen for new mutants that was supported by the National Science Foundation. With any luck at all, we thought, there would be several new genes to work on and no one group could handle all of them. It would be more productive to have complementary assessments of different genes going on in our labs.  What we now understand is that all of the genes our labs ultimately found participate in the same mechanism: there are nine or ten key components that interact with one another to produce an oscillating molecular system that has a natural cycle time of about 24 hours. All of this was revealed by genetics. It wasn’t by anyone coming up with ideas to test; it was by admitting that we didn’t have the foggiest idea how the clock worked. We sought to collect all the mutations that are important to circadian rhythms and to understand them one by one, and then we looked at their relationships to each other. This is a story not of a single big discovery, but of the accumulation of smaller discoveries over many years that together enabled us to see the underlying biology of how cells track time.  We now know that the same clock system that applies to the fruit fly applies all the way to humans. We have also learned, by following gene expression, that flies and humans are a collection of clocks. We did not expect in the beginning that we would have cells outside the nervous system that use these clocks. And we didn’t anticipate the degree to which cells in different organs find it useful to independently determine the time of day. In retrospect, it makes sense, for example, that liver cells are regulated with a 24-hour periodicity that is synchronized with feeding times, and that tissue-autonomous clocks are involved in that regulation. There is some coordination of what happens in different organs, but it is beginning to look like there is as much signaling among organs as there is between the brain and these systems. You can produce an animal that has its head set on New York time and its liver set on Tokyo time, thereby revealing a really surprising degree of autonomy between clock systems in the body.  I came to Rockefeller with a five-year plan and am still here after 40 years. I don’t think there’s any place in the world that would have provided me with the way forward on this adventure in the way that Rockefeller did. It’s such an unusual community and the unwavering interest and encouragement from colleagues early on – particularly Norton Zinder, Jim Darnell, [Torsten Wiesel](https://www.nobelprize.org/prizes/medicine/1981/wiesel/facts/), and [Günter Blobel](https://www.nobelprize.org/prizes/medicine/1999/blobel/facts/) (who to my great sadness died as I was writing this) – made all the difference.  In 1998 Seymour Benzer wrote me – I have saved the letter in my copy of Jonathan Weiner’s biography of him – to congratulate me on our progress. He was thrilled, he said, to see how the work on the clock was going. Seymour had pioneered the notion that you could study genetics connected to behavior, but he met with a lot of resistance. When he started his work, many people just didn’t believe that working on single genes would reveal important things about behavior. And the work couldn’t move very rapidly before the molecular tools became available. It has been incredibly gratifying to bring molecular biology to this field and to prove, with Michael and Jeff, that a gene-based approach could solve a deep problem about behavior and reveal this beautiful circadian mechanism.  For the past several years, research in my lab has focused on both *Drosophila* and humans. The *Drosophila* work now centers on the related problem of sleep: what controls its duration and how is that driven by genes? We know sleep is fundamentally important – when we collect mutants that get 60 percent of the sleep of a typical wild-type fly, their lifespan is cut in half – yet we still don’t know what sleep is actually for, how it is regulated, or what it accomplishes. I think we can use *Drosophila* genetics to get at these questions in as meaningful a way as we did with the circadian work.  On the human side, we think that most clinically significant circadian disorders are probably represented in the very large genetic databases that are available now. The challenge is to figure out which genetic variations are important and why.  Sleep, as I see it, has as much mystery to it as circadian biology once had – and deep progress is still ahead. And so we have a very fundamental set of questions on the *Drosophila* side and a more medically oriented set of questions now on the human side, and I think that’s a nice mix at this point in the lab’s history.  \* \* \*  Life isn’t all research, of course. Laurel, who is a biology professor at Hunter College, The City University of New York and I have been navigating family life and our careers together for a lucky, long time. We had two daughters in the 1980s: Natalie in 1986 and Arissa in 1989. Today, Natalie has a Ph.D. in sociology and Arissa is a medical resident. We built a house in New Mexico, where we retreat to hike, write papers, and explore the natural mysteries that have intrigued us from the beginning. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0518=MW  [Michael W. Young]: Hello  [Adam Smith]: Good morning, my name’s Adam Smith calling from Nobelprize.org. Congratulations on the award of the …  MW: Well thanks, thanks. We’ve got multiple phones in the room running here, my wife’s going to get the other one.  AS: [Laughs] Yes you’re going to be bombarded from this point on.  MW: Yes, this is crazy, I’m … I just told somebody I’m not quite sure how I’m going to get through the day. [Laughs] I need to, I need to replicate myself.  AS: [Laughs] But it all must seem a little unreal having not actually heard from the committee, so you’re hearing it second hand so to speak.  MY: I don’t know. Somehow, somehow, it’s just all spinning around in my head that this has happened. You know about these things and you can see possibilities on the horizon but you never really … Has this really happened?! [Laughs.] I’m still at that stage.  AS: It’s hard to remember how things were 30 years ago and nowadays the idea of linking genes with behaviour is sort of, people expect that. But then it was a very pioneering thing to do.  MY: Oh yeah. I mean this was … You know, I had gone to Stanford to learn how to use this technology, it was brand new in the 70s. And starting up my lab at Rockefeller I had worked a little bit on this problem, circadian rhythms, thanks to these tremendous mutants that Seymour Benzer and his student Ron Konopka had found. And I just thought it was a terrific problem and maybe the toughest thing I could try to tackle because it was behaviour; you know, what could we learn about a fairly complicated behaviour that we all exhibit, which was most easily represented by sleep wake cycles. And frankly I thought we might find out maybe a little bit. I never thought we would really understand what the motor behind this was, at the time. We were very lucky, we managed to find genes that fit together like puzzle pieces to explain how this thing worked. And the techniques and the approaches kept changing and I kept … I was very lucky I kept getting students and post docs that were extremely good and just did everything right. And the other piece of this was, you know, there was sort of a race going on in the early years. My colleagues Jeff Hall and Michael Rosbash and we kind of pushed each other along because … I mean most of it was independently done but we did have to collaborate from time to time, but we worked on slightly different problems but the solutions to those problems all, as I was saying, fit together like puzzle pieces, that kind of bring the picture into view. It was, it’s been really quite satisfying. This really pushes it way, way, over the top. It’s really quite incredible. And I couldn’t … yeah, this is terribly exciting as you can imagine.  AS: You do sound wonderfully amazed, it’s very nice to hear.  MY: Oh I am, I’m just. I’m just, like I think I said I’m just wondering how I’m going to get through the day.  AS: Will we be seeing you in Stockholm in December?  MY: Oh, of course. Are you kidding? [Laughs] I’ll be there, I’ll be there. |
| Interview |  |
| Q1 | What is the origin of your passion in science? |
|  |  |
| Q2 | What sparked your interest in circadian rhythm? |
|  |  |
| Q41 | Are you a night owl or an early bird? |
|  |  |
| Q40 | What are your tips for dealing with jet lag? |
|  |  |
| Q20 | Share your thoughts on competition and collaboration in science. |
|  |  |
| Q41 | Can we control the biological clock? |
|  |  |
| Q41 | Can we increase life span by controlling the biological clock? |
|  |  |
| Q41 | Do you manipulate your own biological clock? |
|  |  |
| Q23 | Can the circadian rhythm be considered a sixth sense? |
|  |  |
| Q22 | What do you enjoy about science? How do you keep your curiosity alive? |
|  |  |
| Q12 | What advice would you give to a younger version of yourself? |
|  |  |
| ID | 0519 |
| Biographical | **1. Early life and influences** I was born in 1945 in Fukuoka, half a year before the end of the World War II, to my father Yoshio and mother Shina. My father was employed at Kyushu University as a professor of mining engineering. At that time, everyone in Japan was equally poor, and even food was not readily available. I was a weak child who continually fell ill, a condition that was perhaps exaggerated by the malnourishment of the era. My mother, after giving birth to me, contracted tuberculosis and spent a long time battling the disease in bed. I can still remember the sight of her in plaster after developing spine caries. Thankfully, a friend of my parents in Hawaii sent just-developed antibiotics which allowed my mother to recover. Words such as streptomycin and aureomycin stuck in my mind as a child, although I didn’t fully understand their meaning. When I was about 8 years old, my mother was finally able to resume a normal life. My brother, Kazuo, who is 12 years my senior, entered the Faculty of Literature at the University of Tokyo as I began elementary school. I was brought up through the efforts of my father, my two sisters Reiko and Junko and many other people who assisted through a difficult period for our family. If I had met a wonderful doctor at such a time, I might have chosen a medical education. However, I had a dream to become a scientist that was fuelled by the expectations of my parents.  I was brought up in a house surrounded by nature, with paddies, streams, hills and the sea all nearby. My youngest years were spent outdoors, catching fish and picking plants. During elementary school, I became interested in insect collecting and spent much time searching for unusual specimens. I also loved to look up at the arching night sky and remembered the names of stars and constellations. But without anyone around to foster these interests, they were left behind as childhood hobbies rather than lifelong passions. Every time my brother returned home from Tokyo during university holidays, he would bring a book, including thoughtfully chosen scientific books that broadened my awareness of the world beyond what we were taught at school. Being a weak child, I had no talent for sports and was neither artistic nor gifted in literature. But I managed to achieve good results at school.  During my high school years, I was a member of the chemistry club, where we would mix chemicals and enjoy watching the reactions between them. I distinctly remember the beauty of the Liesegang phenomenon in agar, but having no idea how to analyse it. I hoped to become a chemist and entered the University of Tokyo. However, the chemistry classes did not rouse my interest and I went through an uncertain period during which I agonised over my future. Thankfully, at that time the exciting field of molecular biology was just being established, and I decided to major in it. As a graduate student, I joined the laboratory of Kazutomo Imahori, who was one of the few scientists running a molecular biology laboratory in Japan at the time. Imahori’s special field was physicochemistry to assess interactions between proteins and nucleic acids. Under the direction of Akio Maeda, I began to study the role of ribosome subunits in protein synthesis. Although I was unable to produce particularly interesting results, my time in the Imahori lab was exciting as we participated in the work of a rapidly developing field and I got my first taste of the joy of experimental work. The experience also provided me with a strong sense of the continuous nature of protein synthesis within cells.  The period when I was a graduate student was characterised by large student protests, and Tokyo University was right in the middle of the social debate and change of the period. I wasn’t able to completely focus on my lab work as I participated in the discussions and demonstrations. However, I believe that I gained a sense that we must be aware of social developments and the direction of society during this time.  From the second year of my doctoral studies, I decided to move to Kyoto University, where Maeda had joined the just-founded Department of Biophysics as an associate professor. Kyoto University provided a very free environment, and I was stimulated by talented new students and friends in biochemistry lab in the Department of Chemistry. In my research, I became interested in colicin E3, which is able to pass through the membrane of bacterial cells and instantly inhibits protein synthesis. I think I was also influenced by my growing interest in biological membranes during this period.  One year later, in 1971, I married Mariko Nakazawa, who joined Imahori’s laboratory two years after me. The year we spent in Kyoto after we got married was very memorable for me. However, Mariko unexpectedly became pregnant, and she therefore returned to Tokyo after less than a year. In order to support our new family, she successfully applied to the newly formed Mitsubishi Life Science Institute. I also returned to Tokyo to follow Imahori, who had moved to the Faculty of Agriculture at the University of Tokyo, and I barely managed to finish a thesis to graduate with my PhD.  At the time, it was not easy to get a good academic position. Imahori advised me that the field of cell biology was just taking off and suggested that I work in the laboratory of G. M. Edelman at The Rockefeller University. At the time, Ichiro Yahara, a senior student of Imahori’s, was playing an active part there, so I was immediately offered a position. It was my first time leaving Japan and was also a very different field to my previous work, so I felt very uncertain. Mariko decided to leave the Institute and joined me in New York. Fortunately, Mariko soon was able to find a research position at the same university, in the laboratory of Norton Zinder.  Initially I was to study mitogenesis in lymphocytes, but Edelman decided to shift the focus of the lab to mouse development, so I became involved in setting up an in vitro mouse fertilisation system. I had only ever handled *Escherichia coli*, so I would agonise daily over how to capture the process of early development with only a small number of eggs. Before long, Mike Jazwinski transferred to our laboratory from [Arthur Kornberg](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1959/kornberg-facts.html)‘s lab. Taking inspiration from the elegant uncovering of the *cdc* mutants by Hartwell, a project began to uncover the mechanism of DNA replication initiation in yeast, which I joined. We had first planned to use isolated nuclei in this project using density-gradient centrifugation, but it proved difficult to obtain undamaged nuclei. I noticed a white layer at the top of the tube, and when I looked at this layer under the microscope out of mere curiosity I realised that we were also isolating highly purified vacuoles. This left a strong impression on me and was one of those serendipitous steps that led me to where I am today.  In the autumn of 1977 Yasuhiro Anraku, a professor at Tokyo University’s Faculty of Science, asked me to return to Japan as an assistant professor in his laboratory, and while I’d just started our work on yeast DNA replication initiation, I decided to hurry back to Japan. In December 1977, I brought my soon to be 6-year-old son back to Japan, while Mariko stayed for several months longer with our recently born second son in New York to finish her work in Zinder’s laboratory.  Anraku’s laboratory was renowned for its work on transporters and the respiratory mechanism in *E. coli*, but Anraku allowed me to start a project on yeast. Looking back, I really appreciate Anraku’s decisiveness in affording me this opportunity. I eventually decided to study not the plasma membrane but rather the membrane of the vacuole, a cellular organelle. At the time, the vacuole was thought of as little more than a garbage dump of the cell, and there were few scientists interested in it, but my position in the Department of Botany as well as location next to Masashi Tazawa’s laboratory went some way in convincing me that the vacuole was an underappreciated, fascinating organelle. I’m sure that many yeast researchers thought it a strange choice for a project.  Soon I had developed a procedure for the isolation of vacuole membrane vesicles from highly purified vacuoles. Although the vacuole makes up approximately one quarter of the volume of the cell, I could only obtain a surprisingly small amount of vacuolar membrane, but was able to demonstrate the active transport of amino acids and calcium over the vacuolar membrane. In addition, we were the first to show the novel proton pump V-type ATPase, which gives the driving force for vacuolar transport, works that were the fruit of collaboration with the late Yoshimi Kakinuma and Etsuko Uchida. Following this, structural and functional studies of V-type ATPase became an active area of research that continues to this day. **2. Moving to Komaba and discovering autophagy** Following this decade of work on the vacuolar membrane, I was offered a place at the University of Tokyo’s College of Arts and Sciences (Komaba Campus) as an associate professor and started my own laboratory – consisting of only myself. My lab was very modestly equipped, with just a shaker, incubator, spectrophotometer, basic light microscope and a few other instruments. I realised that this was a really rare opportunity to start an entirely new subject, and at our first departmental meeting announced that I would examine the lytic function of the vacuole. However, I didn’t have any meticulously crafted strategy for how I could study this question. Since the vacuole is an acidic compartment that contains a range of lytic enzymes, I hypothesised that this organelle would play a similar role to the mammalian lysosome. The segregation of the potentially hazardous degradation process within a membrane compartment makes biological sense, but I knew at the time that if this were true material destined for degradation would have to be delivered across the vacuolar membrane, suggesting that it would require a cell biological approach and not be easy to tackle. My work on protein degradation originates from this research on the vacuole; I was 43 years old.  The lysosome was discovered by [Christian de Duve](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1974/duve-facts.html) in 1955, and soon after researchers at The Rockefeller University observed the delivery of both extracellular materials and cytoplasmic materials to the lysosome by electron microscopy. De Duve coined the term autophagy to describe the latter process, from the Greek for ‘self-eating’. Although some, most notably Glenn Mortimore and Per Seglen, had conducted intricate analyses of the regulation and complex membrane dynamics of autophagy, there were many more questions than answers when I joined the field. The complexity of lysosome and membrane dynamics in mammalian cells prevented the uncovering of the autophagy mechanism. De Duve’s lab was actually in the same building as Edelman’s, and while I had friends from his lab, I never had the chance to meet with this great scientist at The Rockefeller University.  Light microscopes today, including the development of fluorescence microscopy, are advanced instruments, but at that time the power of light microscopy was limited and little information about the intracellular events could be obtained, especially for the tiny yeast cell. However, the yeast vacuole could be clearly observed under phase contrast optics. The inside of the vacuole is somewhat like a salt solution with a very low protein concentration, so I knew that it would be easy to detect structures within the vacuole due to the difference in refractive index. As I would observe the vacuole every day at the microscope, I think I probably spent longer watching yeast cells than anyone else during these years!  First of all, I searched for a condition where yeast would break down their own proteins and settled on sporulation as the best candidate. This dramatic change, from vegetatively growing cell to four spores via meiosis, is induced by the environmental depletion of nitrogen. As nitrogen is key ingredient of protein, I reasoned that the protein synthesis required for such drastic cellular remodelling must depend on the turnover of the cell’s own proteins. I therefore closely observed the morphology of the vacuole during sporulation, but wasn’t able to observe any obvious changes.  One day, I conceived that if I were to use a cell lacking vacuolar proteases, structures delivered to the vacuole for degradation would remain in this organelle and might be visible. Fortunately, Elizabeth Jones had already constructed strains lacking vacuolar proteases and, in an example of the sharing ethos of the yeast community, had deposited them into the Yeast Genetic Stock Center at UC Berkeley, so I immediately requested that they be sent to my laboratory. When they arrived, I subjected them to nitrogen starvation and examined them under the microscope. I observed small, spherical structures moving vigorously within the vacuole. These structures appeared within 30 minutes of the onset of nitrogen starvation and had completely filled the vacuole within a few hours. In the otherwise tranquil yeast cell, this dramatic phenotype really struck me, and I distinctly remember staring down the microscope for hours, unable to tear my gaze away. These structures are immediately degraded in wild-type cells, which is why they had never been properly documented. I was fortunate for two reasons: first, the structures inside the vacuole, which we now call autophagic bodies, were big enough to see under the microscope; and second, the intense movement of autophagic bodies by Brownian motion made their accumulation in the vacuole easy to notice, even with a basic light microscope. The observation of this phenomenon determined the course of the rest of my career.  I decided to immediately determine what causes this phenomenon by electron microscopy and enlisted the help of Misuzu Baba and Masako Osumi. The images they captured were overwhelmingly beautiful and provided unequivocal evidence of the membranous phenomena characteristic of autophagy in yeast. These images showed that autophagic bodies contain the same density of ribosomes as the cytoplasm as well as various cytoplasmic structures and organelles, suggesting that autophagy is a non-selective degradative process. These experiments provided us with our current understanding of the membrane dynamics associated with autophagy. Although the vacuole is vastly larger than the mammalian lysosome, the entire process that we observed was topologically the same as macroautophagy in mammalian cells, confirming that yeast could be used as a model organism in the study of autophagy.  The most attractive feature of yeast as a model organism is its genetic tractability, lending it great power in the unpicking of complex biological phenomena. Two important examples that strongly influenced me were Lee Hartwell’s identification of the *cdc* mutants and their function in the cell cycle, and Randy Schekman’s isolation of the *sec* mutants and their role in membrane trafficking.  As we knew nothing of the genes and proteins that are involved in the autophagy, the first step was therefore to isolate autophagy-defective mutants. But the only means we had of monitoring autophagy was to observe autophagic body accumulation in the vacuole. My first Master’s degree student, Miki Tsukada, was central at this stage of our work. She took thousands of mutagenised cells, individually subjected them to starvation and then checked for mutants lacking autophagic bodies in the vacuole. This approach led us to identify the first autophagy mutant strain, which we called *apg1*. A failure to induce protein degradation in this strain convinced us that autophagic bodies are indeed responsible for degradation during starvation. As expected, we also found that the homozygous diploid mutant was unable to sporulate. However, under nutrient rich conditions no difference was observed between the *apg1* strain and wild-type cells, and there appeared to be no obvious defect in vacuolar function or secretion.  Soon we found that in comparison to their wild-type counterparts, *apg1* cells rapidly lose viability during nitrogen starvation. Assuming that this phenotype was caused by a defect in autophagy, we next conducted a preliminary screen assessing viability. By isolating strains in which viability was reduced and then examining these strains for morphological defects in autophagy, we were able to identify roughly 100 autophagy-defective strains in a single screen. Further genetic analysis showed that 14 complementation groups were among these strains. Looking from our current understanding of autophagy, it’s clear that this screen was extremely effective. We initially predicted that these mutants would be characterised by defects at various stages of the autophagy process, but surprisingly all were essential for the formation of the autophagosome, the most important step in autophagy.  Next, we set out to clone and identify the genes implicated in the mutant phenotypes observed in the screen. Tsukada first succeeded in the cloning of the *APG1* gene, through which we learned that this gene encodes a protein kinase. However, we also found that the remaining genes encoded uncharacterised proteins essential for autophagy, but not required for growth under rich conditions. Therefore, we were unable to deduce anything about their function and went through a difficult period where we were unable to publish our exciting findings. Although we made rapid progress, autophagy genes had somehow escaped the attention of other researchers in spite of the comprehensive genetic analyses of yeast all around the world. I suspect that this is because researchers were interested in essential genes, conventionally defined by inviability in nutrient rich medium. At this time, Takeshi Noda also developed a quantitative assay of autophagic activity, the still widely-used Pho8Li60 assay. These developments together laid the foundations for our subsequent studies on the molecular mechanism of autophagy.  This is how my career in autophagy research began in that small laboratory at the University of Tokyo. The whole process, from uncovering autophagy to beginning the characterisation of the Atg genes, was achieved within eight years in Komaba. **NIBB** The next phase began in 1996, when I was chosen as a professor at the National Institute for Basic Biology (NIBB) in Okazaki. This facility provided an environment very supportive of basic biology, and I selected three researchers to join our team: Tamotsu Yoshimori, originally of Kansai Medical School, who would work to incorporate our findings in yeast into mammalian cells; Takeshi Noda, who was the first doctoral student to graduate from our lab at Komaba; and Yoshiaki Kamada, who had studied at Johns Hopkins University in the US. The following year, Noboru Mizushima, previously a clinician at Tokyo Medical and Dental University, also joined the laboratory as a JSPS postdoctoral researcher and later as an assistant professor. From this point, graduate students and postdocs from all over Japan joined our lab and we entered the most fruitful age of our research. At the NIBB, we were able to produce a truly unique research environment where we extended our work to include mammalian cells and plant cells, which was important in the development of the field. Most members of our laboratory lived near the NIBB, and as both Yoshimori and I were working away from home during this period we would often work late into the night, discussing science over a beer.  I was expecting that it would take a long time to isolate all the genes required for autophagy, but thanks to our collaboration with my wife Mariko’s laboratory, which helped with cloning at the Teikyo University of Science, as well as the sequencing of the entire yeast genome in 1996, we were able to elucidate the genetic context of nearly all the *APG* genes in a relatively short period.  After that, we undertook to identify interacting proteins of the characterised Apg proteins, and were able to confidently identify all 18 of the genes essential for autophagy under nitrogen starvation conditions. A group led by Michael Thumm was studying the reduction of protein levels using antibodies under starvation conditions and was close behind our group, naming genes they identified using the ‘*aut*‘ alias. Meanwhile, Dan Klionsky’s group was investigating the delivery of aminopeptidase Ape1 by cytosol to vacuole targeting, now known as the Cvt pathway, identifying genes using the ‘*cvt*‘ alias. This pathway is in fact a biosynthetic pathway responsible for the maturation of Ape1. Through the collaboration of our groups, we determined that this was occurring through similar membranous phenomena that depend on the core autophagic machinery and very selectively isolate Ape1 for delivery to the vacuole. Klionsky’s group thus uncovered the Cvt pathway, which served as an important model of what was to become the major field of selective autophagy.  With the continued isolation of autophagy-defective mutant strains in yeast by many groups, we collectively decided to unify gene names under the *ATG* alias to simplify nomenclature in the field. As the majority of the key autophagyrelated genes were identified by our group, the gene numbers used by our group when assigning *APG* gene names was retained in this system. With the identification of further autophagy-related genes, most of which are involved in selective autophagy, the number of *ATG* genes has now reached 41.  During our time at the NIBB, important findings came one after the next as we began to look at the *ATG* gene products to gain insights into their function. Mizushima made the first important breakthrough in his investigation of the only very recently cloned Atg12 protein. He discovered an intricate conjugation system that functions in an ubiquitin-like manner to yield a dimer of Atg12-Atg5-Atg16 complexes essential for autophagy. Two graduate students, Takayoshi Kirisako and Yoshinobu Ichimura, also uncovered another ubiquitinlike conjugation system that, unusually for such a system, results in the conjugation of Atg8 with a membrane phospholipid, phosphatidylethanolamine. Atg8, homologues of which were soon identified in mammals by Yoshimori and in plants by our group, remains associated with the autophagosome throughout all stages of autophagy and is therefore widely used as a marker of autophagy progression. We therefore learned that nearly half of the essential Atg proteins were involved in just two conjugation reactions. Important structural details of the complexes involved in these reactions were solved thanks to our close collaboration with Fuyuhiko Inagaki and Nobuo Noda’s groups.  Further details came with the identification of the autophagy-specific PI3 kinase complex, which we termed PI3 kinase complex I. Akio Kihara’s work showed that Atg6 had in fact only just been identified as Vps30, a protein of the vacuole protein sorting pathway, by Scott Emr’s group. Vps30 is a component of the PI3 kinase complex, and we subsequently found that Atg14 affords this complex its specific role in autophagy. Yet another specific component of PI3 kinase complex I, Atg38, was uncovered more recently by Yasuhiro Araki. Meanwhile, we also discovered the important role of Atg13 in the activation of Atg1 kinase function, and identified Atg17, Atg29 and Atg31 as forming a complex required for autophagy induction under starvation conditions. With our investigations of Atg9, Atg18 and Atg2, we were before long able to classify all 18 genes essential for autophagy under starvation conditions into six functional groups. This was further explored by Kuninori Suzuki, who used fluorescence microscopy to discover the pre-autophagosomal structure (PAS), a dynamic structure to which all Atg proteins at least partially assemble and intricately co-ordinates autophagosome formation. Suzuki’s work also demonstrated that the Atg proteins associate with the PAS in a hierarchical manner to perform their essential role in autophagy, shedding further light on the mechanisms of autophagy.  Identification of the *ATG* genes has completely revolutionised autophagy research. One important example of this was Mizushima’s demonstration of the progression of autophagy in mammals by using a GFP-tagged LC3 transgenic mouse, as well as his successful generation of an autophagy knockout mouse, the first for Atg5. Along with the knockout of Atg7 in mice by Masaaki Komatsu, these studies changed our understanding of autophagy in mammalian cells and spurred the widespread genetic manipulation of *ATG*genes in various cells, tissues, organs and whole organisms all over the world. This movement helped to uncover a variety of physiological functions of autophagy. Of these, the recycling function of autophagy is the most fundamental in the cell, helping to survive the commonly-encountered challenge of nutrient limitation. But autophagy is not only important for nutrient recycling: it is also implicated in the often selective purging of unnecessary or harmful intracellular components, which is important in the maintenance of the intracellular environment. Recently, the selective elimination of proteins, supramolecular structures, and organelles have come to the fore as physiologically important applications of the core autophagy machinery. A particularly salient example of this has been the intensely-studied field of selective mitochondrial autophagy, or mitophagy. The removal of old and potentially damaged mitochondria by autophagy ensures efficient energy production and a healthy intracellular environment, underscoring the nuanced integration of autophagy into the cell. **4. Starting my final lab at the Tokyo Institute of Technology** Even in an organism as apparently simple as the yeast cell, many mysteries remain unresolved. My lab has therefore been working exclusively in yeast for 13 years since Yoshimori and Mizushima formed their own groups.  In 2009, another important change occurred in my career. The Tokyo Institute of Technology offered me a position as a specially appointed professor in a laboratory with excellent facilities, so I decided to return to the Tokyo area. With Hitoshi Nakatogawa and Suzuki as assistant professors, and later Hayashi Yamomoto, we started a new laboratory. I brought along many colleagues from Okazaki to this new facility. We have been focussed one subject, how the autophagosome is formed, through the functional analysis of Atg proteins. Recently we found how the early steps of PAS formation are organised. Another area of interest to us was the mechanism of selective autophagy in yeast. In this field, we were also able to identify various receptors for target selection. Hitoshi Nakatogawa identified novel receptors for ER and nucleus degradation.  ow, my lab has shifted its focus to the physiological meanings of autophagy. In order to return to the original questions that intrigued me at the start of my career – the what, when, how and why of autophagic degradation – we need to systematically consider cells as they exist in an array of environmental contexts. This year we have set up a research unit at the Tokyo Institute of Technology, and with Tomoko Kawamata as an assistant professor we are now running a laboratory consisting mainly of postdoctoral researchers that will be my last laboratory. Here we are tackling those original questions that I believe are important to deepen our understanding of autophagy. Yeast is still an extremely powerful model organism, and with the continued development of new biochemical techniques I believe that we still have many ground-breaking contributions to make, especially in identifying the induction conditions and various modes of autophagy. These contributions will necessarily assess the products that arise from autophagic degradation, the mechanism of their export from the vacuole and their implications for cellular metabolism. As a fundamental cellular process, autophagy is linked directly and indirectly to a range of cellular pathways, and the development of quantitative methods that will allow us to grasp the subtle characteristics of this mechanism are essential. A better understanding of autophagy promises to help characterise the ambiguous relationship between genetics, phenotype and disease.  Autophagy research is still at an early stage, and our understanding of the physiological role of autophagy in particular is only in its infancy. Of course, I’m very pleased that we have managed to unveil such intricate detail about autophagy and its associated phenotypes, and the attention the field has attracted from around the world is very exciting. But I am most appreciative for the many wonderful colleagues I have worked with over the years. I was always driven by curiosity rather than immediate practical outcomes in my work, and have been lucky to work with postdoctoral researchers and graduate students who appreciate the importance of basic research. Many of them have shared my passion for studying difficult projects that do not always give immediate outcomes, and fortunately many of them continue to advance the field at a range of universities as researchers. I have also been very fortunate to have worked with many collaborators over the years who have helped us along the way. In particular I want to note the contribution of two researchers who have collaborated closely with us for over a decade in the systematic structural analysis of the Atg proteins: Nobuo Noda, who works now at the Institute of Microbial Chemistry, and Fuyuhiko Inagaki, who regretfully passed away in 2016. I deeply appreciate their collaboration over the years.  I am deeply moved by the interest that has been shown in autophagy research, which for me has represented an incredible journey over the last 28 years. This was only possible thanks to grant support of our fundamental research, which was indispensable in this undertaking. It is my greatest pleasure and honour as a basic scientist if our work was able to trigger a development in our understanding of life. I await the continued development of the field over the years to come with great anticipation. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0519= YO  [Yoshinori Ohsumi]: Moshi, Moshi, Yoshinori speaking.  [Adam Smith]: Hello, Professor Ohsumi. My name is Adam Smith. I’m calling from the official website for the Nobel Prize.  YO: Ah ha, yeah.  AS: First of all, our congratulations on the award of the Nobel Prize.  YO: Thank you so much. Yes, I was surprised.  AS: [Laughs] How did you hear the news?  YO: I had a call from Thomas Perlmann.  AS: Yes, Secretary of the Nobel Committee, yes indeed.  YO: Yeah, Nobel Assembly.  AS: Nobel Assembly, yes. And where were you when you received the news?  YO: I was in my lab.  AS: And your first reaction?  YO: I heard that, single only, me! It was also a surprise for me.  AS: It’s true, because it’s rare that they give the Nobel Prize in Physiology or Medicine to just a single Laureate. What do you think this says about the role of the single researcher these days?  YO: That’s my real surprise because so many people are now working in the autophagy field.  AS: Autophagy is a huge area. But it’s not…  YO: Yeah, recently.  AS: Recently, exactly.  YO: Just recently I think.  AS: Very largely because of your work.  YO: Yes, it’s so, developed fast, yeah. When I started my work, probably every year 20 or less papers appeared on autophagy. Now more than 5,000 or something like that. It’s a huge change within probably these 15 years or so.  AS: A real explosion.  YO: I actually started more than 27 years ago.  AS: It was a good choice of field.  YO: Yeah, it was lucky. Yeah, yeast was a very good system and autophagy was a very good topic to work. Still we have so many questions. Even now we have more questions than when I started.  AS: Once again it underlines the power of yeast as an experimental model.  YO: Yeah.  AS: You can do so much with yeast. And does it surprise you how similar yeast is to ourselves?  YO: I believe there are fundamental functions of the cells should be conserved from yeast to mammals. So that’s my belief. But of course vacuole is different from lysosome, but I thought that most fundamental mechanisms must be conserved. That was my assumption when I started my work.  AS: You sound as if you’re still in a slight state of shock.  YO: Yeah, mmm.  AS: And will you be coming to Stockholm in December to receive your award?  YO: Yeah, yeah.  AS: Wonderful. Well we very much look forward to meeting you then and to talking further.  YO: OK.  AS: Thank you very much indeed for speaking to us now.  YO: Thanks so much.  AS: Congratulations again and we wish you a wonderful day. |
| Interview |  |
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| ID | 0520 |
| Biographical | Before any of the present fuss I was, of course, born; and that turned out to be slightly complicated – not in an obstetrical sense, but in a political one.  Several years before the event, an international border was created between my parents’ rural town and the nearby city where maternity facilities were available at a price. Thus it came about that I was born in Northern Ireland, U.K. (in Londonderry city) but was raised in Eire, the Irish Republic (in Ramelton town, County Donegal). The year was 1930, and that was a long time ago (the Great Depression was in full swing, but I did not learn about that until much later).  My parents were strong believers in the value of education. My father, having had little formal education himself, went so far as to employ a professional teacher, Miss Elisabeth Letitia Martin, as a live-in tutor for me, my two brothers and my sister. (There were cultural factors at play as well as educational values.) For a considerable period I was the only pupil in school (my sister being too young for school and my brothers having departed for boarding school). Miss Martin instilled in me a desire to learn, and to remember the things that were considered good. Science was not mentioned. In those years before and during World War II, it did not, I think, occur to either of us that a multicultural, multidisciplinary transformation was taking place in the tumultuous world outside our attic classroom. I do not think that anyone now cares that I still remember a few lines of Wordsworth and Tennyson; but learning to love learning, through Miss Martin’s influence, was a gift for which I shall be forever grateful.  Having been taught by Miss Martin from the age of 6, I moved at the age of 13 to a boarding school: Campbell College, Belfast, Northern Ireland. The school had a reputation for excellence; it was said to be “the Eton of Ulster” and indeed it was run on the lines of a classic British boarding school. It had been evacuated from Belfast to the seaside resort of Portrush because of the war, and for the same reason the teaching faculty was composed largely of teachers brought out of retirement. On arrival, I did not even know the difference between physics and chemistry (today I begin to suspect that there might not be one). I was thrown into those subjects very much as I was thrown into rugby football – without even a rudimentary instruction as to which way to run. Physics was hard; chemistry seemed like magic. Biology, however, I found fascinating. I was not robust enough or pugnacious enough to be good at contact sports, and playing tennis was not an option until the final years. Perhaps it was that factor, combined with the rather solitary prior period under Miss Martin’s tutelage, that I became more interested in learning than in sports. In those school-days, and especially in the college years that were to follow, there was a great deal of peer pressure to be knowledgeable and “cultured.” Certainly, my scholarly interests did not arise from any effusion of intellectual brilliance.  Life at Campbell College was an awesome adventure for a country boy who had led a rather sheltered life. It was not always fun (nor should it have been) but it was never boring. It meant making new friends in a regimented and hierarchical system. Traveling to school at the beginning of each term meant traveling to a country at war. It meant carrying a gas-mask in a little box slung around my shoulder. As a member of the Air Training Corps, I trained in the methods of, and at camps of, the Royal Air Force. I used to see fighter planes rising from RAF airfields, and I longed to be old enough to fly them. I pictured myself an ace fighter pilot, strolling nonchalantly in my beribboned uniform and impressing the girls. In reality I was sequestered in an all-boys school and didn’t know what I would say to a girl if I met one. The war ended while I was still a school-boy, and with it ended my dream of soaring into the sky in my trusty Spitfire. Campbell College moved back to Belfast.  It was at Campbell College that I first learned of the existence of a parasitic worm. It was *Fasciola hepatica*, the common liver-fluke of sheep and cattle. In the course of a school outing to an agricultural show, I was fascinated to learn that a drug could be used to treat liver-fluke disease. When it was time to move on to university, my biology teacher, Mr. Wells, advised me to go into biology while the head master advised me to go into medicine. I took Mr. Well’s advice, but devoted my subsequent career to biology in the context of human and veterinary medicine.  Upon entering Trinity College, Dublin University in the autumn of 1948, I was again confronted with sciences that were not much to my liking. Swedish chemist [Tomas Lindahl](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2015/lindahl-facts.html) recalls that when he was a child a teacher gave him a failing grade in chemistry, but he went on to get a Nobel Prize in Chemistry (as recorded in Nobel speeches). When I was a university freshman, the standard grade for passing was 40% – and my final mark in chemistry was 39.7%. Fortunately the mark was rounded up to the nearest whole number. But for me chemistry remained mysterious. Physics, too, was a challenge. Perhaps my physics professor ([Ernest Walton](https://www.nobelprize.org/nobel_prizes/physics/laureates/1951/walton-facts.html)) was distracted by the news that he had just won the Nobel Prize in Physics; but I cannot blame my teachers for the fact that I found the “hard sciences” hard. Biology was about to become vastly more chemical and physical: across the Irish Sea, Watson and Crick were building models with a novel twist. Luckily for me, my strong interest in zoology carried me through to graduate from Trinity with first-class honors.  Even in the earlier Trinity years, the pleasures of botany and zoology more than made up for the struggles in other sciences. Soon I came under the influence of Dr. J. D. Smyth, about whom I have written elsewhere [1]. Desmond Smyth was making a name for himself in the field of invertebrate physiology and especially in the area of experimental parasitology. He became (informally, of course) my mentor; and he changed my life. Among the things that Professor Smith did for me as I approached graduation was to respond positively to inquiries from Professor Arlie Todd of the University of Wisconsin, USA. The result of that communication was my application for graduate school at the University of Wisconsin along with two other Trinity students. Both of the others dropped out, and before I set out on that journey alone, one of them sent me a note saying, “For God’s sake, don’t panic when you get off the boat.” I thought that was a very easy thing for him to say.  As it turned out, getting on and off the boat (which turned out to be the liner *Britannic*) was made easier by two wonderful organizations. Prof. Smyth encouraged me to apply for a Fulbright Travel Grant, which led to various complications relating to the foundation of the Fulbright grants and my rather confusing British and Irish citizenship. All was settled favorably and I set off on my big adventure to the New World and graduate school, with all my travel expenses covered by the Fulbright grant. I was therefore one of the innumerable beneficiaries of the generous impulse and astute insight of United States Senator William Fulbright and his conjuring of international good will from the horrors and economics of war. Getting off the boat in the dockyards of New York City (in January 1953) would indeed have been a fearsome affair had it not been for the other organization, the Committee on Friendly Relations Among Foreign Students (founded in 1915, with funds given by Andrew Carnegie and Cleveland Dodge). Its angelic Mrs. Minucci met me on the dock and soon had me installed in a nearby hostel where I was assigned to one of the many beds in a large dormitory room, and was advised to keep my belongings close about me. I am still haunted by the realization that I always intended to write that kind woman a thank-you note, but never did.  I was dismayed to find that the U.S. system required graduate students to take many academic courses, but the requirement proved advantageous. My doctoral program was a “joint major” program in Veterinary Sciences (supervised by Arlie Todd) and Zoology (supervised by Chester Herrick). Professor Todd’s laboratory in the Department of Veterinary Sciences was my campus ‘home’. Since I knew something about the trematode *Fasciola hepatica*, I was delighted to learn that my research project would be on a giant relative, *Fascioloides magna*.  Todd’s method (unspoken by him, unsuspected by me) was to set a new student to some routine task such as tending the snail tanks where the vector snails were raised, and waiting for the student’s curiosity to take its course. Gradually and unwittingly I discovered the joy of being able to do something in the lab to test some item of casual curiosity – the fun of actually doing an experiment that no one had done, to answer a question no one had asked. Those graduate school explorations led to half a dozen scientific papers.  For most of my years in Madison, Wisconsin, I lived rent-free in the old Governors’ Mansion on the edge of Lake Mendota! This extraordinary bit of good fortune resulted from being awarded a Kemper K. Knapp Fellowship – a grant that enables a group of graduate students from various disciplines to live together in a an environment conducive to intellectual ‘cross-fertilization.’ The “Knapp House” experience was a major highlight of my University of Wisconsin years.  In 1957, as the graduate school experience came to an end, Professor Todd responded positively (echo of the end of my Trinity days) to an enquiry from Dr. Ashton C. Cuckler, Director of Parasitology at the Merck Institute for Therapeutic Research. Todd encouraged me to at least go for an interview at the Merck organization in Rahway, New Jersey. With considerable misgiving I decided to give the pharmaceutical industry a try – and stayed for 33 years. It was a marvelous experience – challenging, exciting and (at least in the early years!) remarkably free of workplace politics. I am deeply indebted to Cuckler for his leadership in those early years [2]. Sharply focused research was exactly what I needed to keep me from wandering indefinitely into tangents and sub-tangents of a project; yet at the same time I was always free to make refreshing forays into the most enticing tangential byways.  Given my struggles with chemistry as a student, it is ironic that I went on to have a career in experimental chemotherapy. That happened quite naturally because at the Merck Institute I was surrounded by brilliant chemists and close interdisciplinary collaboration was a way of life. During my years at Merck, collaboration between Parasitology and many other scientific disciplines enabled the company to introduce several anthelmintic (anti-worm) drugs: thiabendazole (ThibenzoleR, TBZR); cambendazole (CamvetR); rafoxanide (RanideR); clorsulon (CuratremR); ivermectin (MectizanR, IvomecR); eprinomectin (EprinexR). For several years I had administrative responsibility for the Merck poultry coccidiosis program, and the amebiasis and trypanosomiasis programs, but my contribution to protist biology was essentially nil.  It was a chemist who imbued me with confidence in the empirical approach to drug discovery. The parasitologists and chemists at Merck had weekly lunch meetings, co-chaired by Cuckler and Dr. Lewis H. Sarett. Sarett was one of the great medicinal chemists of that era (he was renowned especially for his partial synthesis of cortisol). He quickly deflated my naïve assumption that the best way to find a new antiparasitic drug was to devise a rational therapy based on the latest discoveries in the field of parasite biochemistry. Sarett convinced me that, at least in the near term, the probability of finding a drug by empirical screening (for which there was much historical precedent) was higher than the probability of finding one through research on the biochemical processes of parasites (for which there was no precedent). That assessment has, of course, no bearing on the importance of research on parasite biochemistry. Cuckler placed great faith in the use of animal (*in vivo*) models, and dietary medication, for the routine screening of test substances. In the era of biochemical biology there was a high price to pay for adherence to such traditional assay methodology; but I do not regret my espousal of it.  Chemotherapy has by no means been my only parasitological interest, and I will mention just a few of the others. I devoted a lot of time to the study of Trichinella and trichinellosis, including much “burning of midnight oil” to produce a book on that subject. I was privileged to become deeply involved in the activities of the International Commission on Trichinellosis. My passion to be the first person to deep-freeze worms without killing them led to the discovery of a laboratory manipulation that allowed the cryopreservation of strongyle nematodes for at least 10 years [3, 4]. It turned out to be useful because it made possible the maintenance of species and strains of nematodes without the enormous cost of serial passage in sheep, cattle or other large animals. My close association with chemotherapy prompted me to use drugs as tools for the study of stage-specific immunity to helminth parasites. The first of these was a demonstration of the protection conferred by pre-pulmonary migration of *Ascaris suum* in rats [5].  My decades of work at the Merck labs in Rahway NJ were punctuated by two leaves of absence and one temporary re-assignment. I requested, and was granted, leave to travel to the University of Cambridge to become a visiting researcher in the laboratory of Lawson Soulsby (now Lord Soulsby, Baron of Swaffham Prior), who is recognized as an outstanding pioneer in the field of immunity to helminth parasites. My wife and I sailed on the *Queen Elizabeth* in 1963, and our life in England was marked by immunological studies on trichinellosis, many new friendships, and the birth of our daughter Jenifer. Our son Peter was born in the US at the beginning of 1966; and later that year I was granted a brief second leave – this time to accept an Inter-American Fellowship in Tropical Medicine under the auspices of the Louisiana State University. Previously this fellowship had not been open to scientists employed in industry. Professor Harold Brown, a legendary parasitologist at Columbia University, appealed for a lifting of that restriction and I had the great benefit of visiting laboratories and hospitals in Central and South America. A third departure from the United States (1972–73) was not a leave of absence, but rather a temporary transfer from Company headquarters in New Jersey, USA to Australia to assume directorship of the Merck, Sharp and Dohme Veterinary Research and Development Laboratory in Campbelltown, N.S.W. That, too, was a memorable and instructive period, with novel administrative responsibilities, research on the use of cambendazole for the control of tapeworm in sheep (with colleague Richard Butler); further research on the cryopreservation of strongyle nematodes [6, 7], lasting new friendships – and the birth of our daughter Betsy.  Beginning in 1975, and continuing for a period of 15 years, I was mostly preoccupied with matters relating to ivermectin [8]. Advancing years and perturbations in career pathway brought thoughts of retirement. There was no doubt about what to do. I knew that Drew University in Madison, NJ had an unusual program that enables retired industrial scientists to turn their years of experience to the benefit of undergraduate students, while at the same time enabling the scientists to continue to be active in their fields of interest. In doing this, the scientists give up much in absent salary, and they gain much in an incomparable “job satisfaction.” The Charles A. Dana Research Institute for Scientists Emeriti had been founded at Drew University to provide this sort of opportunity. In 1990, Merck and Company announced an offer of increased retirement benefits to employee scientists who opted to take early retirement in order to teach mathematics or science. I therefore moved quickly, at the age of 59, to Drew University. Few experiences are as gratifying as that of mentoring undergraduate students as they discover the joy of doing an experiment that is not a classroom exercise but an experiment that constitutes real research. Several of my undergraduate students have published their research findings in reputable peer-reviewed journals by the time they graduated. I had always enjoyed teaching and had held adjunct professorships at University of Pennsylvania, New York Medical College and Drew University for many years. I was delighted to find new opportunities to teach at Drew University: teaching a course on Parasitology (in the Biology Department) and a course on the History of Biomedical Science (in the graduate school). I cannot imagine a more rewarding professional *finale* than retiring a bit early to profess one’s calling in such an environment.  Leaving the land of my birth (Northern Ireland) and of my upbringing (Ėire) had never been my intent; but circumstances changed and the New World got hold of me. The people of the United States welcomed me, and in 1964 I became a citizen.  In accord with instructions, I have devoted these pages to education and career. Recreational, avocational and social activities have been left out. But that sort of limitation is not the hardest part of writing such a biographical sketch. The hardest part of all is coping with the realization that one is evading the most important part. Without family (at least in the ancestral sense), there would be no biography to write. With family, there is no way a really true biography can be written. I have no words to say how much I love my wife and children; and how much, magically, I feel loved by them. My wife Mary, and my children Jenifer, Peter and Betsy must be counted in whatever honors come my way. And then there is the love that emanated (unspoken, in the manner of the time and place) from my parents Robert and Sarah Campbell, and was shared by my sister Marion and my brothers Bert and Lexie. Without my being aware of it, my younger self must have been molded by the nurturing care of my parents, their commitment to honest and industrious living, their stalwart religious faith and their admiration of learning. Beyond the family circle and our extended families, many other people have granted me the blessing of friendship. I may not be able to express my gratitude here, but of this I am certain: I have a great deal to be thankful for. **Literature**  1. Campbell, W.C. 1999. In Memoriam: James Desmond Smyth, Honorary Member ASP. *J. Parasitol.* 85:992–993. 2. Campbell, W.C. 2001. In Memoriam: Ashton C. Cuckler. *J. Parasitol.* 87:466–467. 3. Campbell, W.C., Blair, L.S. and Egerton, J.R. 1973. Unimpaired infectivity of the nematode Haemonchus contortus after freezing for 44 weeks in the presence of liquid nitrogen. *J. Parasitol*. 59: 425–427. 4. Rew, R.S. and Campbell, W.C. 1983. Infectivity of Haemonchus contortus in sheep after freezing for ten years over liquid nitrogen. *J. Parasitol.* 69:251–252. 5. Campbell, W.C. and Timinski, S.F. 1965. Immunization of rats against Ascaris suum by means of non-pulmonary larval infections. *J. Parasitol.* 51:712–716. 6. Campbell, W.C. and Thomson, B.M. 1973. Survival of nematode larvae after freezing over liquid nitrogen. *Australian Vet. J.* 49:110–111. 7. Kelly, J.D. and Campbell, W.C. 1974. Survival of Nippostrongylus brasiliensis larvae after freezing over liquid nitrogen. *Internat. J. Parasitol.* 4:173–176. 8. Campbell, W.C., Fisher, M.H., Stapley, E.O., Albers-Schonberg, G. and Jacob, T.A. 1983. Ivermectin: A potent new antiparasitic agent. *Science* 221:823–828. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0520=WC  [William Campbell] Hello.  [Adam Smith] Oh, hello, my name is Adam Smith, I’m calling from Nobelprize.org, the official website of the Nobel Prize, in Stockholm.  [WC] Yes.  [AS] Have you heard the news?  [WC] Yes.  [AS] Where were you when you heard this news?  [WC] I was asleep.  [AS] What was your first reaction?  [WC] Well, the first thing I said was ‘You must be kidding!’ and, I thought, the first thing I did after that was to ask for a way to verify that this could be genuine because it just seemed impossible.  [AS] [Laughs] And how long did it take to convince you?  [WC] Not very long because they told me to go on the website. And one of the reasons I thought it was impossible is that I believe the Nobel Prize cannot be given to a group except for one particular area, and this work was the product of a group. It often is, but in this case especially.  [AS] The production of a drug from start to finish requires so very many people doesn’t it?  [WC] Yes exactly, and so I think of it as an award that I’m the representative of the Merck Company’s research team.  [AS] That’s lovely. Can you describe the difference you think that the drug, that Ivermectin in particular, has made to the world?  [WC] Well it has made a huge impact in preventing blindness. Blindness anywhere, and especially in certain areas of the world, is likely to be calamitous and fatal because people cannot be productive and make a living when they are blind, in some circumstances. So it has certainly changed lives and changed the ability of people to live in certain fertile areas of land which they had had to abandon because of the disease, and this enables them to repopulate areas that had been abandoned, so that has been another way it has been important.  [AS] That’s a very important point to emphasise, thank you. And one key step in all this was that you turned to nature to provide the anti-parasitic drugs. Do you think that nature is a store of tremendous numbers of as-yet unknown medicines?  [WC] Yes, and I have written about that, and I have works in press about that. I feel very strongly about that. I think one of the big mistakes we’ve made all along is, and I’ve been writing about that for 40 years, is that there is a certain amount of hubris in humans thinking that they can create molecules as well as nature can create molecules in terms of the diversity of molecules, because nature consistently produces molecules that have not been thought of by humans.  [AS] Lastly, I can hear in your voice that lovely Irish lilt [Laughs].  [WC] [Laughs] I don’t suppose there’s much of it left any more.  [AS] Well actually I was thinking there was a rather surprisingly nice amount. So I guess they’ll be celebrating in Ireland as well today.  [WC] Currently in Ireland, my brother and his wife, who got this before I did, and so I was awakened and put on a radio show in County Donegal. Nobody else, including me, knew about it properly, so my family there were thrilled. They called me to tell me about it.  [AS] That’s nice, I guess you’ll be receiving calls throughout the day and the week and the months ahead.  [WC] My phone is ringing, my cell phone and my landline number are both ringing constantly and it’s a great thrill and a great honour, and a great honour to have been part of this team effort.  [AS] That’s lovely, well thank you.  [WC] And that’s the point I want to emphasise.  [AS] Thank you. Well we very much look forward to welcoming you to Stockholm in December and when you come then we’ll have a chance to talk more.  [WC] When?  [AS] In December. So the Awards ceremony is on December 10th.  [WC] What, of this year?  [AS] Yes, of this year. So it’s in …  [WC] 2015?  [AS] 2015.  [WC] No kidding! Wow. Oh, gosh. That’s a shock. I look forward to being there, of course.  [AS] Thank you.  [WC] Thank you so much.  [AS] I look forward to seeing you in December. Thank you, bye bye. |
| Interview |  |
| Q1 | What brought you to science? |
|  | I came to science I think later than a lot of people certainly nowadays, because I know that I had not heard of science until I was thirteen/fourteen years old because I had a teacher who did not mention science. So I ended up going to boarding school, be thrown into science, not knowing the difference between physics and chemistry or what science was about. And so I came late, I came in the high school years, my late teen years, not my early years. It just happened more or less by chance which I can talk about if you like, but the chance my memories of those chances that made me interested.  At high school, the one thing that I do remember is going to a show when I was in high school, a agricultural show, a school outing and this is at a time when I was sort of struggling with my new exposure to physics and chemistry and I must have been about sixteen or seventeen years old. And the only thing I remember about the agricultural show, the absolutely only thing was coming away with a leaflet, an advertising leaflet from a company and I remember the company, I remember its name and it was about liver fluke disease, in sheep and cattle, caused by a warm parasite and it was advertising this treatment. And that didn’t change my life, I didn’t decide then and there that I wanted to work, but in retrospect I realize that that was the only thing that I remember seeing, the only leaflet I took home, I read it, I re-read it, I was totally fascinated by it. So in retrospect I think that I was predisposed or susceptible or right enough to want to be interested in natural science, so I think that was one thing. And then other things came at college, but I think that was sort of the earliest thing and then my college years were very formative. |
| Q23 | How did your work lead to the Nobel Prize? |
|  | My work was not some very discrete thing that could be associated with the prize. I had become tremendously interested in experimental chemotherapy directed towards parasitic diseases. My objective was finding new drugs and I had had some exposure with that finding the drug called thiabendazole before this new drug ivermectin. So I was deeply involved in this for many many years. And then with this new drug the thing that is difficult to relate and to get through to people is how collaborative it was, not just with professor Ōmura’s contribution to get things started with a new bacteria, but my role … there were a few things that were very specific, one working on heartworm disease of dogs which I did, I did the experimental work on that. And then my work in getting started … interest in human application of the drug. I was already interested in teaching and involved in human medicine as well as veterinary medicine with respect to parasites. I had the dog heartworm, I had initiating the work on human application for river blindness and of course as it turns out that was the biggest thing. I had administrative responsibilities as head of parasitology. So those were sort of three discrete things and as it turns out making things happen with respect to river blindness was the most conspicuous of those. |
| Q16 | Have you had a eureka moment? |
|  | Not in relation to this drug, and in fact not in relation to new drug discovery which is my primary field of interest. And I quite clear that I have not had a eureka moment and I think there is a good reason for it. And that is because I have a lot of experience and if you have experienced that field you know that when you discover a new substance that’s active in the disease you are working on it might be a drug that will be useful you know that the overwhelming probability is that it will not be useful because of so many things can go wrong and the chances of the drug surviving and overcoming all these hurtles is very small. And I think that is the reason, you get excited, but as always a subdued excitement and as it overcomes these various tests it has to go through you can ally yourself to get a little more excited, but that’s very different from a eureka moment and I think I had the eureka moments in stuff that I have done on the side. |
| Q2 | What motivated you to live a life in science? |
|  | I think the thing that really motivated me in the scientific field was a particular professor in my early college years as an undergraduate Trinity College Dublin. I had this professor who changed my life as a good professor will try to do and the good professors succeed in doing, because he was interested in parasites, especially parasitic warms. I found his work interesting and he was very kind and brought me into his sphere of activities and talked to me, he’d meet me in the car, he would talk to me about his work even though I was just a mere undergraduate of the lowliest status and he would have me come to the lab and watch him do experiments and things. He just changed my life by being such a wonderful guy and helping to crystalize what might have been some preexisting interest and certainly focusing my interest on parasites. I was really interested in natural science, but the focus on parasitic worms was entirely due to him and my making it a carrier, well first my coming to the United States was entirely due to him because of contact he had with some of the universities of Wisconsin, so he was the one who initiated the whole business of going from Ireland to the United States. |
| Q5 | What was his name and what do you think he would say if he saw you here today? |
|  | This professor was professor Desmond Smyth, J. D. Smyth, known as J.D. or Prof. Smith, but when I got to know him better after growing up, he was Desmond Smith and I remained in touch with him for the rest of his life and he visited me in the United States, visited my family. I visited him in London when he was based there and so we continued to be in touch for as long as he lived and it was a very good relationship. He inscribed one of his books that he sent to me and I haven’t thought of this recently, but it was an unusual inscription. It said ‘To Bill Campbell, my most appreciated student’, so he understood, I guess, I don’t know how that I appreciated his work. I don’t know if he ever understood how much I appreciated him, but he would be proud. |
| Q11 | Do you have a good relationship with your students? |
|  | Yes, I was just recalling that with someone, cause just yesterday as we were traveling I got a text message from one of my former students who had just heard the news and she was so excited and was telling me about one of the other students and this has been one of the best parts of getting the Nobel Prize, has been hearing from students. One of my first students who’s gone on being a very successful medical practitioner, several of them have, but she just wrote the most exciting letter saying how she and my other students were all in touch with each other now to talk about this. |
| Q43 | When do you do your best thinking? |
|  | I do my best thinking when writing. When you do experiments you are following something that’s in your mind. And the best ones are things that you are desperately curious about, the experiments that you are doing, but you’re involved in the actual doing of the experiment, more than thinking. I have always been lucky that I love to write and that’s because of another teacher that I have not mentioned, but the most important of all in a sense. I learnt to like to write and so even writing very technical reports, I really am interested in writing it, either for clarity or what I hope might be style, but I am interested in writing as writing and I find that that is when other thoughts are most likely to come to me, because you realize suddenly you are saying this and you are thinking have you really made it clear and if not is it because you are not clear yourself? And if so, you start thinking about why you are not clear on it. If it is something that you are proposing in the future, if you are going to write about it you have to ask yourself, not just in some general term. You have to actually think about that. So I think writing is conducive to thinking. |
| Q30 | What did you donate to the Nobel Museum? |
|  | One of the interesting things to me was the question of donating items to the museum and my first response in fact, to the museum, was that I can’t really think of anything, but I will get back to you. And for a long time I couldn’t think of anything, because from examples in the past, I kept thinking of what I might have is an objective from the lab or something. I couldn’t think of anything that made sense, but then I suddenly realized that in fact a large part of my work has been related to non-work, to interest in writing and painting, so those were interests of mine. So what I decided that I would donate to the museum would be two books that I have published myself. I published myself on the assumption that they are too narrow in the focus for anybody else to want to publish them. Because the book of paintings are all paintings of parasites, but they are not illustrations, they are not scientific illustrations, they are expressionistic variations on parasites, but they are certainly identifiable, not only as parasites, but as specific parasites and parasitologist can identify them immediately as to what exactly they are. And I have great motivation to pursue this because they get sold at auctions to raise money for scholarships for parasitology students to enable to attend parasitology meetings. So it is a rather narrow focus, a clientele so to speak, but is a very exuberant one and very active and so I have motivation to paint.  But then also my writing is obviously much more a personal matter because it is a very personal thing to write poetry, but I find it … I decided partly because of other professors, one in particular, who asked if she could have manuscript copies of my poems and she would type them up and then she could use them in her classrooms, because a lot of them are about parasites. Then I realized that maybe I should do this in a book form and nowadays it is easy to do it even if you don’t think it could be something that the general publisher could be interested in and you can actually make a book. So I have made books and I have taken some of those to the auction too, but the book of poems is definitely not all about parasites. There are poems about history, a lot of poems about history, history of biomedical science, some not related to science at all, some quite personal, some written for children so … and that was a period of my life I wanted to write a poem about. I still want to paint, I don’t at present have … I have an amuse at my side, I don’t have poems that want to get out, so to speak and I don’t know if that will come back, but certainly for a period of my life there were poems that I just needed to write and not all scientific. |
| Q34 | What challenges remain in your field of research? |
|  | In my field of research there is a number of specific technical things, but I think the overall importance in the future and the thing that is not talked about is the need to have more natural means of disease control, and I think of disease in terms of parasitic disease. But it is not necessarily confined parasitic disease, but I think although I have devoted a good part of my life to developing agents, chemical agents, natural projects leading to chemical agents to kill worms, I have a feeling in the long run that’s not the best way to go. I think chemical intervention as we have discovered over the years is likely to have not just unforeseen consequences, but natural consequences that lead to unnatural outcomes that can be bad.  So I think that the minimal interference with the natural world is to be desired and that if we can understand for example the immune system so well that we can actually stimulate it or simulate it even better with some natural way, we might have a more balanced approach to control disease and less looking for absolutes. And then that’s with psychological differences, psychological challenges with that because everybody would like a zero disease in 100% of people. But I think we need to try and get away from what we have been doing and try and focus on understanding disease and host parasite relationships, and by parasite then I mean all kind of infectious agents so deeply that we can actually use some control without trying to exterminate things widely and broadly. |
| Q12 | What advice would you give yourself at 20 years old? |
|  | I would advise myself to find work that is hard and gratifying. I think I don’t believe in such a thing as a cushy job, because the cushy job is not really work and I think everybody needs to have hard work, and if you have hard work and you are miserable at it, then your life is miserable and your family is miserable and that’s to be avoided. Some people unfortunately get trapped into being committed to work that they don’t really enjoy and that’s unfortunate. So I think what I would say to myself is find something you would like to do and then don’t shy away from really working at it. I think there are the two things, hard work and getting satisfaction, not necessarily live a life of pleasure, but a life of hard work and pleasurable challenge. |
| Q14 | How are art and science related? |
|  | I think for me the thing about science and art is I like to have them overlap, I think they are different things and that we shouldn’t forget that they are different things, they are definitely different. I look for things not as an avocation or a hobby to keep them separate. I don’t look to writing as an escape from parasitology, I don’t look for one … well I don’t look at either one as a hobby. To me the great satisfaction has been being able to make them overlap so that I write quite a lot about parasites, and frequently I am writing a poem trying to look at things from the parasite’s point of view, so several of my poems are actually written from the parasite’s point of view, and there is at least one actually written as though spoken by the parasite.  I think I am so interested in parasites that I tend to think about them even when I come to write poems, because sometimes I’ve tried to say what I think they would want to say. Sometimes it’s about history, because there again I think feel that I am interested in history, so I write poems about those things in history that interests me in terms of medical history, so there is definitely an overlap. I have written some poems that are not about science, but those are few compared to the numbers that do touch either on parasites or other … or science history. |
| Q39 | Can you tell us about one of your poems? |
|  | Well, in fact one of them is in the context of river blindness which is sort of the most talked about aspect of this all new drug ivermectin which is used to prevent river blindness in the tropics. The cause of the disease is a parasite called Onchocerca and so one of the parasites, Onchocerca, speaks, and it’s in the words of the parasite and it begins with some rather extreme language and not by the day standard, but it says ‘I don’t need your good damn eye’ and that’s because the parasite damages the eye. But the parasite doesn’t need to, the parasite’s got lots of other places to go, the parasite gets through accidently, so here is this poor parasite associated with making people blind, but in fact most of the parasite activity is elsewhere in the body, in the skin. Some of them in the course of their migration, then of course they have to migrate, some of them end up in the eye and as they end up in the eye they cause eye problems and eventually they cause blindness. So I would like to think of the parasite, saying ‘I am not trying to do this to you, I am doing my own thing and this happens’. That’s an extreme case speaking from the parasites point of view. |
| Q39 | What is your favorite poem? |
|  | One of the poems of [William Butler Yeats](https://www.nobelprize.org/prizes/literature/1923/yeats/facts/) that is considered one of his minor ones and I think the critics even convinced Yeats that this was not worthy of him, that this was an early poem when he was not really at his best, but it’s ‘The Lake Isle of Innisfree’. It happens that Yeats was born and grew up maybe 15 miles or so from where I grew up in Ireland, I don’t know if that has anything to do with it, but this particularly poem he wrote when he was in London. He certainly wrote it as, not as someone exiled as punishment or some dishonoured but neverless somebody away from his homeland. I can really identify with that, you are not there because you are forced out, you are there because you have chosen and yet you are longing for something so it’s that ambivalence I think is more subtle than people realize. At least I can, to me that is certainly my favorite poem. |
| Q15 | What role has teaching played in your life? |
|  | Teaching has been one of my great joys and yet I spent most of my professional life not in a teaching situation. Then maybe it’s *because* I spent most of it not in teaching situation that I loved it when I did get to a teaching situation. Because when I retired from industry, I retired from an American company in the pharmacy industry and went to the academia, to Drew University in New Jersey, I went there actually not to teach. I went there to mentor undergraduate students, but I chose to teach as also one other person, colleague did in this institute, The Research Institute for Scientists Emeriti at Drew University, which is a wonderful wonderful institute and the emphasis is on mentoring. A couple of us chose to teach and I taught in an undergraduate biology department and I taught undergraduate school medical humanities program and I just loved that.  All along I used to teach seminars and I taught medical helminthology, I taught about parasitic worms at New York medical college for 25 years overlapping with those other jobs. So I discovered that I loved teaching and I hope to go on doing that, but now it will be largely at conferences and meetings, but especially if there are conferences were a lot of students tend to come and just this past summer I was at one such conference where it was not … it was in the place where there were not expensive hotels and were the tradition of students coming because it was accessible and I greatly enjoyed that and I hope to continue to do that. |
| Q10 | How has your life changed since being awarded the Nobel Prize? |
|  | The way my life has changed mostly since I got that call was in sheer busyness. I have always been busy cause I chose to be busy, but now I don’t get to choose what sort of business I am engaged in. Now I am overwhelmed with messages, the good part of it is that many messages are from old friends, the bad part is that there are so many messages of all kinds and that I am now retired, I don’t have a secretary, I have my wonderful wife who helps, but still we are very much in retirement mode and so this is a major change in our lives to be called upon to answer so many questions and to respond to so many invitations to conferences all over the world. Some of them several years in advance, and at my age I think it is a bit presumptuous to make plans many years in advance. So I am trying to be careful about that and I am trying to also continue to do the things that I have been doing. I still like to go out in season and kayak an early morning and I still play ping-pong three times a week and I am determined not to give up certain things like that, but it certainly has been a challenge just to keep up with the calls on my time. |
| ID | 0521 |
| Biographical | In Japan’s rural Yamanashi prefecture in the mid-1930s, times were harsh and resources were scarce. The local environment had to provide all the agrarian communities with most of the necessities that they needed for survival. This constituted a valuable and unforgettable lesson for Satoshi Ōmura during his formative years. A oneness with, and profound respect for, Nature was irrevocably instilled in him. Seventy years later, he was to encounter similar conditions to those where he was born and raised when he visited Africa to see first-hand the unmatched beneficial impact of one of the drugs he has discovered – a gift from Japanese soil that has improved the lives and welfare of hundreds of millions of people around the world.  Japan is a predominantly uniform society where the group is held above the individual and familial and social responsibilities remain paramount, as Satoshi’s parents taught him from an early age. Those people who understand Japan and the nation’s customs and traditions will sympathise with the dilemma that Satoshi faced and struggled to come to terms with throughout his career. A Japanese proverb illustrates the point – “deru kugi wa utareru” (a nail that sticks out will be hammered down). Within such constraints, when one has to adhere to long-standing duties and responsibilities as well as social and cultural norms, it is difficult to think or act differently. To do so, pioneer new paths and develop innovative concepts and techniques, and yet maintain respect and peer acceptance is a singular triumph which requires courage, vision and determination. Fortunately, there is another version of the proverb that is very true in Satoshi’s case, “deru kugi wa utareru ga, desugita kugi wa utarenai” (a nail that sticks out will be hammered down, but a nail that sticks out a lot will not).  Satoshi was born into a farming household in Nirasaki in Yamanashi in 1935, the eldest son in a Japanese family, which meant profound traditional family responsibilities. His father was a proactive, leading member of his village and his mother an elementary school teacher and gifted piano player. His parents nurtured in him sensitivity and the deep-seated need to constantly think about others, plus his duty to his parents and siblings, as well as ensuring that he developed excellent life skills to be able to cope with whatever he encountered. With his parents mostly working, Satoshi spent much time with his grandmother, who also repeatedly emphasised that for personal development and satisfaction, it was always best to work for the sake of others – a tenet that has accompanied him throughout his working life.  As is common among many youngsters from a physically active, rural farming background, Satoshi’s school years were marked with a perennial struggle between academic and sporting pursuits. He was an adept and successful athlete, excelling in winter sports, such as cross-country skiing, a useful skill in Yamanashi’s Southern Alps. His competitive nature, honed by his rise up to national representative levels in skiing, also helped him succeed in his academic endeavours. His sound educational training in Nirasaki led him to qualify for entry to the Faculty of Liberal Arts and Sciences at the University of Yamanashi – perhaps an omen of things to come, as Satoshi has maintained a deep interest in both science and art throughout his life. As many sportsmen will attest, life in university often becomes difficult because of the huge amount of time that needs to be devoted to training and competing. But vital lessons in learning about one’s own limits and capabilities in dealing with times in competitions when all seems impossible or beyond one’s own limits, can easily be applied to academic challenges, and so Satoshi honed the mental fortitude to succeed in his educational and academic work. Thanks to Professor Senjiro Marut, who would become one of the several key mentors in his life, Satoshi quickly developed an interest in organic chemistry. He also learned about himself, how to try and exceed his limits where possible, to devise his own original approach and methods, based on the evidence of others, but to do things originally, to ‘think differently’ and, furthermore, to apply those novel thoughts to overcome obstacles, no matter where or when he encountered them.  After graduating, Satoshi began teaching evening classes at a high school in Tokyo. He was deeply impressed by the fact that many of his students attended classes and worked with oil-stained and callous hands, having already been working for a whole day at their predominantly menial jobs, but determined to study and improve their prospects. This stimulated him to also consider how he could best advance his own prospects. However, he quickly became concerned that his sporting efforts may have diminished his scholarly expertise and teaching abilities, so he became determined to recommence his studies to allow himself to teach with greater proficiency for the benefit of his students. He started at the Tokyo University of Education (currently the University of Tsukuba), where he studied chemistry under Professor Koji Nakanishi – a leading expert in the field of natural products organic chemistry and Professor Yojiro Tsuzuki of the Tokyo University of Science, whose laboratory was involved in investigations of the chemical structure of organic compounds using nuclear magnetic resonance (NMR) – a truly cutting-edge technology at the time. While today NMR is commonplace, in those days there was only one such machine nationwide, located at the Tokyo Industrial Laboratory. Although it was used during the daytime by researchers, Satoshi was allowed access to the equipment at night. Working throughout the early morning hours, Satoshi became skilled at analysing the molecular and stereoscopic structures of chemical compounds. His schedule became university study during the day, teaching at night and conducting NMR experiments until dawn.  Despite his exhausting schedule, Satoshi still managed to find time to meet and marry his wife, Fumiko. Throughout those taxing times, Fumiko was a source of great support, often cooking and bringing his evening meal to the laboratory. In addition, Fumiko was a mathematics teacher and an expert with an abacus, to the extent that Satoshi often telephoned her and read out some data which she swiftly computed – without the need of a computer.  It took him 5 long years to obtain his M.S. degree but the extensive knowledge and technical skills acquired during that period became an invaluable foundation for all his later research work. Satoshi eventually received his Masters degree from the Tokyo University of Science in 1963, followed by a Ph.D. in Pharmaceutical Sciences (1968) from the University of Tokyo, and a further doctorate in Chemistry in 1970 from the Tokyo University of Science.  Satoshi began his career as a Research Associate at Yamanashi University in 1963, when he started working in the laboratory of Professor Motoo Kagami in the Department of Fermentation Technology at the University of Yamanashi. The post was arranged by Professor Senjiro Maruta, a mentor from his undergraduate days. Professor Kagami was conducting research on wine and Satoshi recalls being indelibly awed and inspired by yeast microbes that could transform sugar into alcohol overnight, much quicker than even the best of chemists. So began his career-long fascination with, and admiration and respect for, microorganisms.  Two years later, in a quest for a more stimulating environment to facilitate research into microorganisms, Satoshi embarked on his career-long association with the Kitasato Institute. Thus, from 1965 onwards, he has been actively engaged in comprehensive research in the field of bioorganic chemistry, focusing on bioactive substances of microbial origin. Satoshi was a key team member of the Kitasato team due to his expertise in the structural determination of chemicals developed through his NMR work. Under the guidance of Institute Director Toju Hata, the first chemical compound he determined the structure of was the antibiotic Leucomycin. He subsequently accomplished the isolation and structural determination of Cerulenin, a compound with antifungal properties but which, based on the compound’s structure which he identified, Satoshi believed should be able to inhibit lipid biosynthesis. He later confirmed this to be the case. Cerulenin, produced by a true fungus, *Acremonium caerulens*, proved to be the first inhibitor of fatty acid (lipid) biosynthesis ever found. It became the lead compound for development of the medically important statins, inhibitors of cholesterol biosynthesis and it remains a pivotal research reagent to this day.  Satoshi quickly realised that this line of work could only be carried out once someone had actually discovered a new compound. He also recognised that finding chemical compounds produced by microbes was a time-consuming and painstaking task. This represented a new challenge that deserved his attention, even though he was, essentially, a chemist. It also meant devising a completely different approach. So began his foray into the development and application of novel screening methods – methods not just to discover antibiotics, but to find any chemical that might be useful to human health and other fields, no matter what they may be. As an example, Satoshi knew that the biosynthesis of alkaloids, which often have specific and pronounced bioactivities, usually follows complex pathways and includes stereospecific steps. Alkaloids (e.g. quinine, atropine, morphine) or alkaloid-containing plants have been used for centuries as remedies, poisons and psychoactive substances. Consequently, he devised a plan to search for alkaloids using Dragendorff ‘s reagent, which simply changed colour in the presence of any alkaloid. Subsequent determination of the structures of any chemical compounds isolated from microbes facilitated identification and understanding of their bioactivity and other properties. Implementing this coordinated approach led him to discover staurosporine, the first indolocarbazole ever identified, which he found had some interesting bioactivity. Indicative of his thinking of working for others, a decade later staurosporine was found by another research group to be the world’s first compound capable of preventing the functioning of protein kinases. This revolutionised the search for anticancer agents, staursporine being the lead compound for development of imatinib (Gleevec®) and several other alkaline chemicals that have been developed into the novel anticancer agents currently in widespread and highly successful clinical use. Staurosporine is said to be the most widely used biochemical reagent originating from a naturally-occurring microorganism, with the number of scientific papers based on staurosporine research averaging over 600 annually during the past 20 years.  He also introduced an innovative cell-based screening technique using specific live animal cells. Hymeglusin (1987), a cholesterol biosynthesis inhibitor, and triacsin (1986), an inhibitor of the acyl-CoA synthetase that activates fatty acids, were found using Vero cells and yeast mutants. Diazaquinomycin (1982), an antimetabolite of folic acid, was found using folate-requiring cells. Exploiting a method that used cancerous neuroblast cells from mice, he looked for substances that induced dendrites in such neuroblasts. This approach led to the discovery of Lactacystin, which was found to be an inhibitor of Proteasomes. Lactacystin quickly became a globally renowned research reagent, utilised by a phalanx of researchers, including some past Nobel Laureates. Satoshi’s success in this field is manifest in the fact that the Nobel Laureate chemist, [E.J. Corey](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1990/corey-facts.html), named an active derivative of lactacystin (clasto-lactacystinβ-lactone) as omuralide.  In 1971, Satoshi decided to take a sabbatical and work overseas in order to exploit new opportunities to further his work and discoveries. With the help and guidance of Professor Yukimasa Yagisawa, he arranged a lecture tour of universities in Canada and the US and approached them to investigate the possibility of a research position. Receiving a favourable response from all of them, he was attracted by a proposition to work with Professor Max Tishler, ex-Director of Merck, Sharp and Dohme Research Laboratories (MSDRL), who had retired and was setting up a new chemistry department at Wesleyan University in Connecticut. When he arrived to take up his post as Visiting Research Professor, circumstances quickly evolved that would allow him to effectively carry out his research as he pleased as well as meet a continuous flow of leading international chemistry experts who were visiting Professor Tishler, who was so busy that he effectively asked Satoshi to help oversee the running of the laboratory. This led to Satoshi meeting and collaborating with Professor Konrad Bloch of Harvard University, resulting in a joint publication on cerulenin.  Although he was originally scheduled to stay at Wesleyan for three years, the Kitasato Institute recalled Satoshi after a mere 14 months to take over the running of the institute’s research programme following the retirement of the existing director. At that point, Satoshi realised that he had to try and secure funding to support the advanced work that he wished to do in Japan and so embarked on a whistle-stop tour of National Institutes of Health (NIH) and several major drug companies in search of funds and to promote the concept of joint research. His idea was to obtain research funding from a corporate sponsor to facilitate and expedite discovery of useful chemical compounds. Development and usage rights would be transferred to the company and, following any commercialisation of a compound, royalties commensurate with the resulting sales income would be paid to Satoshi’s research group.  Thanks primarily to his friend and mentor, Max Tishler, Satoshi was able to establish a mutually favourable arrangement with Merck & Company, which allowed optimal exploitation of the comparative advantages of each partner in what would become a pioneering private sector/public sector collaboration. Within the partnership, the Kitasato Institute was responsible for collecting soil samples, identifying unique or promising microbes, isolating and screening chemical compounds and conducting in-vitro evaluations. Merck handled animal testing (in vivo) in innovative animal models, development, production, marketing and distribution. The initial target was to develop drugs for use in livestock and other animals.  The partnership also encompassed a common philosophy – the Kitasato Institute credo, established by Shibasaburo Kitasato, the father of serotherapy, being ‘the basis of medicine should be the prevention of disease and that achievements obtained by medical research should be actively applied and widely used to improve public health.’ Merck’s mission statement was ‘to provide society with superior products and services’, with George W. Merck’s avowed approach being ‘we try never to forget that medicine is for the people. It is not for the profits.’  The collaboration produced a variety of new compounds but of greatest significance was avermectin, produced by *Streptomyces avermectinius*, and the dihydro-derivative ivermectin. The producing microorganism was isolated from a soil sample collected on the periphery of a golf course at Kawana in Ito City, Shizuoka Prefecture. The microbe was sent to MSDRL in the US where it was found to display superior antiparasitic activity against the nematode worm, *Nematospiroides dubius*, in MSDRL’s unique mouse model. The actinomycete was originally named *Streptomyces avermitilis* (later changed to *avermectinius*) and the active substance was named avermectin. Avermectin represented a completely new class of compound, designated as an ‘Endectocide’, as it killed a range of different parasites inside as well as outside the body. It was also capable of killing insect vectors.  The safer and more potent ivermectin proved to be a remarkable macrolide anthelmintic antibiotic for veterinary use and was introduced onto the animal health market in 1981. Two years later, it became the world’s biggest selling veterinary drug, a position it maintained for over 20 years. In time, and after its unmatched success in animal health, ivermectin was found to be a remarkably effective and safe drug for combating diseases caused by filarial parasitic worms in humans. The world’s gravest intractable human filarial diseases were Onchocerciasis (commonly known as River Blindness) and Lymphatic filariasis (commonly known as Elephantiasis). The control – and subsequently, eradication – programmes for these two devastating, disfiguring and stigmatising tropical diseases, which afflict around 1 in 7 of the entire world population, are based primarily on the use of ivermectin, which is being donated free of charge for as long as it is required. Orchestrated by the World Health Organization (WHO), ivermectin, under the brand name Mectizan®, is being administered to almost 300 million people annually in some of the world’s poorest and remotest of communities. It is envisaged that Onchocerciasis will be eliminated globally by 2025 (if not sooner) and Lymphatic filariasis by 2020. With respect to Onchocerciasis, disease elimination has virtually been completed in Latin America and is well on the way to success in Africa. The *S. avermectinius* organism discovered by Satoshi in a single sample of Japanese soil remains the only avermectin-producing organism ever found, meaning that single organism has been the sole source of industrial production ever since.  Fortunately, Japan is no longer affected by either of these diseases, Lymphatic filariasis having been eradicated from the country several decades ago.  Merck & Co. Inc. currently supplies enough ivermectin to treat over 250 million people annually free of charge, with both these diseases now in great decline. Ivermectin tablets need to be taken only once a year, which makes it relatively easy to deliver the drug to people in hard-to-reach, poverty-stricken communities. One other key factor is the drug’s efficacy at low doses without side effects, the drug is extremely safe and so can be given without the need for medical supervision.  Ivermectin has freed up vast tracts of fertile riverside land for cultivation, creating a secure food supply and work for tens of millions of Africans. With ivermectin preventing blindness and enabling people to continue to farm and work, they are able to experience better living conditions. Thanks to this and other supporting factors, today’s African children belong to a generation whose eyesight is comparatively safe, and who will not suffer from disfigurement, lost educational opportunities or social stigma arising from either Onchocerciasis or Lymphatic filariasis. In 2004, Satoshi visited Burkina Faso and Ghana to see in person the immeasurably beneficial impact ivermectin distribution was having on remote rural communities and where, to his surprise, he witnessed conditions similar to those he experienced growing up in rural Yamanashi.  Alongside his discovery work, Satoshi has studied in depth the mechanisms used by microorganisms to produce various kinds of substances, in particular carrying out extensive research at the genetic level. His elucidation and application of the genetic control of chemical compound formation has made it possible to manipulate living microorganisms to produce novel compounds, as well as creating the potential and ability to produce completely synthetic compounds.  As an example of this, Satoshi and his co-workers obtained various mutants of *S. avermectinius* in which part of the biosynthetic pathway of avermectin was blocked. They determined the production pathway by isolating various precursors accumulated in each mutant. Each mutated point on the chromosome was identified, eventually allowing the cloning of all 17 genes concerned with avermectin biosynthesis. Furthermore, the work clarified the function of each gene, providing a complete understanding of the biosynthetic mechanism for producing avermectin. The ground-breaking genetic analysis of *S. avermectinius* was the world’s first for a commercially-important actinomycete, and it also demonstrated that the actinomycete has genes which produce 37 kinds of organic compounds (secondary metabolites), besides the immeasurably important avermectin.  Following Satoshi’s lead, creation of novel compounds using genetic engineering is now routinely carried out. His original work and continued pioneering research in this area resulted in the appearance of Mederrhodin, created by Satoshi in partnership with England-based Dr David A. Hopwood. This remarkable compound was the first novel synthetic antibiotic created using genetic engineering and is worthy of recognition as being the pioneer compound in a completely new research field with almost limitless potential.  Over the past five decades, Satoshi’s drug discovery group at the Kitasato Institute has undertaken advanced and pioneering research based on the profound belief that organic compounds produced by microorganisms have immeasurable promise for use in improving the welfare and health of mankind. His creation and introduction of several highly original methods of isolating useful microorganisms, has led to the discovery of 53 new species of microbes, including 13 novel genera, such as the *Kitasatosporia*, *Longispora* and *Arbophoma.*  Exploiting a broad spectrum of often newly discovered microorganisms isolated predominantly from soil samples, he has discovered around 500 novel organic compounds possessing interesting chemical structures and/or bioactivities, including many now widely-used antibiotics (all indexed and detailed in *Splendid Gifts from Microorganisms, 5th Ed.*, 2015). Among them, 26 compounds and/or their derivatives have entered into widespread common usage as medicines, agents to improve animal health and husbandry, as agrochemicals and as reagents for biochemical research.  Satoshi has also built up an excellent body of research findings on the relationships between chemical structure, bioactivity and mode of action of many macrolide antibiotics, such as leucomycin, tylosin, spiramycin and erythromycin. Among them, rokitamycin, a derivative of leucomycin, together with tilmicosin, a derivative of tylosin, have been used with great effect as human medicines and in animal health.  Overall, the natural organic compounds which have appeared as a result of Satoshi Ōmura’s initiatives and endeavours have been used worldwide as medicines, agrochemicals and reagents for biochemical research, and have greatly contributed to progress in the welfare and health of mankind, as well as being essential elements in making major steps forward in biomedical knowledge and understanding possible.  Since 1965, when Satoshi joined the Kitasato Institute as a researcher, he has occupied various posts, culminating in his appointment in 1990 as President, serving as President Emeritus from 2008 to 2012. He has an exemplary record of fundraising and administrative management of the institute, which was in an extremely healthy shape when his tenure as President came to an end. He is currently a Distinguished Emeritus Professor and Special Coordinator of the Research Project for Drug Discovery from Natural Products in the Kitasato Institute for Life Sciences, Kitasato University, where he is fully engaged in the continuing search for the treasures that still lie undetected in nature. He was also appointed as inaugural Max Tishler Professor of Chemistry at Wesleyan University (USA) in 2005, a post that he still holds.  Satoshi is being continually recognised internationally in the field of natural products chemistry, and for the application of his discoveries, as evidenced by his numerous awards and honours. Among these are the Hoechst-Roussel Award from the American Society for Microbiology, the Charles Thom Award (Society for Industrial Microbiology, USA), the Robert Koch Gold Medal (Germany), the Prince Mahidol Award (Thailand), the Japan Academy Prize, the Nakanishi Prize of the Japan Chemical Society and American Chemical Society, the Ernest Guenther Award of the American Chemical Society, the Hamao Umezawa Memorial Award of the International Society of Chemotherapy, the Tetrahedron Prize for Creativity in Organic Chemistry, the Arima Award of the International Union of Microbiological Society, the Research Achievement Award of the American Society of Pharmacognosy, the 2014 Canada Gairdner Global Health Award, the Asahi Prize – and now the Nobel Prize in Physiology or Medicine. In 2007 he was decorated with France’s Chevalier de L’Ordre National de la Legion d’Honneur award. In 2012 he was designated as a Person of Cultural Merit in Japan, followed by the Order of Cultural Merit in 2015.  He is a member of the Japan Academy, the German Academy of Sciences Leopoldina and the European Academy of Sciences and is a Foreign Associate of the US National Academy of Sciences, the French Academy of Sciences, and the Chinese Academy of Engineering.  His honorary memberships include those of the American Society of Biochemistry and Molecular Biology, the Royal Society of Chemistry, the Chemical Society of Japan, the Japanese Society for Actinomycetes, the Japan Society for Bioscience, Biotechnology and Agrochemistry, as well as his Special Honorary Membership of the Japanese Society of Bacteriology.  Since 1973, he has been a long-standing member of the Editorial Board of the Journal of Antibiotics, serving as an Editor-in-Chief from 2004 to 2013 and now as Editor-in-Chief Emeritus. He has published well over 1,000 scientific articles, and continues to publish extensively. Among his publications, the *Macrolide Antibiotics* (2nd edition) remains a world-leading textbook. He has also published several volumes of personal essays and annually produces his own personalised calligraphy.  Satoshi retains his commitment to engage and groom young researchers in the field of natural product research and to educate them in the correct approach with respect to scientific research, multidisciplinary collaborations and the fundamental importance of good interpersonal associations in working partnerships. As an example of this, 20 years ago, he established the Yamanashi Academy of Sciences in his home prefecture. As part of the academy’s operations, 130 high-ranking scientific members regularly visit local schools and colleges to give presentations, meet students and try and encourage them to take up and pursue an interest in the natural sciences.  Although his cross-country skiing days are now behind him, Satoshi is a consummate golfer, when he can find the time. He remains a long-standing and leading patron of Japanese art, remaining very active in this sphere of activity. Having held the post of President of the Joshibi Women’s Art University for over 14 years, Satoshi has long championed the concept of Healing Art, it being increasingly accepted that artwork helps create an environment which promotes healing. The extensive collection of original artworks, predominantly by Japanese artists, he has assembled is displayed on the walls of all the hospitals and laboratories with which he is connected. He has also designed and constructed his own art museum, which is open to the public and which he has bequeathed to his hometown of Nirasaki. (see: <http://www.nirasakiomura-artmuseum.com/> – Japanese only). He also constructed and opened a hot spring facility there because he has always felt the need to repay his hometown for everything that it gave him. He profoundly believes that his life as a scientific researcher is inherently linked to the region where he was born and raised and where his approach to life and wonderment and respect for Nature was instilled in him from a very early age. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0521=SŌ  [Satoshi Ōmura] Hello, is this Satoshi Ōmura.  [Adam Smith] Hello, my name is Adam Smith, calling from Nobelprize.org, the official website of the Nobel Prize. First of all many congratulations on the award of the Nobel Prize.  [SŌ] Thank you very much, I humbly accept it. Very surprised [Laughs].  [AS] What is your reaction to the award of the Nobel Prize?  [SŌ] So, there are many, many researcher who made very important research. My research is not so effective to get the Nobel Prize. But I did good things, but maybe there are many, many good researchers in the world. But anyway I may be very, very lucky so far.  [AS] [Both Laugh] It’s a very happy day.  [SŌ] Yeah, very happy.  [AS] And you have devoted your whole life to finding gifts from nature, microorganisms that give us …  [SŌ] Yes, and I think maybe my belief is correct, that microorganisms are very important in the nature and just I learn from microorganisms.  [AS] And I believe you found the microorganism that gave us Ivermectin on the local golf club.  [SŌ] [Laughs] People believe that because I’m fond of golf, but really I think close to the golf course, very close to the golf course. Sometimes maybe we can say in the territory of the golf course. But in the golf course there may be grass and sand, but sometimes wood, we took it near wood.  [AS] OK.  [SŌ] People believe that I’m playing golf in the grass. Maybe, but it’s not grass.  [AS] [Laughs] It’s a nice story. Anyway, its a great pleasure to speak to you, we very much look forward to welcoming you to Stockholm in December.  [SŌ] OK, I’m looking forward to it.  [AS] Thank you, I wish you a lovely evening in Japan.  [SŌ] Thank you very much for calling me.  [AS] Thank you, goodbye. |
| Interview |  |
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| ID | 0522 |
| Biographical | **My Childhood** I was born on December 30, 1930 in Ningbo, a city on the east coast of China with a rich culture and over seven thousand years of history. Although it was a tumultuous age in China when I was a child, I was lucky enough to have completed a good education from primary to middle school.  My father worked in a bank while my mother looked after my four brothers and me, the only girl in our family. According to a recently discovered family tree, my ancestors lived in Ningbo for many generations. Our family’s long history of highly valuing children’s education and always considering this as the family’s top priority allowed me to have good opportunities for attending the best schools in the region – from the private Ningbo Chongde Primary School (1936–1941) and later the private Ningbo Maoxi Primary School (1941–1943) to the private Ningbo Qizheng Middle School (1943–1945) and the private Ningbo Yongjiang Girls’ School (1945–1946).  I unfortunately contracted tuberculosis at the age of sixteen and had to take a two-year break and receive treatment at home before I resumed my study at the private Ningbo Xiaoshi High School (1948–1950) and Ningbo High School (1950–1951). This experience led me to make a decision to choose medical research for my advanced education and career – if I could learn and have (medical) skills, I could not only keep myself healthy but also cure many other patients. After graduation from high school, I attended the university entrance examination and fortunately I was accepted by the Department of Pharmacy and became a student at the Medical School of Peking University. **My university life** My choice of learning pharmacy was driven by my interests, curiosity, and a desire to seek new medicines for patients. In 1941, an Institute of Chinese Materia Medica was found at Peking University. The institute late developed into the Department of Pharmacy in the Medical School in 1943. In 1952, the second year of my university training, the Medical School was divided from Peking University and became the independent Beijing Medical College. By that time, significant efforts and investment were made in building the university’s infrastructure and curriculum. Most pharmacy courses such as pharmacognosy, medicinal chemistry and phytochemistry were designed and taught by returnees such as Professors Lin Qishou (林启寿) and Lou Zhicen (楼之岑) who had received educations and advanced degrees in Western countries. Although pharmacognostical study or called “crude drugs” was my major, my training was not limited to that field and I had great chances to attend all basic training in the pharmaceutical sciences. In the pharmacognosy course, Professor Lou Zhicen conveyed knowledge on the origins of medicinal plants and trained us how to classify, distinguish and identify these plants based on their botanical descriptions etc. In the phytochemistry course, Professor Lin Qishou gave a comprehensive introduction and hands-on training on how to extract active ingredients from the plants, how to select proper extraction solvents, how to carry out chemistry studies and determine the structures of the chemicals isolated from the plants etc. These courses provided scientific insights into the herbs and plants and more importantly, explained how these herbal medicines work, in a way different from traditional Chinese medicine. **My first job and life-long commitment** This December, we celebrated the 60th anniversary of the China Academy of Chinese Medical Sciences (CACMS). This was also the 60th anniversary of my career. After graduation from the university in 1955, I was assigned to work in the Institute of Chinese Materia Medica of the newly established Academy of Traditional Chinese Medicine under the China Ministry of Health. The academy has been growing and expanding rapidly over last sixty years along with change of its name from the Academy of Traditional Chinese Medicine to the China Academy of Traditional Chinese Medicine and now the China Academy of Chinese Medical Sciences. However, its mission of focusing on professional training, research and continuous exploring and development of Chinese medicines for human healthcare through utilization of evolving sciences and technologies has never changed. It is the academy’s mission and establishment that have provided me with good opportunities to utilize my knowledge, skills and experience while being exposed to new areas of research.  My first research project was on *Lobelia chinensis* (半边莲), an herb commonly prescribed in the traditional Chinese medicine for the treatment of *Schistosomiasis*, a disease caused by *Schistosoma* type parasitic flat worms. In fact, my first publication was on the pharmacognostical study of *Lobelia chinensis*, coauthored with my mentor, Professor Lou Zhicen, in 1958. I completed another study on pharmacognostical evaluation of *Radix Stellariae* (银 柴 胡) before I went for a full-time training program on Chinese medical theory and practice organized by the Ministry of Health for professionals with a Western (modern) medical background between 1959 and 1962. This training further added in-depth knowledge on traditional Chinese medicines to my Western medical background.  Over the last sixty years, I have held different responsibilities at the academy, from head of the Chemistry Department (1973–1990) to head of the Artemisinin Research Center of the China Academy of Chinese Medical Sciences (1997–) and various academic assignments from associate professor (1979–1985), professor (1985–), and now chief professor of the China Academy of Chinese Medical Sciences. **Western and traditional Chinese medicine – a unique combination** China lacked medical resources in the early 1950s. There were only around twenty thousand physicians and several tens of thousands of traditional Chinese medical practitioners in the country. To fully utilize these limited resources and explore Chinese medicines, the national leadership launched programs in an effort to promote the ideas of enhancing the healthcare services through a “combination of Western and traditional Chinese medicines.” Medical school graduates or young doctors were encouraged to learn traditional Chinese medicines, while experienced traditional Chinese medical practitioners were asked to enrich their knowledge by attending training courses on Western medicine. This unique combination not only proved beneficial to patients but also enabled further exploration and development of Chinese medicine and its application through modern scientific approaches.  The Ministry of Health of China organized a number of full-time training courses in the late 1950s in which scientists with Western medical backgrounds were given opportunities for systemic training on the traditional Chinese medicine. In my two and a half year training program, I learned traditional Chinese medical theory and gained experience from clinical practice. Another training program I attended was on the processing (炮制) of Chinese Materia Medica.  This processing skill is a unique and exclusive pharmaceutical technology and has been widely used for the preparation of Chinese materia medica. The traditional way of processing was developed and summarized from thousands of years of experience in the traditional Chinese medical practices, with a belief that processing could alter the properties and functions of remedies, increase medical potency and reduce toxicity and side effects. In fact, differences in chemical compositions have been detected between herbs treated with different processes. Knowledge of such processing, in combination with the scientific explanation, benefited my work enormously. **Assignment of the antimalarial research task** Malaria is a life-threatening epidemic disease. It was, however, effectively treated and controlled by chloroquine and quinolines for a long period of time until the development of drug-resistant malaria *plasmodium* parasites, namely *plasmodium falciparum*, in the late 1960s following the catastrophic failure of a global attempt to eradicate malaria. Resurgence of malaria and rapidly increased mortality posed a significant global challenge, especially in the South East Asian countries. In the 1960s, the Division of Experimental Therapeutics at the Walter Reed Army Institute of Research (WRAIR) in Washington, DC launched programs to search for novel therapies to support the US military presence in South East Asia. US military force involved in the Vietnam War suffered massive casualties due to disability caused by malaria infection. Up to 1972, over 214,000 compounds were screened with no positive outcomes.  In China, the military institutes started confidential antimalarial research in 1964. In 1967, the Chinese leadership set up a group office for malaria control (abbreviated as the National 523 Office) to coordinate nationwide research. Several thousand compounds were screened between 1967 and 1969 but no useful medicines were found.  In 1969, two directors and another member from the National 523 Office visited the Academy of Traditional Chinese Medicine and the Institute of Chinese Materia Medica, seeking help in searching for novel remedies among Chinese medicines.  It was in the middle of the great cultural revolution in China. Almost every institute was impacted and all research projects were stalled. A lot of experienced experts were sidelined. After thoughtful consideration, the academy’s leadership team appointed me to head and build a Project 523 research group at the Institute of Chinese Materia Medica. My task was to search for antimalarial drugs among traditional Chinese medicines.  As a young scientist, I was so overwhelmed and motivated by this trust and responsibility. I also felt huge pressure from the high visibility, priority, challenges as well as the tight schedule of the task. The other challenge was the impact on my family life. By the time I accepted the task, my elder daughter was four years old and my younger daughter was only one. My husband had to be away from home attending a training campus. To focus on research, I left my younger daughter with my parents in Ningbo and sent my elder daughter to a full-time nursery where she had to live with her teacher’s family while I was away from home for the project. This continued for several years. My younger daughter couldn’t recognize me when I visited my parents three years later, and my elder daughter hid behind her teacher when I picked her up upon returning to Beijing after a clinical investigation. **Traditional Chinese medicine and its relevance to malaria** Our long journey searching for antimalarial drugs began with collection of relevant information and recipes from traditional Chinese medicine.  Malaria was one of the epidemic diseases with the most comprehensive records in traditional Chinese medical literature, such as *Zhou Li* (周礼), a classical book in ancient China published in the Zhou Dynasty (1046–256 B.C.). Other literature includes the *Inner Canon of the Yellow Emperor* (黄帝内经) published around the time of the Chun Qiu and Qin Dynasties (770–207 B.C.), the *Synopsis of Prescriptions of the Golden Chamber* (金匮要略) published in the Han Dynasty (206 B.C–220 A.D.), the *General Treatise on the Causes and Symptoms of Diseases* (诸病源候论) published in the Sui Dynasty (581–618 A.D.), the Qian Jin Fang or *Prescriptions Worth a Thousand Pieces of Gold* (千金方) and the Wai Tai Mi Yao or *Secret Medical Essentials of a Provincial Governor* (外台密要) published in the Tang Dynasty (618–907 A.D.), a book on malaria (痎疟论疏) published in the Ming Dynasty (1368–1644 A.D.) and the *Malignant Malaria Guide* (瘴疟指南) published in the Qing Dynasty (1644–1911 A.D.), the *Prescription for Universal Relief* (普济方) published in the Ming Dynasty, 1368–1644 A.D.), *etc*.  After thoroughly reviewing the traditional Chinese medical literature and folk recipes and interviewing experienced Chinese medical practitioners, I collected over two thousand herbal, animal and mineral prescriptions within three months after initiation of the project. From these two thousand recipes, I summarized 640 prescriptions in a brochure entitled “Antimalarial Collections of Recipes and Prescriptions” (抗疟单秘验方集). I circulated copies of the brochure to other research groups outside the institute for reference through the national project 523 office in April 1969. **A handful of qinghao immersed in two liters of water, wring out the juice and drink it all (青蒿一握, 以水二升渍, 绞取汁, 尽服之)** We started our experiments on dichroine using animal models. The study was soon stopped due to its severe side effects. From May 1969, extracts of over hundred herbs were prepared and tested in rodent malaria, with few promising results found up to June 1971.  After multiple experiments and failures, I re-focused on reviewing the traditional Chinese medical literature. One of the herbs, Qinghao (青蒿) (the Chinese name for the herbs in the *Artemisia* family), showed some effects in inhibiting malaria parasites during initial screening, but the result was inconsistent and not reproducible. I repeatedly read relevant paragraphs in the literature where the use of Qinghao was recorded as relieving malaria symptoms.  In Ge Hong’s *A Handbook of Prescriptions for Emergencies* (肘后备急方), I noticed one sentence “A handful of Qinghao immersed in two liters of water, wring out the juice and drink it all” (青蒿一握, 以水二升渍, 绞取汁, 尽服之) when Qinghao was mentioned for alleviating malaria fevers. Most herbs were typically boiled in water and made into a decoction before taken by the patients.  This unique way of using Qinghao gave me the idea that heating during extraction might have destroyed the active components and the high temperature might need to be avoided in order to preserve the herb’s activity. Ge Hong’s handbook also mentioned “wring out the juice.” This reminded me that the leaf of Qinghao might be one of the main components prescribed. I redesigned experiments in which the stems and leaves of Qinghao were extracted separately at a reduced temperature using water, ethanol and ethyl ether. **Sample no. 191, a symbolic breakthrough in artemisinin discovery** We produced extracts from different herbs including Qinghao using the modified process and subsequently tested those ethyl ether, ethanol and aqueous extracts on rodent malaria. On October 4, 1971, we observed that sample number 191 of the Qinghao ethyl ether extract showed 100% effectiveness in inhibiting malaria parasites in rodent malaria. In subsequent experiments, we separated the extracts into a neutral portion and a toxic acidic portion. The neutral portion showed the same effect when tested in malaria-infected monkeys between December 1971 and January 1972.  On March 8, 1972, I reported these findings at the National Project 523 meeting held in Nanjing. This encouraging news evoked overwhelming interest from antimalarial drug research teams across the country. **“Shen Nong tasted hundred herbs,” why couldn’t we?** Starting in March 1972, the team started to produce large quantities of Qinghao extract in preparation for clinical studies. Most pharmaceutical workshops were shut down during the great cultural revolution. Without manufacturing support, we had to extract herbs ourselves using household vats etc. The team worked very long hours every day including the weekends. Due to lack of proper equipment and ventilation, and long-term exposure to the organic solvents, some of my team members included myself started to show unhealthy symptoms. This, however, did not stop our efforts.  Some conflicting information was seen from the animal toxicological studies. It was already in the middle of the summer and very limited time was available to us before the malaria epidemic season would end. We would have to delay the study for at least a year if we continued our debate on toxicity. To expedite the safety evaluation, I asked to take the extracts voluntarily. The leaders at the institute approved my request. In July 1972, two other team members and myself took the extracts under close monitoring in the hospital. No side effect was observed in the one-week test window. Following the trial, another five members volunteered in the dose escalation study. This safety evaluation won us precious time and allowed us to start and complete the clinical trial in time.  Traditional Chinese medicine started with a story: “Shen Nong tasted a hundred herbs.” Shen Nong was an ancient Chinese medical practitioner. To understand the efficacy and toxicity of the herbs, he tasted over a hundred herbs himself and recorded all the details, which left us with a lot of precious information. Although Qinghao was prescribed as an herbal medicine for thousands of years, the dose of the active ingredients in these prescriptions was much lower than that in the Qinghao extract we tested. Our desire to get the clinical trial completed and have the medicine for our patients as soon as possible was the real driving force behind our action. **Success in the first clinical trial** The first clinical trial on the Qinghao extract was carried out in Hainan province between August and October 1972. We treated a total of twenty-one local and migrant malaria patients, nine infected by *Plasmodium falciparum*, eleven infected by *Plasmodium vivax* and one with mixed malaria infections.  The patients were divided into three groups with different dose regimens. We closely monitored the patients’ body temperature and the changes in the numbers of parasites in their blood specimens. The trial was successful: all patients recovered from the fevers and no malaria parasites were detected after treatment. Nine malaria patients were also successfully treated with the Qinghao extract in Beijing No. 302 hospital.  The results from the first clinical trial in Hainan and Beijing No. 302 hospital were reported in the National Project 523 meeting held in Beijing in November 1972. The success of the first clinical trial and previous evidence observed in rodent malaria and monkey studies steered nationwide antimalarial drug research toward Qinghao. **Artemisinin and dihydroartemisinin** We started isolation and purification of neutral Qinghao ethyl ether extract parallel with the clinical trial in 1972. Between April and June of 1972, a few crystals were isolated from the extract. The team finally isolated several crystals using silica gel column chromatography in November 1972, of which one showed effectiveness against malaria. The compound was later named artemisinin, or Qinghaosu (青蒿素) in Chinese.  We carried out a clinical trial of artemisinin between August and October 1973 using artemisinin tablets, which however did not yield the desired results. We examined the tablets returned from the clinical center and found that the tablets were too hard to disintegrate. We resumed the study using artemisinin capsules at the end of September 1973. Since it was already toward the end of the epidemic season, we only treated three patients and all of them recovered after administration of artemisinin capsules.  Dihydroartemisinin was found in September 1973 in an experiment where I tried to derivatize artemisinin for a structural activity relationship evaluation. The carboxyl group related peak disappeared and was replaced by the hydroxyl group related peak in the IR spectrum after a reduction reaction using sodium borohydride. This experimental result was verified in a repeat experiment carried out by team members. In a subsequent test in rodent malaria, we noticed that a significantly reduced dose was sufficient to achieve the same efficacy as artemisinin when dihydroartemisinin was administered.  We completed a series of development activities on the chemistry, pharmacology, pharmacokinetics, stability, and clinical trials on artemisinin and dihydroartemisinin according to regulatory requirements. The China Ministry of Health granted an Artemisinin New Drug Certificate to the Institute of Chinese Materia Medica in 1986 and a Dihydroartemisinin New Drug Certificate in 1992, respectively. Dihydroartemisinin is ten times more potent than artemisinin clinically, again demonstrating the “high efficacy, rapid action and low toxicity” of the drugs in the artemisinin category. **“Bench to bedside” – collaboration expedited translation from a discovery to a medicine** We started to determine the chemical structure of artemisinin in December 1972. The first thing we verified was that the compound did not contain nitrogen. This gave us a hint that the compound we found could be a new chemical different from quinolines. The team late confirmed that the compound was a new sesquiterpene lactone containing a peroxy group with a formula of C15H22O5 and a molecular weight of 282.  In the 1970s, instruments and capabilities were very limited at each individual institute. The team at the Institute of Chinese Materia Medica collaborated with the Institute of Materia Medica, China Academy of Medical Sciences, who confirmed the formula of the artemisinin molecule. We started collaboration with the Shanghai Institute of Organic Chemistry and the Institute of Biophysics of the Chinese Academy of Sciences on artemisinin chemical structure analysis in 1974. The stereo structure was finally determined using X-ray crystallography at the Institute of Biophysics. This was one of the first applications reported in China in determining an absolute molecular configuration utilizing the scattering effects of oxygen atoms by X-ray diffraction technique.  No doubt, collaboration and collective efforts expedited the translation from discovery to new medicine. Colleagues from the Academy of Traditional Chinese Medicine, the Shangdong Provincial Institute of Chinese Medicine, the Yunnan Provincial Institute of Materia Medica, the Institute of Biophysics of the Chinese Academy of Sciences, the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences, the Guangzhou University of Chinese Medicine, the Academy of Military Medical Sciences and many other institutes made significant contributions in their respective areas of responsibility during the development process. The leadership team from the National 523 Office played an important role in ensuring logistic support and coordinating nationwide collaboration. **Qinghao and artemisia annua l.** The herb Qinghao was frequently mentioned in the traditional Chinese medical literature for various clinical applications besides alleviating malaria symptoms. These applications include relieving itches caused by scabies and scabs, treating malignant sores, killing lice, retaining warmth in joints, improving visual acuity, etc. However, little explanation was given on either the species or effective parts of the plant in the traditional Chinese medical literature.  According to plant taxonomy, there are at least six species in the *Artemisia* family: *Artemisia annua* L., *Artemisia apiacea* Hance, *Artemisia scoparia* Waldst. et kit., *Artemisia capillaries* Thunb., *Artemisia japonica* Thunb., and *Artemisia eriopoda* Bunge. The traditional Chinese medical literature only mentioned Qinghao (the general name of *Artemisia* in Chinese). By the time that our research on artemisinin was being carried out, two Qinghao (*Artemisia*) species were listed in the Chinese Pharmacopoeia and four others were also being prescribed.  We carried out a thorough investigation and confirmed that only *Artemisia annua* L. (sweet wormwood) contains artemisinin. In addition to identification of the right species, we also verified the best regions for growing Qinghao, the best collection season and the officinal part of the plant. **Our discovery saves patients’ lives while scientific communities recognize our contributions** I always feel that nothing can be more rewarding than the fact that artemisinin, since its discovery, has saved many malaria patients’ lives. Over the past several decades, more than two hundred million malaria patients have received artemisinin or artemisinin combination therapies.  The scientific community never forgets any significant contribution to healthcare. I appreciate the numerous awards granted by the government and organizations in China. This includes the Award for Progress in Antimalarial Research Achieved by the Project 523 Scientific Team by the China National Science Conference in 1978, the National Scientific Discovery Award for the Antimalarial Drug Qinghaosu by the China Ministry of Science and Technology in 1979, the Invention Award (as the first inventor) by the China National Congress for Science and Technology in 1982, the Award for Young and Middleaged Experts with Outstanding Contributions by the China State Council in 1984, the Highest Honorary Award of the China Academy of Traditional Chinese Medicine in 1992, the Top Ten National Achievements for Progress in Science and Technology award from the China State Scientific and Technological Commission in 1992, the First-rate Award of National Achievements in Science and Technology by the National Award Committee for Advances in Science and Technology in 1992, the National Model Worker award from the China State Council in 1995, the Award for Outstanding Achievement in Traditional Chinese Medicine by the Guangzhou Zhongjing Award Foundation for Traditional Chinese Medicine in 1995, the Outstanding Scientific Achievement Award by the Hong Kong Qiu Shi Science and Technologies Foundation in 1996, the Top Ten Healthcare Achievements in New China by the China Ministry of Health in 1997, the Woman Inventor of the New Century award by the China National Bureau of Intellectual Property in 2002, the Golden Medal of the 14th National Invention Exhibition by the China National Bureau of Intellectual Property in 2003, the Award for Development of Chinese Materia Medica by the Cyrus Chung Ying Tang Foundation in 2009 and the China GlaxoSmithKline Award for Outstanding Achievements in Life Science in 2011.  I sincerely thank the Prince Mahidol Award Foundation (Thailand) for presenting me with the 2003 Prince Mahidol Award, the Albert and Mary Lasker Foundation (USA) for presenting me with the 2011 Lasker-DeBakey Clinical Medical Research Award and the Warren Alpert Foundation and Harvard Medical School (USA) for awarding me the 2015 Warren Alpert Foundation Prize (co-recipient). I am, once again, sincerely grateful to the Nobel Foundation (Sweden) for awarding me the 2015 Nobel Prize in Physiology or Medicine as a co-recipient. **Research efforts continue** The discovery of artemisinin inspires us to approach research through the integration of diversified disciplines. Exploring the treasury of traditional Chinese medicine has provided us with a unique path leading to success, while utilizing modern scientific techniques and approaches are no doubt an effective and efficient way of realizing and expediting discoveries.  We are continuing our research efforts on artemisinin to understand its action mechanisms and to prevent or delay the development of artemisinintolerant or -resistant malaria. Expanding the clinical applications of artimisinin is also of interest to public health. We know what it can do, but we need to know why and how it does this, what else it can do and how it can do better … |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0522=JL  [Jin Li] Hello.  [Adam Smith] This is Adam Smith, calling from Nobelprize.org, the official website of the Nobel Prize, in Stockholm.  [JL] Yes, this is Professor Tu Youyou’s home.  [AS} So first of all, may we ask what is Professor Tu’s reaction to the award of the Nobel Prize?  [JL for Youyou Tu] Yes, Professor Tu Youyou is very glad to own the Nobel Prize.  [AS] Thank you very much. And what does the award of the Nobel Prize mean for her and for Chinese science?  [JL for TY] I’m very glad that the new anti-malaria drug artemisinin earns international recognition from the Nobel Prize committee.  Also, I want to show my gratitude and respect to Nobel Committee, Karolinska Institute and Sweden people.  Yes, Chinese people wish to win Nobel Prize for long time, and this time artemisinin win this Prize. Shows that our work to research anti-malaria drugs is at a high level and achieve good result.  So at the moment when we begin to research anti-malaria drug this old drug had already got drug resistance. As a result we worked very hard to find anti-malaria drug artemisinin and to save millions of lives. It shows that as a scientific worker we need innovation spirit to find new things.  [AS] It’s a great pleasure to speak to you and to Professor Tu, thank you very much. May we convey our …  [JL for TY] Yes, thanks, yes.  [AS] We would like to convey our congratulations and also say we are very much looking forward to welcoming her to Stockholm in December.  [JL for TY] Yes, thanks a lot.  [AS] Thank you. One last question, it’s late evening there in Beijing. Will Professor Tu have time to celebrate tonight?  [JL for TY] I have many friends to come home to share my happiness. Even for Chinese people is also a good thing, a good news for the national holiday. Thanks a lot.  [AS] Yes, it’s perfect timing, yes. Thank you very much. OK, well, Xie Xie, thank you.  [JL for TY] Thank you. Thank you very much.  [AS] Thank you, bye bye. |
| Interview |  |
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| ID | 0523 |
| Biographical | **Early Years** I was born in November 1939 in Harlem, New York to Irish immigrant parents and grew up in the South Bronx. My parents had landed in New York on the eve of the depression; my father’s hope was that I would never have to live through one myself. My mother’s passage was funded by an uncle and redeemed by seven years’ indentured labour. Neither had completed elementary school in Ireland but my father studied in the evening in New York and attained a high school degree. His dream to become an aircraft mechanic was thwarted by a shipyard accident during the war. Most of his life was spent as a nightshift mechanic on the New York bus system where he repaired the buses which became inoperative during the daytime and which couldn’t be fixed by the daytime mechanics. My mother worked as a welder in the Newark shipyards during the war, which reinforced her strong sense of confidence and mastery. Following elementary education at my local Catholic school, I won a scholarship to Regis, the academically ambitious Jesuit high school in Manhattan, while my best friends went to local Bronx schools. My time at Regis was unsuccessful. I felt like an outsider and never got to grips with Latin and Greek. Four years of poor grades and low test marks left me demoralised and prevented me from getting any help with college fees, which even then were unaffordable. So I went out to work: an entry-level clerical job in a stock brokerage house on Wall Street was followed swiftly by a bookkeeping job in the engineering department of an insurance company. I did not see this as my long-term future and decided to have another crack at the academic world. It was the era of Sputnik, aeronautical engineering was a glamorous profession, and I wanted to put as much distance between myself and the classics as I could. I spent three years studying aeronautical engineering at New York University in the evening while working in the daytime. After the first year I was lucky to attend a talk by one of the project engineers at Grumman Aircraft Corporation on Long Island who encouraged me to apply for a job there, which I duly got. I worked on several different aeroplanes, spending considerable time on the shop floor as well as at the drafting board. In the end, however, the gruelling schedule involving over 100 miles commuting a day in rush hour traffic and 12–16 hours of evening lectures per week in addition to a full-time job took its toll and I pined for the freedom of a full-time college student. It was also during this time that I became interested in philosophy through some of my non-engineering courses and decided that many of the perennial problems in philosophy might be solvable through brain research. **City College of New York and McGill University** So in 1960 I give up my job and went back to college full-time. This was a particularly difficult decision since Grumman’s response was to offer me a substantial raise and a role in the development of the Lunar Expedition Module component of the Apollo spacecraft programme, which they were preparing to tender for and eventually were awarded. A path not taken … I was fortunate to be accepted for full-time study at City College of New York, a part of the City University of New York and one of the few tuition-free colleges in the United States. At CCNY, I took courses across a wide range of subjects, paying scant attention to faculty or discipline boundaries. I studied filmmaking, advanced English literature, physics and a wide range of psychology and philosophy courses. I met my wife Eileen in an advanced philosophy course on ethics. There were of course no neuroscience courses in those days but I was fortunate to take courses in physiological psychology (as it was then called) with Daniel Lehrman, one of the early neuroethologists, and Philip Ziegler, a young enthusiastic researcher just starting his own laboratory. Phil allowed me to join his team working on the effects of lesions of the wulst on pigeon exploratory behaviour. I got a firsthand taste for experimental brain research and was hooked. During this period I supported myself working in the library, showing classic European films for various courses, and driving a taxi cab in the evening. I loved every minute of it and had no thought for the future. Eventually I was summoned to the office of an irate Dean who pointed out that I had accumulated enough credits to receive several degrees and would I please choose one and get out. I opted to major in psychology and minor in philosophy and graduated in 1963. Faced with the unthinkable prospect of working for a living again, I took the advice of one of my professors and applied for graduate school. Again I was lucky and was accepted to study in the McGill University Psychology Department, where Donald Hebb was still active and influential. Hebb was one of the founders of physiological psychology who, in his landmark book *The Organisation of Behaviour*, provided the theoretical framework which enabled us to think about the neural network basis of cognitive representations. McGill at that time was the Mecca for the study of physiological psychology. In addition to Hebb, the faculty included Peter Milner, who had discovered rewarding electrical self-stimulation of the brain with Jim Olds, Brenda Milner, whose investigations of the famous patient HM had identified the memory functions of the hippocampus, Wilder Penfield and Herbert Jasper at the Montréal Neurological Institute, who had pioneered electrical stimulation of the brain of conscious patients undergoing surgery for epilepsy, and Ronald Melzack an expert in pain who became my PhD advisor. McGill provided a wonderful environment where students were encouraged to think hard about the brain and creatively about experiments but where resources were initially extremely limited. Fortunately just after I arrived Melzack received a large grant to study alternative techniques for monitoring brain activity and generously allowed myself and Ken Casey, a postdoctoral fellow who went on to become Head of Neurology at the University of Michigan, to build a state-of-the-art electrophysiological recording laboratory. Ken also taught me the fundamentals of electrophysiology during experiments in which we looked for the midbrain targets of the ascending somatosensory projections. During my final year there I learned a considerable amount of experimental technique from Dr Herman Bouma, who had originally come to work with Hebb on vision but joined me in my amygdala project. On his return to Holland, Herman became the head of the Perceptual Research Laboratory at Phillips, Einthoven where he subsequently had a successful career discovering important principles governing reading.  During my PhD thesis work I developed techniques for recording from chronic animals and concentrated on the amygdala. Jim Olds, although he had left McGill before I got there, was revered there as the co-discoverer of self-stimulation with Peter Milner. In 1966, I learned from Ken Casey, who had visited Olds’ laboratory at Michigan as part of a job interview, that he was successfully recording from single units in awake rats using implanted microwires. I purchased the minimum order of 50,000 feet of coated nichrome microwire, set up a poor man’s version of Olds’ gold-plated lab and improved on his techniques in three ways. Firstly, I used differential recording between adjacent electrodes, which eliminated much of the movement and muscle artefact. Secondly, I introduced the use of preamplifiers made from miniature field effect transistors (which had just become available in 1965) on the animal’s head which greatly improved the signal-to-noise ratio and allowed us to move away from the thick and cumbersome microdot noise reduction cables to lightweight flexible hearing aid wires, greatly improving the animal’s mobility. Finally, I started playing with head-mounted microdrives, first at McGill but then more extensively when I went to London. Many of our early microdrives had four independently movable electrodes and it was only when Caroline Harley came to London on sabbatical and asked for a simpler single drive electrode that I developed the “poor lady’s” single-screw microdrive that we still use extensively and which is now sold by Axona. For the amygdala work, I had recorded from several silent cells for long periods (in some cases days and weeks) before discovering the specific ethological stimulus which caused them to first become active: cells there responded to highly specific stimuli approximating to the classical muchmaligned grandmother cells of Jerry Lettvin. I found mouse detectors, specific food detectors, and bird song detectors. In contrast, the more active cells were sensitive to a broader range of stimuli, for example responding to pure tones of a wide spectrum of audio frequencies. On this basis I formulated my first law of the nervous system, which is that the silent cells are the important ones. I was intellectually and methodologically prepared to tackle the hippocampus and in particular its silent cells. But not quite yet. **Postdoc at University College London** After McGill, Eileen and I decided we wanted to go to Europe and in particular to England. I originally went to University College London in 1967 as a US-NIMH postdoctoral fellow to work on somatosensation with Patrick Wall. We immediately fell in love with Britain. Our first son was born soon after we arrived and, in contrast to our experience in Québec where agencies found us insufficiently religious, the adoption of our second son proceeded smoothly a few years later. British institutions such as the National Health Service, the Ordnance Survey Map with its well-marked walking trails, and the BBC offered a cultural and social landscape that meshed with our lifestyle. University College London also proved the ideal location for me to carry out single unit recording in the freely moving animal. After my NIH Fellowship ran out, I applied for and obtained several grants from the Wellcome Trust and various British research councils which paid my salary as well as providing monies to carry out experiments. This high-risk strategy of funding my own salary as well as my research allowed me to minimise my teaching and administrative duties and maximise research time, and I carried on doing this for my entire career. I got used to letters from the University Human Resources Department advising me to prepare to exit the lab and UCL if my next grant wasn’t funded. Thankfully the emphasis now given to high-impact translational research and rapid, frequent publication had not yet gained ascendancy in those days, allowing for the funding of the risky time-consuming basic research that is my addiction.  I first began recording single units in the hippocampus following an experiment which went astray. The time was 1970 and my project was to record from the dorsal column nuclei during various behaviours in the behaving rat to see whether the descending afferents from the neocortex would modify the excitability of these first-order sensory cells. This was an extremely difficult project, since the juncture of the foramen magnum and the C1 spinal vertebra is designed to be maximally flexible and obtaining decent stable recordings was well-nigh impossible. After two years, the project was clearly not going anywhere. A much easier task would be to record from somatosensory thalamus and neocortex and that’s what I did in my spare time. During one of these experiments I tried to implant a microelectrode in the somatosensory thalamus, but the coordinates I used were too lateral and it strayed into the hippocampus. The first hippocampal cell I recorded was an interneuronal “theta” cell and I was immediately struck by the strong correlation of its activity with the hippocampal sinusoidal 8–10 Hz local field potential theta pattern on one hand and the animal’s motor behaviour on the other. I had previously made LFP recordings from the hippocampus at McGill and was aware of Case Vanderwolf’s claim that theta activity in the rat was correlated with voluntary movements. And here, at the single unit level, was striking confirmation of his claim. I decided then and there to leave the somatosensory system and begin research on the hippocampus. I was intrigued by the apparent conflict between the motor correlates of the cells at single cell level and the widely accepted memory function which had been ascribed to the hippocampus by Brenda Milner on the basis of her research with HM and which I had completely accepted. Brenda had been one of my teachers at the McGill Psychology department and I and many of the other graduate students routinely traipsed across the frozen campus to attend her lectures at the Montréal Neurological Institute.  In addition to the theta unit it was clear that there were other cells in the hippocampus which were mostly silent except for the occasional action potential to announce their presence. Again I was hooked. My amygdala-inspired first law of the nervous system was that silent cells are the important ones and here was a brain region chock-a-block full of them.  I will always be grateful to Pat Wall for allowing me to make this shift to a part of the brain which was outside his immediate field of interest. In addition to his support he signed off on grant applications and provided space for many of the early years of our hippocampal research, turning a deaf ear to the many naysayers who considered the whole approach a waste of time. **Discovery of the Place Cells** Around this time Jonathan Dostrovsky, an MSc student, joined the laboratory. We recorded single units while the animal was engaged in a wide variety of tasks including basic everyday behaviours such as eating, drinking, grooming, exploring novel environments, searching for foods as well as during simple learned tasks such as lever pressing and approaching different stimuli for food. We noticed two things almost immediately. First, there were two types of cells distinguishable on the basis of strictly physiological properties: spike amplitude and width, and baseline firing rates. As I had originally observed, many of the cells with large amplitude action potentials were silent most of the time, only occasionally showing a burst of spikes when the animal sat quietly or during slowwave sleep. These bursts occurred on large sharp wave spikes in the extracellular hippocampal LFP accompanied by a high frequency waveform which we originally called “wiggles” but quickly changed to the more euphoneous term “ripples.” When we mapped the distribution of these two potentials we found that the ripples were largest in the centre of the CA1 pyramidal cell layer but that the associated sharp wave peaked several hundred microns below in the apical dendrites of the pyramidal cells. More recently, Gyuri Buzsaki, Matt Wilson and Bruce McNaughton have suggested that ripples represent a form of replay of immediately previous spatial learning and might be involved in consolidation of recent memory traces.  It was also immediately obvious that the correlate of the second cell type, which had a much higher resting firing rate and showed a clear phase locking to the ongoing LFP theta oscillations, was a tight coupling to some aspect of movement as I had noticed on my first foray into the hippocampus. This movement correlate was not related to any single limb movement or any specific behaviour but was associated with some higher aspect of the movement such as the vigour or speed with which the movement was executed. Movements which changed the animal’s location seemed to be particularly important. It took much longer for us to identify the correlate of the major cell type, the low firing-rate pyramidal cell. Over a period of months, I began to suspect that their activity didn’t depend so much on what the animal was doing or why it was doing it but had something to do with where it was doing it. And then on one electrifying day I realised with a flash of insight that the cells were responding to the animal’s location or place in the environment. We quickly verified that changing many aspects of the environment one at a time had little effect on the locational response of the cell but if major alterations were made, e.g. by removal of the curtains surrounding the platform, the cell activity altered abruptly. In thinking about these results over the next day I was assailed by a montage of ideas about the potential significance of this finding: the first was that it might mean that the hippocampus was the neural site of Tolman’s cognitive map, a vague hypothetical construct that he had used to explain some aspects of rodent maze behaviour but which had never gained much acceptance in the animal learning field and which was little discussed in the 1960s. It was clear he had given little thought to the neural basis of this ‘map’, much less envisaged that it would be localised in a particular brain structure. This spatial map idea provided a clear function for the movementrelated hippocampal cells and the LFP theta activity, since a map would need information about higher order aspects of an animal’s behaviour such as speed in order to calculate the distance it had travelled. I decided subsequently to christen these movement-related cells “displace cells” to reflect this idea. It also dawned on me that the difficulties that animals with hippocampal damage had in experiments such as those of the Blanchards might be in identifying places in the environment as opposed to objects as the source of threat. The Blanchards had shown that hippocampal-damaged animals could learn to avoid specific threatening objects but were less good at identifying less specific threats such as electric shocks delivered through the floor. Perhaps the hippocampus in rodents was a specialised type of memory system, a memory system for places which, when elaborated, might provide the basis for the more general episodic memory system of the human. Finally, I realised that if the hippocampus were involved in spatial representation we could draw on several millennia of mathematical, philosophical, and geographical thought to help us understand its functions. One of my philosopher heroes had been Immanuel Kant, who had suggested that our sense of space was a special property of the brain which provided a framework for the representation of other aspects of the world such as objects and which existed prior to experience with those objects. Had we found the neural basis for Kant’s a priori spatial faculty of sensibility? Would the hippocampus provide brain researchers with a neural Rosetta Stone, a portal into the mysterious world of cortical brain function? Throughout the day, I experienced a prolonged euphoria of the classical Archimedean type.  I decided to write a short paper on our findings and also to announce the idea that the hippocampus was Tolman’s cognitive map. The paper was originally rejected by *Brain Research* but after minor modifications finally accepted. I confidently sat back and waited for the chorus of approval from the hippocampal community. Instead there was a deafening silence, with the exception of a small number of isolated voices (see below).  Unbeknownst to me, Jim Ranck at the University of Michigan and subsequently Downstate Medical Center in Brooklyn was carrying out similar recording experiments in the rat hippocampus and finding similar behavioural correlates. His ‘theta’ cells were identical to our displace neurons and his approach-consummate and approach-consummate mismatch cells might be place cells since they consistently fired when the animal approached a reward location on a particular trajectory, i.e., passing through the same place. Ranck did not explore this possibility but on a subsequent sabbatical visit to our laboratory agreed that the animal’s location might be the primary correlate. In subsequent work with Phil Best he confirmed our findings and supported our interpretation. Importantly, he went on to discover the head-direction cells, providing strong support for the cognitive map theory (see below). **The Hippocampus as a Cognitive Map** Around this time Lynn Nadel joined the UCL Anatomy Department to work on the visual system. He quickly became interested in place cells and the cognitive map idea and we decided to write a short review article fleshing out some of the ideas and showing how they applied to the literature on the effects of hippocampal lesions on behaviour. Pat Wall was strongly supportive of the idea, but I’m sure he had no idea how extensive and ambitious the project would become. Our first draft ran to several hundred pages and it was clear that we had a book rather than a review article on our hands. In 1972, we sent the first draft to 50 colleagues and asked for their opinion, and I am still grateful to all those who replied and gave us such constructive comments. However, Oxford University Press, which had agreed to publish the book, also sent the manuscript to reviewers, one of whom was the foremost expert on animal behaviour. He gave it a long, detailed blisteringly negative review, making it clear that we knew little about animal behaviour and that the book suffered badly from this lack of expertise. We could either scrap the project or become experts in animal learning theory and totally rewrite it. We chose to do the latter and found to our amazement that many of the ideas we were expressing about the role of hippocampus in behaviour made a lot of sense within the context of animal learning theory. In total it took us six years to write the book and since many copies of the 1972 version had found their way into the hands and minds of a large number of physiological psychologists, a degree of scepticism developed about whether the book would ever be published at all.  *The Hippocampus as a Cognitive Map* (HCM) was an ambitious book in conception, daunting to write, and an unavoidably demanding read. The modest OUP run of a few thousand protected many from the effort. It remained cited by many but read by few, until around 2005 when I had it laboriously scanned and made available on the web where it has been and still is free to download (www.cognitivemap.net/).  During the writing of the book, I continued to work on place cells and explore their properties, leading to a more extensive publication in 1976. I reported that in addition to the standard place cell there were other types of spatial cells in the hippocampus including *misplace* cells which fired maximally when the animal went to a familiar location and found a new object there or failed to find an expected object, and *displace* cells which Jim Ranck called theta cells because of their close relationship to the ongoing LFP theta and which I characterised as being related to the same aspects of movement as Vanderwolf had attributed to the LFP. In the discussion section of the paper, I speculated that there were two independent ways in which a place cell could be activated. The first was by direct activation from the environmental sensory inputs which impinged upon the animal in a particular location and the second was through a path integration mechanism internal to the hippocampus itself, which used abstract measures of the animal’s behaviour such as its direction and distance of movement since the previous known location to update the representation. This idea has received considerable support since, most recently from work in our lab by Guifen Chen showing that, in a virtual reality environment, 25% of place cells are influenced primarily by the visual inputs while most of the rest receive a significant path integration input as well, i.e. receive a combination of both. **Experimental Test and Support: Lesion Studies** Nadel and I were joined in our analysis of the lesion literature by Abe Black from McMaster University, who came to London every summer and worked with us on ideas about the application of the theory to the normal animal learning literature and the lesion literature. Abe was a world leader in the field of animal learning theory, with a particular interest in avoidance learning, and the three of us published a paper on this in 1975. To our great regret Abe was diagnosed with stomach cancer and died in 1978 at the very young age of 49. I sometimes wonder what the hippocampal field would look like today if he had survived.  What was lacking however was a spatial memory task specifically designed to depend on the capabilities we had attributed to the cognitive map. In the mid-1970s, a newly graduated animal learning theorist, Richard Morris, came to visit Lynn Nadel and myself announcing that he had experienced a Pauline conversion and would like to work on the cognitive map idea. The theory made the strong prediction that hippocampal damage would lead to deficits in allocentric spatial navigation. Lynn and I had tried to develop a land-based navigation task which would be a sensitive test of this hypothesis. The basic idea was that the animal would be started from several locations and had to find a safe location in the environment despite having to move in different directions on each trial to get there. We failed to come up with a workable task, but Richard succeeded. His important idea was to require the animal to go a hidden platform in a swimming pool where there were no local cues to guide it. Together with Nick Rawlins, we subsequently tested rats with hippocampal lesions and found they had pronounced deficits: the Morris water maze was a superb test of hippocampal function and is still the best and most widely used behavioural assay available. **Experimental Test and Support: Single Unit Studies** The Cognitive Map theory also made strong predictions about the existence of other types of spatial information in the hippocampal formation, for example predicting the existence of cells representing distance and direction which would bind together the place representations into a map-like structure. Cells signalling the animal’s heading direction were found by Ranck, Taube, Muller and colleagues in the presubiculum in the 1980s; grid cells in the entorhinal cortex which may be signaling distance travelled in a particular direction have recently been described by the Mosers and their colleagues in 2005 (see below). In the early ’80s I was lucky enough to attract Bruce McNaughton and Carol Barnes to spend a year as postdocs in my laboratory. They were already experts in intracellular recording, long-term potential studies and behavioural studies. It was during an earlier visit to Graham Goddard’s (another McGill graduate) lab in Dalhousie that I first met them. Using a minicomputer and an overhead camera head tracking system to record unit activity on an 8-arm maze, we carried out the first quantitative measurement of place fields. We showed for the first time that the firing rate of place cells was dependent on the animal’s speed. Surprisingly, unlike on open platforms where the rat was free to move in all directions, on the behaviourally constraining narrow arms of the radial maze almost all of the cells had unidirectional fields, firing as the animal moved in one direction but not the other. We also implemented an idea of Bruce’s that two electrodes looking at the same cells might enable us to separate action potentials from anatomically close cells by giving us a stereoscopic view. The stereotrode was born to be followed in a short time by the tetrode, a 4 electrode version which is now in wide use (see below).  Over the next few years, our group showed that place cells could learn to distinguish between square and circular enclosures (Colin Lever) and under certain circumstances could do so in an all-or-nothing manner reflective of attractor dynamics (Tom Wills). A particularly revealing experiment during this period was one in which Neil Burgess and I showed that the firing fields of place cells stretched as the enclosure was stretched from a square shape to a rectangle. This led to the idea that one set of inputs to the place cells reflected the distance to one or more walls of the enclosure in particular allocentric directions. As the box was stretched, these inputs maintained their relationship to the opposing walls resulting in expanded fields. The predicted *boundary* cells were subsequently found in the subiculum by Colin Lever in our lab and in the medial entorhinal cortex by Trygve Solstad in the Moser lab. **Phase Precession** For many years, I struggled with the functional role of the hippocampal sinusoidal LFP theta and tried unsuccessfully to integrate it into the cognitive map theory. I knew from my own unpublished work in the late ’70s that at any given time different hippocampal place cells could have different theta phase correlates and even that the same place cell could have different phase correlates at different times. Every so often I would run into Gyuri Buzsaki, who has had a lifetime interest in theta and other hippocampal oscillations and he would ask me what was the relationship of theta to pyramidal cell activity. Given my experience I told him that unlike hippocampal interneurons, they didn’t have a fixed phase of firing relative to theta. I had also been troubled by the possibility that the dentate granule cells might fire like interneurons (it appeared that there were just too many theta cells in the granule layer for them all to be interneurons) and was trying to understand how the interactions between several high-rate dentate granule cells might be translated into low-rate CA3 place cell activity. This got me thinking about interference patterns and led indirectly to my 1985 philosophy paper which suggested that the hippocampus might store and manipulate theta-frequency holograms and that theta was the neural substrate of consciousness (O’Keefe, J. (1985), “Is consciousness the gateway to the hippocampal cognitive map? A speculative essay on the neural basis of mind,” in D.A. Oakley (ed), *Brain and Mind*, 59–98, Methuen, London.). Around this time I also began exploring the relationship between hippocampal theta sinusoids and vectors. In particular, I pursued the phasor coding idea from engineering in which sinusoids are represented by rotating vectors, but inverted it so that the sinusoids were used to represent vectors and not vice versa. In this version, the length of the vector is represented by the amplitude of the sinusoid and the angle relative to some reference direction is represented by the phase shift relative to a reference sinusoid. This would enable the hippocampus to do vector algebra using sinusoids to represent the locations of environmental landmarks in a polar co-ordinate system (see my paper O’Keefe, J. (1991) “The hippocampal cognitive map and navigational strategies,” in, J. Paillard (ed)., *Brain and Space*. Oxford University Press, 273–295).  So with all of these ideas in mind, I thought I should have another go at trying to make sense of the relationship between place cells and theta. I went back and looked carefully at the data from one particular place cell from a spatial memory experiment on a +-shaped maze with narrow arms that Andrew Speakman and I had published in 1987. We had also recorded the slow-wave theta LFP from the same electrodes. I quickly confirmed that the phase relationship between the firing of this cell changed from one wave to the next. But how? Was there some systematic relationship between the two? Over several days I looked at run after run on the maze over and over again but couldn’t make any sense of the pattern until one day I found one run on which the spikes fired on every wave and realised that they were systematically moving to earlier phases on each successive wave as the animal ran straight through the field on the narrow track. I also noticed that quite often the phase would continue to precess in the second half of the field despite the fact that the firing rate was falling. This suggested that a simple depolarisation model might not be adequate to explain the effect. Harking back to my thinking about interference patterns, I realised that the wavelet produced by the interference pattern between two waves of slightly different frequencies would produce the required effect. The number of spikes on each theta burst would increase towards the centre of the field and then decrease while the peak of the interference wavelet would continue to progress relative to extracellular theta LFP. I guessed that the phase might correlate with the animal’s location in the field rather than with time or some other variable and this proved to be the case. Following rejection from several journals, the paper by Michael Recce and myself was eventually published in *Hippocampus*. This was also the first published paper in which tetrodes were used. We considered the possibility that there was a second higher frequency wave in one of the inputs to the hippocampus, so Kate Jeffery looked for it in the entorhinal cortex and Charles King looked for it in the medial septal. Neither found it and we were forced to conclude that if it existed it was located in the dendrites of the pyramidal cells themselves. **Grid Cells** I first met Edvard and May Britt Moser, my Nobel co-laureates, when they were graduate students in the lab of Per Andersen in Oslo. They were clearly very bright and ambitious and I was more than happy subsequently to agree to their spending some time in my UCL lab to learn the techniques of single unit recording in free-moving animals. Following a string of high-profile important papers on place cells in journals such as *Science* and *Nature*, they and their students Torkil Hafting and Marianne Fynn produced their monumental 2005 paper announcing the existence of grid cells in the entorhinal cortex. The grid cells looked like they might provide the metric for the map, completing the spatial information necessary for creating the hippocampal cognitive map. Although others including ourselves had looked in the entorhinal cortex for spatial cells we had all missed the grid cells. I have no doubt that this discovery together with the findings on the spatial role of the human hippocampus (see below) have had a major impact on the neuroscientific community’s acceptance of the cognitive map theory. But how were the grid cells constructed? Neil Burgess, Caswell Barry and I suggested that a generalised two-dimensional version of the oscillatory interference model using interference patterns between several theta-like oscillations might provide a good model for the generation of grid cells. And how universal is the grid pattern? Recently Julia Krupic and Marius Bauza in our group have shown that the walls of the environment have a much greater influence on the structure of the grids then had previously been realised, even to the point of destroying the grid pattern in highly structured asymmetrical environments such as trapezoids. We still have a lot to learn about the function of the grids and how these remarkable cells are created by the brain. **Human Hippocampus** One of the major obstacles to the acceptance of the cognitive map theory was the belief that the human hippocampus had a broader function than the spatial one proposed for the rodent hippocampus. The strongest contestant here was the declarative memory theory championed by Larry Squire. Declarative memory theory held that the deficit following hippocampal damage included both factual memories as well as episodic memories for events of the past. The cognitive map extension to the human disagreed with this, predicting that the global memory deficit was limited to episodic memories comprised of memories for what happened in a particular place at a particular time. The idea was that episodes were built upon the basic spatial framework through the addition of a linear sense of time amongst other higher-order cognitive capacities.  One problem in studying the role of the human hippocampus in spatial memory was that most of the tasks had usually been presented on a tabletop or as video displays which, could also be solved by non-hippocampal strategies in particular egocentric ones in which objects were located relative to axes fixed to the eyes, head or trunk as well as by hippocampal-dependent allocentric ones. What was needed was a large-scale environment comparable to the mazes in which rodent spatial navigation was tested. Better still if navigation could be carried out by participants whose heads were immobile, so that their brains could be scanned using the rapidly developing imaging technology. The solution was to use one of the newly developed first-person shoot-em-up virtual reality games which were just becoming available in the ’90s and were all the rage with teenagers. Importantly, some came with editors which allowed the games to be modified and components added or deleted. Neil Burgess, with help from Jim Donnett removed all of the monsters, guns etc. from the game Duke Nukem, which provided an excellent complex 70 x 70 m virtual environment with multiple rooms and pathways, and the layout of which participants could explore and learn to navigate around in a reasonable amount of time. Eleanor Maguire and Neil carried out an imaging experiment in which healthy volunteers had their brains scanned while they navigated between locations using either a cognitive map strategy or a route-finding one in which they followed a series of marked paths, a non-hippocampal strategy. To our delight, the hippocampus and surrounding parahippocampal gyrus become active during mapbased way-finding in virtual reality environments. Importantly there was a good correlation between the accuracy of navigation and the amount of blood flow in the right hippocampus. Subsequently, we used fMRI to study the role of the hippocampus in episodic memory within a virtual reality context and showed that the left hippocampus is more involved than the right. We also studied the spatial and episodic memories of patients with bilateral and unilateral mesial temporal lobe damage in virtual environments and corroborated the imaging work, with the left temporal patients displaying selective recognition deficits in episodic memory and the right showing deficits in spatial memory, object recognition and navigation. The bilateral hippocampal patient showed deficits in both episodic and spatial recognition memory but interestingly not in object recognition memory, suggesting that this deficit in the right temporal-lobectomised patients was due to the additional damage to other areas of the temporal lobe outside the hippocampus. Eleanor Maguire went on to develop these ideas to include the notion that the human hippocampus is involved in the construction of spatial scenes and the prediction of future events. She also showed that the posterior hippocampus of expert and highly practised human navigators (London taxicab drivers) was larger than in the rest of us, including bus drivers who extensively travel the streets of London but along fixed routes.  Another obstacle to the acceptance of the cognitive map theory was the evidence that the left human hippocampus was involved in memory for language and narrative. The problem here was that many psychologists believed that visual-spatial processing was at the opposite end of the cognitive spectrum from language processing, the former held to be represented in a two-dimensional static space while the latter being based on serial processing along a single dimension. How could language be processed and stored in a two- or three-dimensional spatial structure? Nadel and I had suggested that one clue might come from spatial language, which might be easier to store in a spatial structure and, if adequately modelled, might form the basis for much of non-spatial language by metaphorical extension. In follow-up articles, I have explored the use of a specific model of hippocampal spatial function to create a mathematical model underlying the meanings of the spatial prepositions in English, prepositions being one important way in which location and movement are captured. Spatial prepositions are part of the closed class elements of language, are usually limited to around 20 in most languages, and are more or less consistent across languages although not necessarily appearing as independent words in the surface structure. This ‘vector grammar model’ was based on the idea that place fields can be located in an environment on the basis of the distance of the animal’s head from a landmark (usually a wall or boundary of the environment) in a specific allocentric direction (for example the wall of the room between the window and the door) generated by Neil Burgess, Tom Hartley and myself (see above). The vector grammar model postulated that almost all of the prepositions had a primary spatial meaning and these identified the underlying places, objects and vectors connecting them. For example in the phrase “to go from London to New York,” “from” would be represented as the origin or tail of a vector at the place “London” with its head at the place “New York.” The meanings of most prepositions can be described in a similar vector-based fashion. **Translational Possibilities** We are optimistic that our understanding of hippocampus function at the network level will allow us to address the neural basis of neurodegenerative and psychiatric brain diseases. There is evidence that some of the earliest neuropathological manifestations of neurodegenerative diseases such as Alzheimer’s occur in the entorhinal/hippocampal formation. One approach is to create mouse models of some aspects of AD and ask how place cells and other aspects of hippocampal physiology become dysfunctional during disease progression. We already know from work with Francesca Cacucci and Tom Wills that place cells are less able to identify the animal’s current location in these mice and this functional loss correlates with the animals’ inability on spatial memory tasks and its increased amyloid plaque burden. In another related approach, Neil Burgess and Dennis Chan are developing sensitive allocentric spatial tasks as diagnostic tests to look for changes in spatial memory during the early stages of dementia. **The Future** Having spent most of my career as a bench experimenter with a small lab, I have recently accepted the position as Inaugural Director of the Sainsbury Wellcome Centre for Neural Circuits and Behaviour at UCL. As the name implies, the SWC will provide a framework for the study of the neural correlates of perception, emotion, memory and behaviour using the latest techniques in optical and electrophysiological recording to identify the underline neural patterns and optogenetic manipulation of cell activity to control those patterns in a causal manner. It is a thrilling time to be taking on this job, given the numerous possibilities opening up for behavioural and systems neuroscience by these new technologies. So now back to the bench … |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0523=JO  [John O’Keefe] Hello.  [Adam Smith] Hello, this is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize.  [JO] Hi there!  [AS] Hi. First of all many congratulations on the award of the Nobel Prize.  [JO] Thank you very much, I’m over the moon actually.  [AS] Where were you when you got the news?  [JO] I was working at my desk at home. I sometimes work in the mornings here. What I tend to do is I try and get as much writing done … I get as much writing done at home before I go into work.  [AS] What was your first reaction on the call, on receiving the call?  [JO] I thought it was terrific. I thought it was … I had just been to Oslo a couple of weeks ago to receive the Kavli Prize, and I thought “Oh this couldn’t possibly be, this couldn’t possibly be what I think it is.” But of course it was. So I’m absolutely delighted of course. It’s a tremendous honour. It is the acme of scientific prizes and I think it’s, you know I’m very humbled by the whole thing, but I’m delighted as well.  [AS] And you know your co-Laureates very well indeed; the Mosers.  [JO] Yes, they came … I had known them actually for many, many years. I knew them when they were students with Per Andersen in Oslo, and they were already clearly destined to be stars and I was delighted when they wanted to come and spend some time in my laboratory to learn some of our techniques. And I think they put them to very good use I must say.  [AS] It’s 43 years since you first found these place cells in the hippocampus, I suppose the lesson from that is that one has to be pretty patient in unravelling the secrets of the brain.  [JO] [Laughs] Yes, I think I have a reputation for being patient. Actually I hadn’t realised it was that long, but it is, yes it is 43 years. And I have to say that at the beginning most people were quite sceptical at the idea that you could go deep inside the brain and find things which corresponded to aspects of the environment. People were a little bit surprised and sceptical about that. I think it’s taken a while, but there were some people early on who accepted it and of course I’m grateful and of course now the field has blossomed. And I think the Prize actually is as much for the field as for myself and the Mosers. I think, you know, we’re just representatives of a large number of people who are working away at the hippocampus and memory and spatial navigation.  [AS] Yes, there must be an enormous number of happy people around today.  [JO] Yeah.  [AS] OK. Well, thank you very much indeed, I hope you have the most splendid day. And are you still at home? Are you still …  [JO] I’m hiding at home, yes. [Laughs]  [AS] Probably wise to do that for as long as you can.  [JO] What we’re … I’ve been of course in contact with the people in my office and what we’re proposing to do is set up a press conference, probably at the Wellcome Trust media centre, which is up the road from University College London, probably this afternoon I think. So I have another hour.  [AS] Stay relatively low key in that hour, yes, and avoid too many glasses of champagne.  [JO] Yes, I’ll certainly do that.  [AS] OK, Alright, well many, many congratulations and thank you very much for talking to us.  [JO] Thank you very much Adam.  [AS] Thank you, bye bye. |
| Interview |  |
| Q23 | Could you explain your awarded work in easy-to-understand terms. |
|  | One of the fundamental things that humans and animals do, is find their way around the world. So, to do that they need to know where they are, and they need to know where other things are, and they need to know the relationship between these places. And the way the brain does that, is it represents the place where you are now, and it represents distances and directions. Over the years what we have been able to establish is, which parts of the brain do this, particularly a part of the brain called the hippocampus and its related areas, especially one of them, the entorhinal cortex and what types of cells that are there which represent these different kinds of spatial information. And we know that there are cells representing places so when you are in a familiar environment, different cells represent different locations in the environment. We know there are cells which represent directions so that when you are looking in a particular direction or moving in a particular direction, there are cells which tell the rest of the brain that. And then we also know there are cells which appear to tell the distances that are moved in particular directions. And if you put all these together what that provides you with is something we call a cognitive map which is a framework for identifying where you are, where other things are in the environment and how to get from one place to another. |
| Q16 | At what point did you realize your work was a breakthrough? |
|  | When I first discovered the place cells, which is what I received the prize for, I very quickly realised that if my interpretation of these cells was correct and of course, one never knows, one has to do further experiments, control experiments and I’ve had several instances in my career where I thought I had really made a wonderful discovery which turned out just to be something much much more simple when you looked into it carefully. But when I saw the place cells and realised that they might be representing the abstract concept of a place and not a much more concrete things such as where a particular object is or visual stimulus. Then I realised this probably would have very important implications because there were much work in the past, much interest in space and how it is represented by psychologists and philosophers, mathematicians. So, I realised if we had actually found the system in the brain which was the basis for representing space in the brain that this would potentially be very, very important. |
| Q1 | What brought you to science? |
|  | To be honest, I had a very variegated early carrier. I worked in various jobs, and at one point I was an engineer working making airplanes. And while I was studying engineering, I became interested in philosophy. And particularly in those areas of philosophy which were dealing with the mind-body problem, how things were represented in the mind and things like that. And I began to think that it was just possible that if we understood more about the brain, we will be able to understand some of the problems which people have been dealing with for centuries and millennia. So, I set out on a course where I decided it would be great to study the brain. In those days there wasn’t anything called neuroscience, there were several people studying the brain, but it wasn’t a very developed subject. So, I went back to university full time and ended up doing psychology because that was one of the few areas where you could study the brain. So, I came to the field of studying the brain, neuroscience, really through my interest in philosophy and trying to answer some of the fundamental questions. I think I have been very lucky that it turns out that I have made a contribution towards one of those questions and I am very fortunate to have done so. |
| Q19 | What were you doing when you heard you had been awarded the Nobel Prize? |
|  | I actually spend, quite often I spend, mornings at home and I try to do a lot of the paperwork and quite a bit of my writing at home, so I was at home. So, the call was taken at my workplace by one of my colleagues, and she called me, and she said: “Are you standing up or sitting down?” because I think she knew what the implications were and then she said: “ I have a call here from a gentleman, he’s Swedish, he is from Stockholm and he says it is rather urgent that you call him back in the next 45 minutes”. So, I then took a big deep breath, and, actually I have to admit that I looked up whether the phone number was a Stockholm number and then called him back and of course and he told me and it was quite a thrill. |
| ID | 0524 |
| Biographical | I was born and raised in Fosnavåg, a small town on an island on the west coast of Norway, in one of the most beautiful parts of the country (Fig. 1).  My parents owned a small farm, although my father worked as a carpenter. My mother took most of the responsibility for the farm and cared for me and my four older siblings, in addition to having small jobs now and then. Before I was born, we had a lot of animals on the farm, with cows, chickens and a horse, but by the time I was born, we only had sheep. Both my father and mother worked very hard all the time, and I learned at an early age that work makes you happy.  I was a happy, curious child with a lot of dreams and a lucky star above my head. I was also a tomboy who played with the boys a lot. But because we were five children, we didn’t have much money and we didn’t have a car, so I would stay home during the summers when my friends would go away. I was the youngest child by 10 years, and had a lot of time to myself to study animals on my own, and I loved it. I would spend time out in our fields where I would play by myself. I even studied the behaviour of snails as they ate grass. As I watched, I would always wonder about the reasons behind what the animal was doing.  My mother liked to tell me fairy tales, but she didn’t want to frighten me with the scary parts. Instead, she would tell me the parts of the stories that talked about hopes and dreams, like “Askeladden,” a boy who had nothing, but he used his head, he was kind and he worked hard – so he succeeded. I loved it when my mother would read me these fairy tales. It also made me believe that even though you have nothing you can become something – it was a bit of the American dream!  My mother had her own dreams, too: she wanted to be a doctor. The area where I grew up is somewhat religious, so I also met missionaries who had travelled to distant countries. My mother’s dream and the experience of meeting missionaries made me eager to go abroad so I could work as a doctor and save the world. I also loved animals, so I thought perhaps if I didn’t study to be a doctor, I could be a veterinarian. My dad had taught me to care for animals, and was a warm, good role model for me. **Schoolyears** I was not always the best student with the highest grades, but my teachers saw something in me and tried to encourage me. My mother had persuaded the local school officials to let me start school a year earlier than other students because my birthday was in January (the cut-off was the end of December) and because she saw that I was ready. My main primary school teacher would say “Wow, you are the youngest child in the class, and yet you still know this!”  I also had a teacher in high school who would call on me in class and say, “Frøken Andreassen, you know the answer! I believe in you!” And I had a physics teacher who really encouraged his female students by telling us that he wanted us to come back and show him that we had become engineers. There were other teachers, too, like my Norwegian teacher who said she thought my writing was good, but the bottom line is that I felt like I got a lot of special attention, and I was noticed. It made a difference.  At the same time, though, I wasn’t that motivated in high school, because I spent too much time with friends, and I didn’t have the drive to get the grades I needed to get into medical school. But my grades were still good, because my mother warned me that if I didn’t work hard I would have to go to school to study home economics and be a housewife. That thought horrified me. **The University of Oslo** When it came time to go to university, I decided I would go to the University of Oslo, in part because I had two older sisters in the Oslo area. I was also able to live for some time with one sister in Asker, an hour outside Oslo, while I looked for a place to live.  I loved university, it was fantastic – there was so much freedom, and I was very social. But I still wasn’t sure what I wanted to do. I loved mathematics and physics in high school, and thought about studying biology or geology and maybe becoming a teacher, but I didn’t see myself as a teacher. I also applied to dentistry school, in part because I had a boyfriend at the time who was studying dentistry. The dentistry school accepted me, but I decided not to pursue that either.  It was about that time that I met Edvard with a friend of mine on Karl Johans gate, the main pedestrian mall in downtown Oslo. I recognised him, of course, as the smart kid from my high school. He was visiting before he started at the university, and when I found out that he would be coming back to Oslo to start his studies in January, I told him to look me up so that I could show him around. And he did.  We quickly became friends. We decided that we would study psychology together, so we could learn about the brain. That brought me back to my dreams of my childhood, when I was so eager to understand why we do things. I was in heaven.  During our first year in the main psychology programme we were in the same social psychology class, called Psychology of Small Groups. We published a paper with several classmates and our teacher, Professor Skårdal, as a result of our research from that class. This was our first paper – “The interactional effects of personality and gender in small groups: A missing perspective in research,” published in the *International Journal of Small Group Research*. Professor Skårdal liked us so much he tried to encourage us to study social psychology, but we said, “No thanks, we want to study the brain!” We simply burned with eagerness to understand the brain. **Terje Sagvolden and Per Andersen** We started in Terje Sagvolden’s lab during our second semester. He was studying hyperactivity in rats. At the same time, our own relationship had changed from a friendship to a romance, and we got engaged on top of Mt. Kilimanjaro. It was a dream place for both of us – Edvard loves volcanoes, all volcanoes, and since my childhood encounters with missionaries, I had always wanted to go to Africa.  Working in the Sagvolden lab involved studying pure behaviour for two years. It was quite exciting, and it was interesting to work with rats, to try to understand why these animals were hyperactive. He taught us experimental design, especially the need to have controls in an experiment, and we learned a lot of behavioural theory. But we pushed him very hard, we kept asking him, “Can’t you go into the brain?” We had this crazy energy, this drive to know – it wasn’t just Edvard, or just me, it was the two of us together.  Eventually it came time for us to do our master’s thesis work and we realised that if we were going to have any opportunity to study the brain directly, we needed to work with Per Andersen in the neurosciences group. This was a problem, because we knew he didn’t really like psychologists – all the people in the Department of Neurosciences at that time were medical doctors – and that his research group was full.  When we finally got to talk to him, I decided that I was not going to leave the room until he accepted us as graduate students. I felt like I had been glued to the chair. In the end, I think he just realised he couldn’t get rid of us. He finally told us, “Fine, if you are going to do your master’s research here, you have to read this paper (by Richard Morris on water mazes), see if you understand it, and then build a water maze lab. If that is a success, then you will be allowed to do a master’s thesis in my lab.” I remember I said, “Oh wonderful, because we want to do a PhD with you, too!” **Building a Water Maze Lab** Per wanted us to build a water maze literally from scratch – a tank 2 metres in diameter by 50 cm high. When we left the meeting, I said to Edvard, “This is crazy!” Fortunately my brother-in-law worked at Det Norske Veritas and I called him, and he was able to help us buy a tank. We also had to get a marine pump so we could pump 1,250 litres of water out of the tank – we had a hose so we could pump the water into a toilet across the corridor. The water had to have milk in it because it had to be murky. That meant we had to change the water every day or it would smell, because the water temperature had to be at 25 degrees C so that the rats would feel comfortable in the pool when they searched for the hidden platform.  So we were psychology students during the day, and then worked in our lab at night. Per had a programmer who helped us write a programme so that we could track the rats as they swam in the maze – this was at the point where you couldn’t buy anything off the shelf. Early on we realized we had to use hooded rats rather than the albino Wistar rats, because it was easier to track their movement and because they are dark eyed and have better vision than the red-eyed albino rats.  Per showed us how to make tiny lesions in the hippocampus, because he had this idea that he wanted to study LTP in the living brain. Long-term potentiation, LTP, is how the connections between neurons in the brain are strengthened, and had actually been discovered in 1966 by Terje Lømo, in Per’s group and supervised by Per. We first had to make lesions in the dorsal and ventral parts of the hippocampus so that a hippocampal slice was left on both sides of the brain. Per’s idea was that it would be easier to detect LTP in the living brain if the area where such changes could occur was restricted. This was a brilliant idea, but in order to find out how big this slice had to be to support learning we had to make lesions of different sizes, both in the dorsal and the ventral hippocampus. Theodor Blackstad helped us to figure out where the boundaries of the hippocampus and the subiculum were.  The challenge for us was that we were psychologists, we didn’t know much about the brain’s anatomy. We first had done one brain dissection on a human cadaver, and that was it. But we learned fast. **Looking for LTP** Per’s idea was to give the animals extensive training in the water maze so after they had learned a lot, we could measure the changes in the tiny hippocampal slice that was left in the brain. He predicted that this slice would have increased synaptic efficiency (LTP) compared to animals who did not learn. He was so excited when he told us about his dream. His excitement was so important for us, and he was a great inspiration.  We thought that we first needed to find out if the animals could learn at all if they had these kinds of lesions, and then we also needed to have controls. We needed to know if we left the middle part of the hippocampus untouched, would the rats be able to learn if we removed the dorsal part, and what would happen if we removed the ventral part.  Once we did this, we found out that when the rats had a lesion in the dorsal part of the hippocampus they didn’t learn, but if they had a lesion in the ventral part they were fine – if we made large lesions in the ventral part they could still navigate perfectly well. The hippocampus was known to be involved in this behaviour, but what we found out was that it was only the dorsal part of the hippocampus that was involved in spatial learning and memory, and that the hippocampus was functionally heterogeneous even though it looked like a smooth sausage from the outside. **The Pink Poster** Per was president of the European Neuroscience Association (ENA) at that time, and so he allowed us to bring a poster of our research to a meeting of the ENA in Sweden. I have to confess that when I made the poster, I made it pink as a way to tease Per a bit. But maybe the pink also helped it to stand out, because when Richard Morris walked past the poster he commented that he thought our findings on the dorsal-ventral difference were interesting, and he also saw that we had used the water maze.  But he told us that he didn’t like our lesion method, because we had used aspiration, which can cut passing axons. He encouraged us to work with Len Jarrard who had just had a sabbatical in Edinburgh and who was an expert in making lesions without removing the fibres, and he thought that was crucial. Richard gave a plenary talk at the meeting and he mentioned our poster, and I thought that was pretty amazing. Edvard and I were so proud!  We published our results in *The Journal of Neuroscience*. This was also our joint master’s thesis – we were able to write it together. It was a pretty thick thesis, and a pretty thorough study of the two parts of the hippocampus. We got help from a few external people who came to the lab because Per was an internationally recognised scientist. These visitors included [Eric Kandel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2000/kandel-facts.html) from Columbia University, who told Per, “You really have to publish this with them,” and Larry Squire from the University of California, San Diego, who also encouraged Per to let us publish our results. **Funding for Two PhDs** Our experiment also raised the question, if the dorsal part is involved in memory, what does the ventral part do? So we started to read a lot about anatomy, and wondered about the nature of the connections between the entorhinal cortex and the dorsal and the ventral parts of the hippocampus. That was the first time we wrote to Menno Witter at the Free University in Amsterdam, because he had done a lot of work on hippocampal connections.  As we finished our master’s thesis, we both wanted to continue with Per on our PhDs, but the challenge was how to get two fellowships to study with him. At the time it was very difficult to get this kind of funding. The Research Council of Norway at the time was concerned about geographic distribution of these grants.  Per had one question that he felt certain would be funded, the relationship between long-term potentiation and memory, which was both a timely and very interesting question. Per told us that we would have to decide which one of us would take the topic and get funded for a PhD. I told Edvard that I thought Per’s question was a good topic for him, since he was so interested in the question. Then Per told me that he thought I should also get a PhD, and that he would help me find money.  His plan was for me to collaborate with a colleague of his, Jørg Mørland, in the Toxicology Department, to study what happened to hippocampal synapses if you gave alcohol to an animal. But I didn’t like the topic, because I thought the manipulations were too general to learn anything specific about learning and memory and also because I couldn’t see myself giving rats the high, high doses of alcohol that you would need to see an effect. So I found a way to convince him that I couldn’t do the project – I told him that I was from the Bible Belt of Norway and I simply can’t do this. He pushed me but I just refused.  But I was very interested in the fact that we could see synapses with a laserscanning confocal microscope. This was very new at the time – we had just got the microscope, and it was new enough that people didn’t believe that it was possible to see synapses with this equipment. But Per had a dream, and was enthusiastically convinced that it should be possible. Per was still trying to get me to do experiments with alcohol, but I said, no, I’m a psychologist, I want to do exactly the opposite – instead of trying to see if alcohol will reduce the number of synapses, I want to train the animals to see if there is an expansion of the number of synapses with learning. So I started to read, and I was convinced it was possible.  What was interesting was that Per was so sure that this project would be a failure and that it would not be funded that he tried to stop me from sending the grant proposal to the Research Council. I kept going to his office with the application I wrote to see if he had changed his mind, and finally he just gave in – he always had to give in, like my dad typically gave in when I insisted. Then I sent in my application, and both Edvard and I got grants – a surprising and joyful moment in our lives. **PhD Research** By then we had gotten married, on July 27, 1985 in Oslo. We had the same supervisor, we were studying the same structure in the brain, but we still both got funded from the Research Council of Norway. It was about this time that I realised how insistent I could be – I was always very nice and polite, but if I really wanted something, no one could stop me.  My PhD research involved offering an enriched environment to rats, so I made a big animal enclosure that had different floors. By this time I had Isabel, our oldest daughter, so I made all these toys for the animals when she was there with me, and I changed the environment every day and even moved the floors so that it would be a new environment. I had Isabel on my lap when I observed the animals in the large enclosure.  After 14 days of 4 hours of daily exposures to the enriched environment I took living slices of the hippocampus and filled individual hippocampal cells with Lucifer yellow to stain them. That allowed me to visualise and count the spines in 3-D.  I counted spines blind to the group to which each rat belonged, and found that there was a difference between the rats who lived in the enriched environment and those who didn’t. I then trained animals with similar experiences in the water maze, and showed that the animals that had lived in the enriched environment were faster and better at remembering the hidden platform in the water maze. I published two papers on my work on spines, one in *PNAS* (Proceedings of the National Academy of the Sciences of the United States) and the other in *The Journal of Comparative Neurology*. I also published a third paper on dorsal and ventral differences in the hippocampus in *PNAS*. **Children and the Lab** Many people ask me how I managed to do all this work with two small children – Isabel was born in June 1991, right after we started our PhDs (Fig. 2 and Fig. 3), and Ailin was born in 1995 (Fig. 4), right before we completed our PhDs. The answer is that we were so driven to understand the brain that we simply made things work, we could not see any problems – nothing could stop us. From the earliest days, we took the girls to the laboratory – they were both very good children, very well behaved. Or if I couldn’t take them with me, Edvard could take turns watching them. Of course we had nannies and preschool places for the children – both of them attended preschool in Edinburgh, but in the afternoon and in the weekends they often played in the office.  If people objected, I would ask them what was the harm in what I was doing? It wasn’t that I had the freedom – I just assumed I could do things, like take my children to scientific meetings and breast-feed them in public, or bring them to the lab. I just didn’t see the barriers that others might have seen. We were somewhat naïve – we couldn’t imagine that people would object – so people mostly were very nice and didn’t try to stop us. **Edinburgh and London** During our PhD work, Richard Morris had invited Edvard and me to the University of Edinburgh to follow up on our master’s research findings on the difference between the dorsal and the ventral part of the hippocampus, but using chemical lesions instead of aspiration.  We went there several times during our PhDs, and confirmed our earlier results – that the dorsal and the ventral parts of the hippocampus are different. We also conducted another experiment with him on saturating hippocampal synapses with LTP and testing the animal’s ability to learn to find the platform in the water maze. We later completed this work after we came to Trondheim and published the results in *Science*.  We defended our PhDs in Oslo in December 1995, but by that time we were already in Edinburgh with Richard Morris – we even had the girls in a preschool there. In the spring of 1996, Per Andersen and Morris graciously suggested that we go work with John O’Keefe at University College London to learn how to do single cell recordings. We had already met John O’Keefe in Oslo when we defended our PhDs, because he was the opponent for Ole Paulsen, who was one of Per’s six students (including us) who defended our theses in the same week.  We had an incredible party after the defences, with all of these top international scientists who served as our opponents, with seminars and sleigh ride! Many of the opponents later became important members of our scientific network, which helped us to win status as a centre of excellence from the Research Council of Norway.  The stay in London, in John O’Keefe’s lab, was one of the most learning-rich periods in our lives. John spent an enormous amount of time with us and taught us everything about single cell recordings. He sat with us in the surgery room, showed us how to turn down the tetrodes and do the recordings, how to cluster the data, he talked about the literature – it was all absolutely formative for our future. Edvard had three months with John, and I had just one, in part because of the difficulty of finding care for the children. In Edinburgh we had spots in a preschool for them in Edinburgh only, so in London my brother’s wife, Olaug Andreassen, came for a month to help care for them. **Two Positions and a Lab** At the same time, one position had opened up at the Norwegian University of Science and Technology in Trondheim, and our former supervisor, Terje Sagvolden, encouraged us to apply for it, just for the experience if nothing else. We knew it was a long shot – when we applied we were still months away from defending our PhDs, and we really weren’t thinking that we were ready to settle down just yet.  Suddenly we were called in for an interview, in the autumn of 1995. We told the interview committee that we would not be interested in one position, but Sturla Krekling, the individual at the Department of Psychology who was most involved in the process, really pushed for us and so they offered us two positions. They were in the process of trying to build up the department.  We then said we need a new lab because we wanted to do research – we didn’t just want a salary to teach – so we came to them with a list of all the equipment we needed, the prices, the suppliers, because we had been through the process with Per to build the water maze in Oslo. We also knew what was required to build a combined electrophysiology-water maze lab, we had the experience, and we basically got it all. The only condition was that we begin in August of 1996 so that we could teach.  That completely upended our plans, because we had hoped to stay longer with John O’Keefe, or go to the University of Arizona to work with Carol Barnes and Bruce McNaughton’s memory and hippocampus group. Both Barnes and McNaughton had been involved with us as PhD examiners, and Arizona was a real neuroscience mecca at the time. We really wanted to go there. But that wasn’t possible once we had the offer of positions in Trondheim – the prospect of two jobs and a lab just seemed too good an opportunity to turn down.  (In fairness, we eventually did get a six-week sabbatical in Arizona in 2001, where we learned to do what is called parallel recordings from many dozens of hippocampal cells. It was a technique that was invented by Bruce in the 1990s in Tucson.) **Funding for Collaboration** In parallel with teaching we managed to have our lab operating after a half year of set-up, and after a year or so we had the first results. It took a long time to get data because there was only Edvard and me, and we had to do all the technical aspects of the work along with the actual science – everything from cutting brains to cleaning the rat cages. Our daughters learned to become real “Trøndersk,” an expression that describes the residents of mid-Norway in the counties of Norand Sør-Trøndelag, where Trondheim is located.  One of the first questions we started with was how are the place cells that O’Keefe discovered generated? What is the basis for the place cells in the hippocampus? To answer this question, we applied for – and received – a collaborative grant from the European Commission in 2000 that gave us three years of funding (Fig. 5).  At the same time, we also applied for funding from the Research Council of Norway’s Centre of Excellence programme, a 10-year grant for basic research. This was also approved and as of the December 2002, our group became known as the Centre for the Biology of Memory.  The Centre of Excellence money allowed us to bring internationally recognised researchers to Trondheim for brief but significant periods. We had Menno Witter from the Free University in Amsterdam, Richard Morris from the University of Edinburgh, Bruce McNaughton and Carol Barnes from the University of Arizona, Alessandro Treves from the International School for Advanced Studies in Trieste and Ole Paulsen from Oxford University, all experts in their field, to make a coordinated effort to conduct integrated neural network studies of hippocampal memory. In addition we brought in Randolf Menzel from Freie Universität Berlin who studied neurobiology and spatial memory in the honeybee. **Finding Grid Cells** A few weeks after the centre of excellence grant was announced we published a paper that guided us to search for the spatial signal that resulted in place cells in the hippocampus (Brun, Otnæss, Molden, Steffenach, Witter, Moser and Moser, 2002, in *Science*). These exciting data suggested that we should search for the spatial signal in structures upstream of the hippocampus – like the entorhinal cortex. That is what helped us to eventually discover grid cells.  In the Brun et al. (2002) paper we asked where the signal to the place cells came from. The reason this question was so intriguing is that the place signal is buried so deeply in the brain, it really can’t be traced back to any sensory input, so how is it made?  We tried to answer this question by making small lesions in the early stages of the hippocampal circuit, in the CA3 area, as a way to interrupt the intrinsic circuit. We then put electrodes in the CA1 area of the hippocampus, which is where most of the place cells had been recorded.  If the place cells were a product of processes that happened at earlier stages of the hippocampus, we should have been able to block those signals by interrupting the hippocampal circuit. But what we found was that we still had spatial signals, even after we made the lesions that should have stopped the signal.  That led us, together with PhD students Marianne Fyhn and Sturla Molden and our colleague Menno Witter, to go to the part of the entorhinal cortex that few other groups had recorded from, the dorso-medial entorhinal cortex. For many reasons people had not worked in the dorsal part of the medial entorhinal cortex before, partly because it was technically difficult, and partly just because of convention.  And this turned out to be the spot, in 2005, where we found grid cells (Fig. 6). Even before we realised that we had discovered a new kind of cell, we realised in 2004 that something was going on in this region with respect to space. The cells there had spatial activity, they had multiple firing peaks and the pattern looked regular – but we really didn’t understand what was going on until we extended the size of the environment that we let the rats roam around in a 200-cm-diameter cylinder. And finally, there it was, a clear hexagonal pattern, and that was the discovery of grid cells.  That last sentence makes our discovery sound very simple, but when we first had our results, they were so clear we almost didn’t believe them. We thought perhaps that the hexagonal pattern was an artefact of how we made our measurements. But over time we were convinced that this was in fact how the cells were firing.  We did this research with our students Torkel Hafting, Marianne Fyhn, and Sturla Molden. Marianne came to Trondheim in 2004 to work with us, and Torkel was her boyfriend (and later husband). We offered Torkel a position as a technician in our lab so that they could stay together, and we asked him to work with Marianne on the grid cell project. He later became a postdoc with us. The grid cell results were published in *Nature* in 2005. **The Brain’s Own Internal Code** Finding grid cells was exciting because it gave us another piece in the puzzle of how we navigate in space. But the larger significance of the find is that for the first time, we were able to see how the brain takes complex information – in this case, information about where we are and how we move in space – to generate its own internal code to make use of that information. There is no grid pattern out in the world – this is just how the brain makes sense of the environment.  The door was opened on this discovery by John O’Keefe’s discovery of place cells, which fire when an animal is at a specific place. In the past, it has been difficult make associations between the firing of neurons deep in the higher parts of the cortex and sensory input, because as the distance between the sensory input and the neuron increases, the firing of the neurons may be triggered by a multitude of converging sensory channels along with intrinsic processes that we don’t really understand.  But O’Keefe and his colleagues found that most hippocampal cells had place fields with distinct firing patterns that collectively allowed the brain to create a map of that environment. Here we had neural activity – the firing of the place cell, deep in the hippocampus – that was clearly associated with a property of the environment, the animal’s location. The discovery of grid cells took this a step further – and it raised new questions that have continued to shape our research, as we seek to understand how grid cells operate and are generated and how they interact with other cell types and in more distant brain structures. Here, we think, lies a key to unlocking the mystery of how the brain computes. **Border Cells and Becoming a Kavli Institute** We have made a great deal of progress since our 2005 discovery. In 2006, for example, we and our colleagues, led by Francesca Sargolini, a postdoc, found cells in the medial entorhinal cortex that tell the animal which direction it is facing, called head direction cells. Previously these had been reported in the dorsal presubiculum by Jim Ranck in 1983.  In 2007, we were selected by the Kavli Foundation as the fourth Kavli neuroscience institute, an award that provides funding for basic research in perpetuity. This meant our lab had two names, the Kavli Institute for Systems Neuroscience and the Centre for the Biology of Memory, and a significant increase in funding and support.  In 2008, we and our colleagues, led by then PhD candidate Trygve Solstad, discovered a third type of entorhinal cell type that we called border cells, because they fire at the edges and boundaries of the local environment. We had already seen these kind of cells when Francesca Sargolini discovered the head and conjunctive grid-head direction cells in the medial entorhinal cortex, but we needed a student to search systematically for them and to do the manipulations that were required to call them border cells – like inserting a wall in the box and seeing that the cell would fire again, along the new wall. **Gamma Oscillations, Map Resolutions and “A Protein”** Parallel with studying border cells, we asked how CA1 cells in the hippocampus were able to cope with receiving what appeared to be conflicting information from the hippocampus itself – from CA3 and from the upstream structure, the entorhinal cortex, at the same time.  Laura Colgin, our then-postdoc, published a paper in 2009 in *Nature* showing that the brain uses gamma oscillations to route information between grid networks in the entorhinal cortex and the place and memory networks in the hippocampus, which effectively allows the brain to filter out distracting information and focus on one bit of information. We worked for more than five years to finish this amazing story, which shows that passion and persistence go hand-in-hand to produce ground-breaking results.  Also in 2008, with our PhD candidates Kirsten Kjelstrup and Vegard Brun (who were also a couple), we described how the brain makes maps of different resolutions both in the hippocampus and in the entorhinal cortex, thus using place cells and grid cells to create everything from a larger overview map to a finely detailed map. That led the way to the discovery in 2011 led by our colleague Lisa Giocomo that the brain’s ability to make these detailed maps at fine resolution was controlled by a single protein. This last paper was published in *Cell* with a companion article in the journal *Neuron*, published by our sister Kavli Institute in New York, headed by our friend and colleague Eric Kandel, whose laboratories had created the mice used in the experiments. **Recording From Many Grid Cells** By 2012, with the ability to record from many grid cells from individual rats, and as many as 186 neurons in one rat called Flekken, we were able to describe how the brain shifts between different map resolutions in a step-wise fashion rather than continuously, and that the brain has at least four difference maps of location, where grid cells are organised into different independent modules in which the scale, orientation and phase relationships are all preserved. These results were published in *Nature* with another fantastic couple and PhD candidates Hanne and Tor Stensola as first authors.  It had not been possible previously to record from so many cells, which is why we suddenly could show that the hippocampal maps were independent. What was also exciting about these data was that we showed in 2007 that when cells in the hippocampus formed statistically significant different ensembles of active cells – different maps for each environment (Fyhn et al., 2007), this was accompanied with a re-anchoring, or shift of the position of the grid cells relative to the boundaries of the boxes in the different rooms.  The models that had already been developed in 2005, just after we discovered grid cells, suggested that place cell activity was the result of the linear summation of grid cell activity (see Solstad, Moser and Einevoll, 2006, for example). Thus, the discovery of different independent grid modules solved the question we faced in 2007, which was to figure out how grid cells could contribute to the activation of several thousands of different ensembles of hippocampal cells if the grid cells were all part of the same map. Independent grid modules suggested that the entorhinal cortex cell activity could trigger the separation of different memories. However, we have not yet been able to prove that this is the way it works. **Optogenetics and Viruses** To address this issue, we first needed to know that grid cells project to the hippocampus. In 2007, we got an email from Sheng-Jia Zhang that eventually led to us being able to answer this question. He asked if we would be interested in having him come to our lab to set up a molecular lab so that we could use a new molecular tool called optogenetics to address questions we were interested in. He came at a moment when we were very eager to understand the entorhinal – hippocampal circuit so we accepted him, his wife Jing Ye and two students he brought with him, Chenglin Miao and Li Lu. They built a molecular lab with the help of a technician in our lab, Alice Burøy.  In 2013 we were able to use defanged viruses to introduce a gene for a fluorescent marker in addition to a gene for the light-sensitive protein channelrhodopsin. The AAV virus was injected into the hippocampus. It was manipulated in a way so that it would go into the axons of cells projecting to the hippocampus. In this way we could examine which neurons in this part of the brain send axons to place cells in the hippocampus. Thus, when we found grid cells, border cells and other cells in the entorhinal cortex responding to the light at a very short latency (less than 10 ms) coming through an optic fibre that we had inserted into the entorhinal cortex along with the electrodes, we started to believe that these cells sent information to hippocampal place cells. Of course we had to do a set of control experiments to be sure. This is why such ground-breaking data usually takes more than four or five years to write up and get published. This story tells us that the way we like to work is not limited by the lack of methods or tools. Either collaborate with other good labs or set up the method in your own lab to follow your dreams! **Remapping** We have also worked with cells inside the hippocampus. Since we know from the late 1950s (Scoville and Milner, 1957) that the hippocampus is important for encoding and storing episodic memories, it is exciting to understand how the hippocampus solves problems like not mixing similar information and recognizing an object or an environment with only slight changes. These processes are called pattern separation and pattern completion.  In the mid-1980s, Bob Muller and John Kubie showed that small changes in the environment caused large changes in the hippocampal place maps, in a process they called remapping. In 2005, with Stefan Leutgeb, his wife Jill Leutgeb and others, we found that there are at least two types of these kinds of remapping processes. One we called global remapping and the other rate remapping. Rate remapping is recognised by cells keeping their place preference in the test box, but changing the rate when there is a minor change in the environment, such as changed colours on the wall of the test box.  In contrast, global remapping was typically seen if the changes in environments were big, for example that the test rooms were different even though the test boxes were almost identical. In CA3 of the hippocampus, different cells were active or if they were active in both rooms the spatial preference would be shifted, for example a cell with a place field in the middle of the box in the first room could then have a place field in one of the corners of the box in the other room.  This year we published a study, led by PhD candidate Charlotte Alme, showing that the hippocampus can form ten significantly different new maps when rats were tested in ten new rooms over two days. The ten-room experiment demonstrates that when graduate students are passionate about their work and their animals, impossible data collection is made possible. **Teleportation** The remapping experiments in the lab led us to ask what happens if there is a conflict in the animal’s current idea of where it is and the sensory inputs the animals perceives. In order to address this exciting question, Karel Jezek, a postdoc in the lab, ran the animals in a science-fiction inspired experiment. The experiment involved making the animals feel as if they had been teleported from one box to another in a fraction of a second. We were able to create this illusion by training the rats in different boxes that were differentiated only by their lighting schemes. First the rats ran between the boxes, which were connected with a corridor, then the corridor was closed and the rats were tested in only one box where we were able to flip a switch to change the lighting scheme that was associated with one box to the lighting associated with the other box. Thus, while the animal was foraging for chocolate crumbs in one box, we could flip the switch and it would suddenly perceive itself to be located in the other box.  This procedure allowed us to see that each map can be represented in chunks of one theta cycle, or 125 milliseconds, and that the brain’s two maps would compete until one took over, and the hippocampus reliably represented the box that was consistent with the landmarks for that given box. This experiment can typically be compared with a situation we all have experienced: We suddenly wake up in the middle of the night in a hotel room. We are confused, and before we realise that we are not at home but in a hotel, our brains have been switching back a forth between the map for the hotel room and our bedroom at home. **Six Research Groups** Our centre now consists of six research groups, led by Menno Witter (functional anatomy), Yasser Roudi (statistical physics of interference and network organization), Clifford Kentros (transgenic investigation of neural circuits), Jonathan Whitlock (cognitive motor function) and ours (space and memory). Our sixth and newest research group is headed by Emre Yaksi, who studies sensory computations in zebrafish.  The strength of this structure is that we can collaborate across groups. One beautiful example of this was a collaboration between three of the six groups which led us to resolve a question that we had puzzled over for almost eight years. Even with new analyses, new ideas and a lot of discussions of the data both in the lab and at international meetings, we could not figure out what was going on, which is why we did not publish the data.  Menno Witter’s group had discovered that stellate cells did not communicate directly with each other, but with a re-route through inhibitory cells. Thus, the grid cells were surrounded by inhibition. At the same time, Yasser Roudi and some of the people from his group had made a computer model of this network and were able to show that this kind of network could produce a functional grid cell network. The excitation could come from the hippocampus and head direction input. The prediction from this model was thus that by removing the excitation from the hippocampus, the grid cells would change from being grid cells to becoming highly head direction modulated.  This is exactly what we found in our lab – but could not explain before the collaboration. We submitted two manuscripts to *Nature Neuroscience* and were lucky enough to get them published back-to-back in 2013. We were so happy and proud to finally be able to publish 8-year-old data that had been so intriguing and yet so difficult to decipher – and to be able to work so closely between the different groups at the centre. **The Norwegian Brain Centre** The Norwegian government recognised the importance of neuroscience in Norway by funding the Norwegian Brain Initiative in 2011, which led to us open the Norwegian Brain Centre in 2012 as a collaboration between our lab and research groups working with medical imaging from St Olavs Hospital. The University of Oslo’s Centre for Molecular Biology and Neuroscience is a partner in the Norwegian Brain Initiative. We got a new, big, beautiful lab, with the equipment we need to do ground-breaking science.  We are also working hard to make sure that some of our most important lab workers, the rats and mice, have the best environment a science lab can offer. Most of the animals live in big enriched cages, with toys and nests and together with their cage mates. We also try to let animals that wear electrode implants live with their siblings, since rodents are such social creatures. We have a veterinarian who works full-time for our centre, and four well-educated animal care-takers who love animals. In order for them to always remember that the animals are individuals, they have their own pet animals in the animal quarter. Our goal is that our animals be as happy as possible. **A Second Centre of Excellence** Our lab was also awarded funding at the end of 2012 for a second 10-year-long Centre of Excellence by the Research Council of Norway, just as our first decade-long grant ended. Our new centre is called the Centre for Neural Computation, and is directed by me. It was such a relief when we got that grant. We had just ended the first ten year of CoE funding and we were so worried that we could not keep our lab running at the level we had ambitions for if we did not get new funding.  The day the second CoE funding was announced we were euphoric, and we celebrated (Fig. 7)! And celebrations are important as motivation and glue for the team. The support made us even more inspired and enthusiastic than we had been before, and I was handed an exciting new challenge – to serve as director of a centre that had grown from two people to almost one hundred people from different backgrounds and nations (Fig. 8).  The continued support from our colleagues, the Kavli Institute, the Norwegian University of Science and Technology, the Norwegian government, as well as the city of Trondheim and the county of Sør-Trøndelag has made it possible for us to pursue our dream of unravelling the mysteries of how the brain computes and makes memories and behaviours.  Early on in our careers we realised the importance of bringing in different kinds of expertise in the pursuit of common goals. We also recognise the risks that come from being wedded to only one kind of investigative tool. We’re continually looking to expand our neuroscience “toolbox.” Our six groups are all eager to work together towards our vision: how does the brain generate cognition and mental function. We have an exciting future in front of us. **Two Children and a Lab** Through hard work and persistence together with fantastic colleagues, I have worked towards my dreams and vision from my childhood: to understand how the neural activity in the brain generates behaviour and cognition. By discovering the grid cell network, we suddenly understood something fundamental about the mystery of the brain – how the brain generates a universal map of the environment. The grid cells that do this are located far away from the senses that tell the animal what is out there. In the same deep structure, the entorhinal cortex, we have also discovered other functional cell types that signal the boundaries of the environment, cells that signal the direction the animal is moving in and cells that combine the head direction and grid signals.  We have shown that with changes of sensory input the universal grid map is shifted and anchored differently to the environment – probably changing the active ensembles of hippocampal place cells. Knowing that the hippocampus contains engrams involved in episodic memories, we have shown that this magic circle of entorhinal and hippocampal cell interactions is part of the mechanism for memory. We are working with findings that are the very essence of being a human being: our conscious memories are what make us who we are, and these memories are anchored in space, in knowing where we are in the environment.  Our two daughters have long joked that our lab is like our third child, and in many ways, they are not wrong. We are proud parents to all three of our children. Having real “biological” children in addition to our laboratory “child” has brought an amazing happiness to my life. I think that makes it easy for me to do good science.  I have been lucky to live a fairy tale life, with a partner and a long-time collaborator, Edvard Ingjald Moser, who has supported me and helped me fulfil my dreams ever since we met. We have two wonderful daughters, Isabel Maria Moser and Ailin Marlene Moser. They are wise and loving human beings. Being an internationally recognised scientist brings a lot of adventures and a large network of friends and colleagues across the world (Fig. 9). We have travelled to so many different places and learned so much. Our children have come to think it is quite normal to live like this. Ailin was still a pre-teen when she asked us: why haven’t we visited Easter Island yet? She could also have asked; why haven’t we understood our brains yet? |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0524=MBM  [May-Britt Moser] (Answers telephone speaking in Norwegian)  [Adam Smith] Oh hello, this is Adam Smith calling from NobelPrize.org. First of all many congratulations on the award of the Nobel Prize.  [May-Britt Moser] Thank you, so Göran called me earlier today as you know and I was crying. I was in shock and I’m still in shock. This is so great.  [AS] Where were you when you received the call?  [MBM] I was in a meeting, so we normally have meetings with the lab on the Monday morning to go through some data and we had such a great discussion. I had another meeting waiting for me so it was in the middle of two meetings and we were discussing the last part of the data, and those data are so exciting. [Laughs]  [AS] Too many exciting things to deal with at the same time I suppose. [Laughs]  [MBM] The only, only sad thing on a day like this is that Edvard, my husband, is still on a plane. So he doesn’t know. It’s so frustrating because we can’t get in touch with him.  [AS] That’s deeply frustrating, yes. When and where does he land?  [MBM] So he will land in Munich and I think he said around 1 pm.  [AS] Right. So there’ll be a posse of people waiting for him I imagine, perhaps you too.  [MBM] [Laughs] That would be fantastic if there would be people waiting at the airport. He would be in shock.  [AS] So you are a married couple and it’s very unusual for married couples to receive the Nobel Prize. One thinks of the [Coris](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1947/) and the Curies, but what’s the secret of your partnership?  [MBM] I think it’s the secret … Ask me about the secret of why we could come so far together in science.  [AS] OK  [MBM] I think that is that we have the same vision. We love to understand and we do that by talking to each other, talking to other people and then try to address the questions that we’re interested in, in the best way that we can think of. And to be able to discuss this when you get an idea on the spot instead of plan a meeting in one or two or three weeks, that makes a huge difference.  [AS] So there’s a lovely spontaneity about it.  [MBM] Yeah, and it’s so funny because you know we have the Kavli Institute here and we had this meeting with the Kavli Directors and they said “Yah, and then we have to plan all these meetings” and I said “It’s easy for us because we can have breakfast meetings almost every day” [Laughs]. And of course when you want to select your colleagues you want to have colleagues who respect you, who you can trust and who will support you and I think that is the clue, isn’t it.  [AS] Exactly. And talking of colleagues you know your co-Laureate John O’Keefe very well.  [MBM] Yeah, that’s so fantastic. You know, he was the supervisor of how to start to do these recordings in ’95, in the summer of ’95.  [AS] And you’ve remained close ever since?  [MBM] Yes. I think it’s also so extremely important to say that this is an honour for all the people who have supported excellent science in Norway. Of course our group, our family. But also the local people and the politicians and the research council, all have been extremely, extremely supportive to us. And I think it wouldn’t have been possible if that wouldn’t be the case.  [AS] That’s very nice. And so it’s a celebration not just for neuroscience but for Norwegian science today.  [MBM] Absolutely. And also that people trusted us and supported us, it’s a celebration of that.  [AS] Lovely, well, many, many congratulations again and thank you for speaking to us.  [MBM] Thank you so much.  [AS] Enjoy your day.  [MBM] [Laughs] Thank you. OK, it was nice to talk to you.  [AS] Nice to talk to you too.  [MBM] Bye! |
| Interview |  |
| Q19 | Could you please explain your Nobel Prize awarded work for 13-14 year olds? |
|  | Edvard Moser: We have discovered parts of an internal map that we have in our brain, a map that tells the rest of the brain where we are in the room or in the world.  May-Britt Moser: It is like a GPS-system almost.  Edvard Moser: There are different types of cells. O’Keefe, who is the third prize winner, he found a type of cell that is called place cell, which is active only when animals or humans are in one certain place. We found another type of cell that fires active in many places and those places where the cell is active tend to form strictly hexagonal patterns so the many locations in the room where the cell is active form a grid or like a coordinate system that tells the brain where we are.  May-Britt Moser: The animal is walking, and it can be an animal, it can be a human being, then you can record with tiny sensors in the brain and you record the electrical pulses that are released from the cells and you magnify them 10 000 times and then we can listen to one by one cell. And then if we now listen to one place cell and this is the area where the animal is walking around – this is the rat and then it is silent, silent, silent and then suddenly you start to hear: “Po, po, po, po, popo, popo, popopo” and then the rat is moving out again. And whenever the animal is coming back to this place, it is the same thing happening: “Po, po, po, po, popo, popo, popopo” and it doesn’t matter how the animal is coming in, from which directions. And the interesting part is that these place cells, they are located in different areas in the environment. So, one place would be active here, and another here and so on, but then the grid cell that we found doesn’t have one single active field, but it has several ones and they are separate like Edvard said, like each field look like a checkerboard, how do you say? The chess …  Edvard Moser: Like hole in a Chinese checkerboard.  May-Britt Moser: Yes, like a Chinese checkerboard, thank you. So then where the marble should go, that is where the activity field is. And we know that this Chinese checkerboard, they have all these small triangles in between all marbles and that is exactly the firing patterns of the grid cells. Then the grid cells come in different sizes, big fields, big distance between the fields, small and so on. This is the information that goes into the hippocampus, which is the place cell, where John O’Keefe found the place cell. And the interesting part is that, the hippocampus with the place cells, if you lose your cells in this structure, you can’t remember what you had for breakfast, if you had breakfast at all. And if you lose the same cells you can’t find your way in the environment and the input to these cells, that is the grid cells. So, the grid cells are tightly involved in both space navigation and memory. |
| Q1 | What brought you to science? |
|  | Edvard Moser: For me, I was interested in science already when I was a child. I didn’t really know what is was, but I read a lot about scientists and their work and I thought becoming a scientist was like digging dinosaurs, that is what I thought, but I thought that was exciting. And then I read about meteorology and about volcanos and about physics, everything that I could come over, so I nearly knew that I wanted to do this but didn’t really know much what is was like. And then many years later, when I came to university, then … Because I knew wanted to go to university, and then together with May-Britt I then began studies of psychology and then the part of psychology that excited both of us by far the most, was the brain and trying to explain behaviour by the brain and that is an experimental science. And I think I never really had anything else on my mind at least, except perhaps for very short breaks, so I wanted to be a scientist from the beginning.  May-Britt Moser: You wanted to study volcanoes.  Edvard Moser: Yes, I mean the field was open. For a long time I wanted to become a physicist and work on elementary particles, but now I am so glad that I ended up in the brain.  May-Britt Moser: I didn’t read that much as Edvard did but I was extremely curious. And I was curious on humans and animals and I really wanted to understand why they do this and why they don’t do that. And when I became older I knew that I have to go to the university in order to do this, but I didn’t, as Edvard said, I didn’t know how, so when I went to the university finally then I started to study mathematics and physics because those were the topics I loved in the high school, but I didn’t know what kind of job I could get. And then luckily I met Edvard, even though we had been at the same high school, we didn’t know each other that well and then we decided, hm, should we do this together, and then we just made a new path step by step without knowing other things standing star in front of us. We want to understand why the brain or how the brain is working to give behaviour. That is what we’re still doing, and it is fantastic. |
| Q5 | Who is your role model, and why? |
|  | Edvard Moser: I’m not sure there is a single role model.  May-Britt Moser: Me!  Edvard Moser: No, I think it is part of becoming a scientist that you actually have to trust your own judgement as well and go for the really long term goals that no one else has put up, but there are many scientists who I admire but I think it would be kind of wrong to mention one by name because then I always forget the second one.  May-Britt Moser: As you say it is extremely important the support that we have got from other scientists and that they have believed in us and given advice when we needed advice. For example, when we started with our labs just half-year after our PhD:s. That was a crazy decision but still people supported us and said, you can do it if you focus on this and that if you collaborate instead of splitting and trying to build two labs and so on.  Edvard Moser: But since the context is Nobel Prizes, you can always mention a few names at least, so [Eric Kandel](https://www.nobelprize.org/prizes/medicine/2000/kandel/facts/), his work we got exposed to very early and already in the 1980’s was work that we read about and thought was super exciting and then we met him and he has sort of followed us all the way. Another one is [Torsten Wiesel](https://www.nobelprize.org/prizes/medicine/1981/wiesel/facts/), who is also related to Sweden. His work in the 60s especially, was extremely important.  May-Britt Moser: [Hubel](https://www.nobelprize.org/prizes/medicine/1981/hubel/facts/) and Wiesel, it was just like the bible, and the same with Eric Kandel’s book.  Edvard Moser: Defined our field. So those two are at least persons that have meant a lot both for our field and for us personally.  May-Britt Moser: And also for my PhD, then I studied structural changes after different experiences, like living in a enriched environment and then it was so fantastic for me to read about the *Aplysia* work of Eric Kandel because he had shown the same thing in the *Aplysia* when this tiny sea slug is learning. And then I could believe also in my own data because I have read his work. On a lot of different occasions, these people have been important, and also when we were master students. |
| Q16 | At what point did you realise your work was a breakthrough? |
|  | Edvard Moser: I think pretty early actually, when we saw that the firing pattern of this cells forms a strictly hexagonal structure, so very, very regular, almost like a coordinate system then …  May-Britt Moser: That was crazy.  Edvard Moser: … and it was so different from what anyone had expected that we knew that this would be kind of revolutionary, so we worked on really, being sure that there was no mistake in the data. We did lots of control experiments and we sent it to *Nature* and it went right in, so that kind of confirmed our suspicion that it was important. Yet it was of course, difficult to imagine that only nine years later it will be a Nobel Prize. That is perhaps beyond, but still we knew that it was very important from the beginning.  May-Britt Moser: The exciting part of these cells is, like Edvard said, that we tried to do all these controls to find out – is there a specific order, does the rat see something specific that make this grid pattern – and there is none. That means that this pattern is generated by the brain itself and then it’s like going into the brain and detecting the mystery of the brain by studying these cells. And if you start to understand even more how they are generated we understand so much about how the brain is working. |
| Q19 | What were you doing when you heard you had been awarded the Nobel Prize? |
|  | Edvard Moser: In my case, I was actually out flying, so the rest of the world knew about it and I didn’t know anything. So I only got the news when I landed and that was also a bit peculiar because I came out of the airplane and then I was met like a VIP with flowers and name sign at the gate, not after the baggage as usual. I sensed something was strange, but it wasn’t on my mind that this was the day when the Nobel Prize was announced. I would have known it, but I didn’t think about it. And then I asked: “Why all this special attention?” and the lady who picked me up she didn’t know, she knew that it was a prize, but she didn’t know which prize. So she mixed it up with something else and was still not clear and what made it clear to me was when I checked my phone because on that flight to Munich, two hours, then there had been hundreds of calls and then there was a text message from Göran Hansson, the secretary of the Nobel Committee and then I, sort of, finally sensed it. |
| Q19 | And where were you, May-Britt? |
|  | May-Britt Moser: When I heard about the prize, then I was in a lab meeting at a lab and it was such an exciting meeting and it went over time and I was expecting to have another meeting with other people. I got this phone call and I saw it and I said: “No, I don’t recognize this number, I don’t want to speak to this person, I am so busy”. And then I thought, hm, maybe I should take this phone and pick it up and I did, and I heard that it was Göran Hansson and then I was just, hm, why are you calling me? And then I thought maybe this is something serious, I went to my office and then I realized that it was about the Nobel Prize. Then I thought maybe he wants to have some comments about another Nobel Prize winner, just let me sit down and relax and then he said “No, it is you. You and O’Keefe and Edvard who got the Nobel Prize” and I said: “No, I don’t believe you, please can you send me an e-mail so that I can read it because I don’t believe my ears”. And then I got the e-mail and still I didn’t believe it. So it went on and off, I believed it and then I didn’t believe it and then I went to the dean and showed the letter on my phone to the dean and said: “Do you read the same thing as I do?”. He was just: What do you have here?” and then he: “You won the Nobel Prize?”, and it was crazy. So that was an experience, but then I realized that I was so grateful. Especially also about getting this focus on the work that Edvard and I had done and the whole team and also the support that we have got from Norway, from NTNU, from the local university, from politicians abroad, Kavli Institute and it was just “oh wow”, finally we can say thank you to them, that they believed in us. |
| ID | 0525 |
| Biographical | I was born in 1962 on the west coast of Norway, about 200 kilometres north of Bergen. I spent the first 9 months of my life on Haramsøy (Fig. 1), an island with fewer than 500 inhabitants and, at that time, only a single daily ferry connection to the mainland. In 1963 my parents and I moved to a more urban environment, relatively speaking, and settled on another island, in Hareid, a village with about 4,000 inhabitants spread across four different settlements (Fig. 2). My two younger sisters were born there, and I lived there until I finished high school at age 18 in Ulsteinvik, on the same island. **My German Roots** My parents were German immigrants, a rare species in Norway during the first decades after World War II. They met during the war in Kronberg im Taunus, a small village north-west of Frankfurt am Main. My father was the oldest son of the pastor in Kronberg; my mother was the daughter of a famous butcher in Essen, in the Ruhr area near the Dutch border. Together with her siblings, my mother was sent out of Essen when the bombing of the Ruhr area began in 1943. Her father could afford to send his children to a private family in Kronberg through a teacher they knew in the village. The children were brought back to Essen in 1944 because my grandfather feared that Germany would be divided, with Kronberg and Essen going to different territories. After the war, my parents met again in Kronberg and later in Bonn.  Both of my parents wanted an education but did not get an opportunity to pursue one. In my father’s family, the oldest son was expected to be a pastor, which had been the tradition for the last six or seven generations. My father, however, liked to play cello and wanted to study music. After the war there was no money for him to pursue a formal education, so instead he learned a trade in Bonn, with Klais Orgelbau, where he made church organs. After a few years, he came across an advertisement by a small organ factory on an island off the west coast of Norway that was looking for skilled labour. My father applied for the job, got it and moved to Haramsøy in 1953.  My mother wanted to become an interior designer but this type of career was all but closed to her because it required work experience and companies were not willing to accept women for training. Instead she went to a business college and subsequently got a job in Essen as a secretary with AEG, a large German producer of electrical equipment. While she was working at AEG, she came in contact with my father again. He had by then moved to Norway, and my mother visited him on a nice summer day in 1957. In 1958 she gave up her AEG job and moved to Haramsøy.  Norway was a big change for my mother. She came from quite a wealthy family in a big city in Germany. In Haramsøy, she was expected to be a housewife like all other women at the time. The shops had only three types of vegetables – cabbage, turnips and carrots, and there was still outdoor plumbing, which my mother had never experienced before. The weather was harsh and the laundry often flew off the outdoor line where she hung it to dry. **School Days** I was born into two different worlds – a poor community on an isolated but beautiful island that offered little more than was needed for work and survival, and a rich cultural tradition that had its roots in the European continent. A third dimension was added when we moved to Hareid, which in spite of its small size, had an exceptionally active community life centred around the church and the Christian meeting house. But I was still in the middle of the Norwegian Bible Belt – no alcohol, no playing cards, no dancing. My parents’ love for good wines remained a well-kept secret.  I went to primary school in Hareid. As was the practice at that time, all students were taught at the same level, and I had to learn everything at the same pace as everyone else. I was the only child who wanted to learn French, so I was put in a bookkeeping class instead. Occasionally I got a few extra assignments to feed my academic interests, but it was my mother who saved me, by giving me tons of books. I started with Donald Duck comics, which my mother gave me when she wanted me to be quiet during the early morning hours. At the age of 4 or 5, I was so motivated to understand the content of the speech bubbles that I cracked the reading code largely on my own. Later, after I started school at the age of 7, which was when children commonly began school at the time, I got real books – with a strong emphasis on science. I read a lot – about geology, meteorology, palaeontology, astronomy, all of the sciences – and I asked for more. I was totally absorbed by these books.  The books introduced me to science and it became my passion. With a friend I started an astronomy club where we learned everything we could about planetary systems, and we memorised the distances between all of the planets and the Sun (I had an affection for numbers). I bought a globe with the first money I ever earned from mowing the lawn. I learned about all of the countries on that globe, all the capitals, the mountains and rivers, and dreamed about visiting all these places.  My father took me around in Norway in his travels to tune church organs, and we visited remote islands and mountain areas, which fuelled my interest in exploration. I collected stones, I had a herbarium, and I got a chemistry set, which enabled me to create some noxious gases in the bathroom. I played school with my younger sisters – I was the teacher and taught them about everything I had read. My parents encouraged my interests further by feeding me more books. As I got older, I even sent my mother to the university bookstore in Tübingen to get astrophysics books that I could not buy in Norway.  It became clear to me that someday I might become some sort of scientist, but I didn’t really know what kind, nor did I have any idea about what it really meant to be a scientist. Scientists in the books I read spent their time digging up dinosaurs. During summer holidays in Germany, I visited the Senkenberg Museum in Frankfurt, every time – it was my favourite holiday destination. I saw dinosaurs, fossils, mummies, rock collections, and insects. I wanted to understand evolution and natural history and in my imagination, scientists were people who provided things for the natural history museum.  High school offered me more challenges. The school was in Ulsteinvik, on the same island as Hareid, but on the other side of the mountains. The teachers there were really warm and motivated and suddenly school was much more fun. I was no longer the only one who liked to learn and I could study without disguising it. I liked mathematics and natural sciences but was also fascinated by history and literature, perhaps due to my teachers in these subjects, in particular my form teacher Gunder Runde. With him as a guide, I wrote my thesis about Ibsen. My fascination with Ibsen is still alive to this day. I graduated from high school in 1981 with a top grade in all subjects except physical education (I was never very good at football).  And – I met May-Britt at Ulsteinvik. We were in the same mathematics, physics and chemistry classes, but since she came from another island, and high school cliques were defined by islands, and I was quite shy, we did not interact all that much. When I was not at school and not studying (which I did most of the time), I walked in the mountains on the island. I visited every single peak. **Leaving the Island** I grew up during the Cold War. Military service was compulsory for men who were not absolute pacifists. Most men from my region of Norway were sent to stations in the far north of the country, near the Russian border, and I was no exception. After working for three months at a local shipyard when I had finished high school, I was ready for military service in October 1981. I was trained as a communications officer and worked in an underground bunker in Kautokeino, a Sami village near the border of Northern Finland, in the far north of Norway. I got to know a few people in the village and enjoyed their openness and different life style. I also liked the endless open country, and took long walks when I was not on duty. My task in the bunker was to receive and send secret messages about military activity in the airspace near the Russian border. Not much happened though, so I had time to study differential equations and think about my future.  My year-and-a-half of military service meant that I had to start at the University of Oslo in the middle of the academic calendar, in January 1983. By this point I was still unsure of what I would study but certain that it would be in the sciences. I considered elementary particle physics and nuclear physics but signed up for a course in chemistry. I was fascinated by biochemistry and genetics but had to start with the basics. The first course was in inorganic chemistry. I thought there was too much rote learning and I felt like I wanted to use my energy on other things.  It was about this time that I bumped into May-Britt again by chance. Just before I had moved to Oslo, we met on Karl Johans Gate, Oslo’s main pedestrian zone, and she offered to show me the university. She had been there for a year-and-a-half already and was an obvious guide. It turned out she had also puzzled over studying different science topics – she had taken courses in mathematics, physics and astronomy and was considering a future in geology, since the oil adventure had just started on the Norwegian continental shelf. She even considered becoming a dentist but none of the subjects were as interesting as she thought they would be. So we had something in common (Fig. 3). **Turning to Psychology** At the time I had just finished reading Freud’s *The Interpretation of Dreams*, and I found it fascinating. May-Britt was also attracted to psychology. In August 1983, we signed up for a one-year bachelor’s programme in psychology. The coursework covered the entire field of psychology, which was much broader than we had imagined. We became aware of behaviourism, which had a scientific rigour that we thought outshined other subfields of psychology. We saw that behaviour could be broken down into elementary laws and that behaviour could be predicted based on the correct timing of discrete stimuli in relation to the animal’s behaviour. At the same time we realised that behaviourist psychology was simple – too simple – and we missed explanations that involved the underlying neural mechanisms.  During our studies, we attended a lecture by Svein Magnussen, in which he described the pioneering work of [David Hubel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/hubel-facts.html) and [Torsten Wiesel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/wiesel-facts.html), who by the early 1960s had already shown how the visual image was broken down into elementary neural responses in the visual cortex. We went to see our teacher in behaviourism, Carl Erik Grennes, and asked how we could learn more about the interface between psychology and physiology. He gave us a copy of a special issue of *Scientific American*, published in September 1979, which was all about the brain. The magazine included [Eric Kandel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2000/kandel-facts.html)‘s demonstration of synaptic mechanisms of memory in *Aplysia californica*, and the characterisation of the mechanisms for feature analysis in the visual cortex done by David Hubel and Torstein Wiesel. There was even a piece by [Francis Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/crick-facts.html), who at the end of his career argued for neural circuit studies and speculated about what was needed for the discipline of neural circuits neuroscience to be born. It was enough to tell us that there was science there to be done.  But in order to get any further, we had to wait a year after our bachelor’s courses before we could start our professional studies in psychology. At that time, psychology was such a popular subject that there was a one-year waiting list, even for those who passed the admission threshold. That year I worked in a psychiatric hospital. I had a full-time job, working with psychotic patients at an acute ward, before they received medication. In my spare time, I studied mathematics, statistics and programming. I took these courses only because I thought mathematics was fun but it turned out to be very useful for my later work, although I did not realise it at that time. While I was at the psychiatric hospital, May-Britt worked in a geriatric institution while she also took classes. During this waiting period, our interests merged and we started thinking about a common future. We went to Kilimanjaro to get engaged in 1984 and decided to marry in 1985, just before we took up psychology again.  The first semester of the professional studies programme in psychology focused on social psychology. May-Britt and I got involved in a research project on small group dynamics and even contributed to a paper – our first publication. But our interest in the brain persisted and we continued to bug Carl Erik Grenness. Carl Erik advised us to approach Terje Sagvolden, the only psychologist at the university with research projects in neuroscience at that time. Terje was working with neurochemical mechanisms of attention deficit disorder in rats. His idea was that if he found out why a certain strain of rats was hyperactive, that might give us some clues about what causes hyperactivity in children. We learned how to design experiments, we learned behavioural analysis, and we learned more statistics in Terje’s lab. The work resulted in three papers on behaviour in hyperactive rats. The results were perhaps not all that revolutionary but we were proud to see our own work published.  But we were impatient. The focus was still too much on behaviour while the underlying neural operations remained in the dark. Terje saw our willingness to go further and sent us to Uppsala for a collaborative project on neurochemical modulation in hyperactive rats. We stayed for a month but in the end concluded that there was no reason to go all the way around the barn to find the door. In Oslo, there was a famous professor at Terje Sagvolden’s department who was working on the neural mechanisms of memory – Per Andersen. We had seen Per on TV but had never dared to approach him. One day though, after he and his group gave a seminar on the mechanisms of long-term potentiation (LTP) of synaptic transmission and the possible relationship between LTP and memory, we decided that this just might be our future. LTP might be the bridge between physiology and psychology that we had searched for so long. **Working with Per Andersen** One day in 1998, we went to Per’s office and asked if he could take us on as master’s students in preparation for a PhD. Per was quite sceptical. He really didn’t want new people, because he already had enough students. Moreover, he might not have had the highest opinion of psychologists, although he also wanted to make the connection to behaviour. But we were persistent and shared our ambitions with him. In the end he gave us a paper by Richard Morris, who was at the University of Edinburgh and had invented the water maze, and issued us a challenge: he told us that if we successfully built a water maze laboratory, he would take us on.  A water maze is a big tank, roughly 2 metres across, filled with milky water. There is a platform in the tank that is hidden by the water, which rats can learn to find. As part of our “test,” Per wanted us to actually construct the tank in the basement, but we convinced him that it would be acceptable to buy a tank from a plastic factory on the West Coast that made fish tanks. A few months later the water maze was in place in a small room in the basement. The pool was filled with 1200 litres of water and 3 litres of milk. Every day we emptied the pool, filled again with water, and went to the shop to buy new milk.  We used the water tank to address one of Per’s greatest dreams. He wanted to make an *in vivo* hippocampal lamella that was as small as possible but at the same time large enough to support learning. The idea was that synaptic changes would be denser in such a preparation – dense enough to be detected by physiological recordings or microscopic analyses. To make this lamella, we removed the remaining hippocampal tissue by aspiration under the microscope. Per wanted the *in vivo* lamella to be in the dorsal hippocampus but to be sure that the enhanced plasticity of the lamella did not reflect the location of the lamella, we asked Per to include a control group where the lamella was in the ventral part of the hippocampus. We also agreed that we might need to try lesions of different sizes, since we did not know how large the lamella had to be to be functional.  The control group turned out to be the key to our first success in the lab. We found it took only quite small lesions to impair navigation, and we were not able to make the *in vivo* lamella that Per wanted so much, but there was an interesting dependence on the location of the lesion. The rats with dorsal lesions (ventral remnants) were not able to find the platform but those with ventral lesions (dorsal remnants) could actually navigate very well.  As it became clear that there was a difference between the dorsal and ventral hippocampus in their involvement in water-maze learning, we searched the literature to try to understand it. We came across the work of Menno Witter, who with David Amaral had shown that the dorsal and ventral hippocampus have quite different cortical inputs, and we were able to put the findings into a meaningful context. We wrote up the master’s thesis as a joint thesis of 127 pages and published the results in the *Journal of Neuroscience*. It was the first behavioural study from Per’s lab and he was probably a bit anxious about publishing it, but after some strong encouragement from several visitors, including Eric Kandel and Larry Squire, we submitted it. It was published in 1993, 3 years after we completed our thesis.  As we finished our master’s thesis in 1990, we both wanted to continue with Per on our PhDs, but the challenge was how to get two fellowships to study with him. At the time it was very difficult to get this kind of funding. There were not many fellowships to hand out and it was not like today, when the labs have the money themselves and get to decide. The Research Council of Norway at the time was concerned about geographic distribution of their fellowships.  My proposed dissertation research was about the relationship between LTP and memory, which was what really got us interested when we first started working with Per, and which had motivated our dorso-ventral hippocampal lesion study. LTP had been discovered 20 years earlier, in Per’s group, and it seemed like the right place to pursue the question.  There were several indications that LTP might be involved in memory, but what Per wanted, and what I also found very interesting, was to see if this phenomenon could be directly observed *in vivo*. At that time, Carol Barnes had shown that LTP decay correlated with forgetting, Bruce McNaughton had shown that saturation of LTP blocked subsequent memory formation, and Richard Morris had found that learning could not take place if LTP was blocked by an NMDA receptor antagonist. But no one had observed changes in hippocampal excitatory postsynaptic potentials (EPSP) as a direct consequence of learning. So that was the PhD funding I applied for.  At the same time, May-Britt applied for a project where she wanted to see if learning and memory involved changes in the number of synaptic connections, in the same way as seen after induction of LTP. Against all odds, we both did get fellowships.  In 1991, we were ready to learn how to make electrodes and implant them in the brain. We got help with this skill from Bolek Srebro at the University of Bergen. He showed us how to make electrodes, how to implant them into the hippocampus, and how to read out the field potentials in an awake, freely moving animal. Once I had learned the technique, I implanted chronic electrodes in the performant path and dentate gyrus and let the rats wander around in a box. As they learned about their environment, the EPSPs got stronger, usually for 20–30 minutes. That was by itself no surprise and had been reported previously, but what was strange was what happened when I put the same animals in the water maze. The animals learned to find the platform but the EPSPs got consistently smaller, which really did not make sense. The hypothesis was that they should be larger as a result of naturally occurring LTP.  We finally figured out that the reason for the decrease in EPSPs was that they are very sensitive to the temperature of the brain, so the higher the temperature, the larger the potentials. The water maze was room temperature, much below the body temperature of the rat. I varied the temperature of the water maze and found that the lower the temperature, the more the EPSP was reduced. Per advised me to insert a thermistor in the rat’s brain to monitor the temperature directly and in collaboration with master’s student Iacob Mathisen, I was soon able to show that the strength of the synaptic connection was determined directly by the temperature of the brain. I showed that exploration and other learning behaviours increased brain temperature sometimes by more than 2 degrees and that EPSP changes previously reported to accompany learning were due to temperature, not LTP. We published these findings in *Science* in 1993. I defended my thesis in 1995, with Bruce McNaughton and Tim Bliss as public examiners, or opponents as they are called in Norway. The thesis defence was part of Per’s ‘Grand Slam’, where 6 of his students publicly defended their work within a week, with an impressive collection of 12 world-leading scientists as thesis opponents (Fig. 4).  I was able to show in my thesis that if temperature was subtracted, there remained small components of EPSP enhancement that reflected behaviour and possibly learning. However, the findings that temperature could so dramatically affect EPSP shook the field. Like several other scientists, when I submitted my PhD thesis in 1995, I was inspired to move on to individual cell recordings, which were much less temperature dependent. This is what finally led me to John O’Keefe’s lab at the University College of London. **Edinburgh Intermezzo** Long before we submitted our theses, May-Britt and I had decided to do our postdocs with Richard Morris at the University of Edinburgh. We met Richard for the first time at the European Neuroscience Meeting in Stockholm in 1990. This was the first time we presented our dorsal-ventral lesion study at a conference and we were extremely proud when Richard referred to our poster in his plenary lecture. Later he invited us to repeat the study with more selective ibotenic acid lesions in his lab, in order to rule out the possibility that behaviour was impaired by dorsal lesions simply because those aspiration lesions severed bypassing fibres. At the same time, ibotenic acid lesions gave us another opportunity to make the *in vivo* lamella that Per wanted. Perhaps, with more selective lesions, it would be possible to get animals to learn with only a small remaining piece of the hippocampal circuit.  The collaboration between Oslo and Edinburgh started in 1991, when we went to Richard for a month to make the first ibotenic acid lesions. We brought our first daughter Isabel, who was less than a year old, and Richard’s wife Hilary looked after her. We visited several times, and Per visited Edinburgh, and in 1995 we published the results, showing the same dorso-ventral difference in spatial learning, but now with intact learning even with quite small remnants in the dorsal part of the hippocampus. The remnant was still a lot thicker than Per had hoped for but it showed that hippocampal learning could be maintained with minimal hippocampal circuitry.  Finally, in 1995, after we had submitted our PhD theses in Oslo, we went for a longer visit to Edinburgh. By this time, we had two small girls: Isabel, now 4 years old, and Ailin, who was only 4 months old. Our focus was now on LTP. The aim was to saturate LTP using a protocol developed by Bruce McNaughton and colleagues some years before. Many studies had failed to replicate the learning impairments Bruce and colleagues had demonstrated, but we suspected that the induction of LTP was incomplete and so devised an electrode array that covered a much larger part of the perforant path input to the hippocampus. We struggled a lot to obtain saturation, and I am not sure we ever got it, but at least our induction protocol produced a learning impairment much like that seen in Bruce’s early studies. It took a while to complete this particular project, however. We worked on it in Edinburgh in 1995, then in Oslo during Richard’s winter sabbatical in 1995–96, then in Edinburgh in 1996, and finally in Trondheim in 1996–97, where we got it to work. We did not spend many months in Edinburgh but we learned a lot, met scientists from all over the world, and had great discussions that helped us define and refine our goals. Moreover, I developed a life-long friendship with Richard. **A Quick Visit to London** My postdoc in Edinburgh was paid for by a Human Frontiers grant that Richard Morris had obtained for a group of labs interested in synaptic plasticity. The LTP saturation experiment was part of this project, but based on my experiences from Oslo, I wanted to go ahead with single unit recording and look for changes in neural activity related to memory. I had hoped eventually to set up unit recording in Edinburgh but it was expensive and at that time, the lab had no experience with single units. Richard understandably hesitated but suggested that I instead go work with John O’Keefe at University College London to learn how to do single cell recordings. This suggestion was especially gracious since by this time we were already committed to moving to Trondheim later in 1996. It would also allow us to set up our own single-unit recording lab there.  I have often described the period with John as the most learning-rich time in my life, and it was. John spent an enormous amount of time with me so that I could learn everything about how to make single cell recordings. He showed me how to do the surgery, how to make the electrodes, how to do the recordings, and how to analyse the data. I had a little desk inside his office, which gave me almost unlimited opportunities to ask all the questions I wondered about. In his office, and while I was recording, we discussed what was known and not known about place cells and he alerted me to all the pitfalls in the field – it was all absolutely formative for my future.  I moved to London in March, while May-Britt stayed in Edinburgh to run LTP saturation experiments, but two months later May-Britt came too, as well as our two young daughters, along with May-Britt’s brother and sister-in-law as babysitters. Our visit was a training visit and nothing more but the animals we implanted ran on tracks that could be shortened and extended to dissociate the contributions of landmarks and path integration, a question that we have continued to pursue in our research to this very day. In July, finally, we flew back to Norway, ready to set up our own lab. **The Unexpected Move to Trondheim** Many things happened in parallel in 1995–96. During the course of completing our PhDs and preparing for our postdocs, May-Britt and I were called in for an interview at the university that would become the Norwegian University of Science and Technology (NTNU), in Trondheim, right before Christmas in 1995. Earlier that year, Terje Sagvolden had advised us to apply for a faculty position at NTNU’s Psychology Department and we did so, mostly just to test the waters. We were confident that we would not even be shortlisted, given that we had only a few papers and had not yet defended our PhDs. Yet they were indeed interested and we went to check out the location, even though our plan was to spend at least a few years abroad, in London with John O’Keefe and perhaps later at the Centre for Neural Systems, Memory and Aging in Tucson with our PhD thesis opponents from 1995, Bruce McNaughton and Carol Barnes. At that time, this centre was the mecca for neural population codes for memory.  We told the search committee that we would not be interested in only one position, but Sturla Krekling, the head of the committee, really pushed for us and so they soon offered us two positions. We then said we needed a new lab, and we came to them with a list of all the equipment that such a lab required – right down to the prices and suppliers. We had, after all, been partly through the same process before, both in Oslo and in Edinburgh. They basically gave us everything we asked for and we were offered lab space in an empty bomb shelter in the basement under the department. The only condition was that we begin in August of 1996 so that we could teach.  The request for us to start almost immediately completely upended our plans. But the prospect of two jobs and a lab just seemed too good an opportunity to turn down. **Trondheim – From Bomb Shelter to Lab** May-Britt and I started work in Trondheim on August 1, 1996. We bought a small house near the lab, so that we could run back and forth between the lab and our home to feed the rats and start deprivation at appropriate times, sometimes late in the evening. There were no animal experiments at the department at that time, so we had to build an entire vivarium at the same time as we ordered and set up equipment for place cell recording. We ordered our first recording system from a company associated with the O’Keefe lab – Gignomai, now Axona Ltd – and Jim Donnett and Kate Jeffery came for a few days to help us set up the equipment.  After about a year, we had our first place cell. This was an exciting moment. We brought Sturla Krekling to the lab and he was as proud as we were. With his background from visual-cortex neurophysiology in cats, Sturla was perhaps the only one at the department who really appreciated the spike sounds from the loudspeaker. But the Dean of the Faculty, Jan Morten Dyrstad, a social economist, also showed interest. He was impressed and has since then been one of the strongest supporters of our work. Today he is the chairperson of the Kavli Institute fundraising committee.  It took a long time to collect data because there was only May-Britt and me, and we had to handle routine technical work in addition to the experiments – everything from making cables to cleaning rat cages. In addition, we did most of the teaching in biological psychology, which was quite a lot. The students were excited, and we enjoyed lecturing, but most students were still interested in a clinical career – none of them wanted to spend the rest of their life in a rat laboratory. Thus recruitment was minimal.  In 1999, three years after we started, we managed to attract one student, though. Stig Hollup was different from the other psychology students and liked the technical challenges in our lab. At the same time, we got one part-time technician – Kyrre Haugen, who is still with us. He was able to join our lab because at the end of the year, in 1999, Hans Hellebostad at the Research Council called us and said that they had NOK 100,000 of extra money (about 11,000 euros) that they thought we might be interested in. We were euphoric. Suddenly we had a part-time technician who could section brains and do the histology for us.  But our luck did not end there. At about the same time, the department needed a technician to administer test batteries in the human neuropsychol- ogy section. Luckily for us the HR section misunderstood what a test battery was and recruited an electronics engineer for the job. His name was Raymond Skjerpeng. He knew nothing about neuropsychological test batteries but was an expert on the type of batteries we used in our lab. Since the neuropsychologists could not use him, we convinced the department to let him join our lab. He was extremely creative and spent day and night in the bomb shelter, helping us build up a state-of-the-art neurophysiology lab.  At the turn of the millennium, May-Britt and I recorded routinely from place cells but the cell yield was quite modest. We knew that to understand memory, we needed simultaneous recordings from large numbers of cells. The place to go to learn large-scale parallel recording at that time was the Barnes-McNaughton lab in Tucson, Arizona, where we had wanted to go as postdocs. In 2001, we were able to take a six-week sabbatical in Tucson where we learned to do parallel recordings from many dozens of cells in the hippocampus. It was a technique that had been developed by Bruce in the 1990s.  The visit in Tucson was another intense learning period. During the day, we wired electrode arrays and used them to record from hippocampus cells while the rats ran on circular tracks. In the evening, we went home with Bruce and Carol, lived in their guest house in the saguaro-studded desert next to the Catalina Mountains, and enjoyed long discussions over a glass of wine in the Jacuzzi in their garden. In the early morning, before it got too hot, we went for a walk in the desert, with their dogs (or half wolves, really) every day. Our two girls went to a Baptist school – the only school that could offer them a place for just 6 weeks. The school was radically different from anything they were used to – the children had to walk in the streets to proclaim the gospel – a different way of expressing religion than what I was used to from the Norwegian west-coast islands – but our two girls learned tolerance and the visit was as formative for them as for us.  During our first years in Trondheim, we were primarily interested in hippocampal mechanisms of memory. We set up a water maze and started recording place cells while rats navigated in a water maze. This was a technically challenging task, as we had to keep water away from the animal’s headstage, but the electrical silence of the bomb shelter helped, and in 2001 we could report our first findings in *The Journal of Neuroscience*. We showed that place fields were not evenly distributed in the water maze but were more abundant in the area where the animals found the platform. Many experiments failed though, because water leaked through the insulation around the headstage, so we gradually turned our focus to simpler behavioural paradigms, while at the same time we switched to multi-tetrode parallel recording, based on our experiences from the visit in Tucson. **From Four Hands to Two Dozen** One of the questions that intrigued May-Britt and me most was quite fundamental: What was the origin of the place signal in the hippocampus? With CA1 and CA3 cell recordings up and running in our lab, we saw early on that place cells could be used not only to understand place coding as such but also to more generally understand computation in the hippocampus.  There is no place signal in the sensory inputs to the brain, so how does it come about? Is it generated by the hippocampus itself? Since John O’Keefe discovered place cells in 1971, almost all studies had been performed in the CA1 subfield, the last stage of the hippocampal intrinsic circuit. We wondered if the earlier subfields – the dentate gyrus and CA3 – played any role in the formation of place correlates, and if any part of the signal came from the outside, from the entorhinal cortex, which provides most of the cortical input to the hippocampus.  To address this and related questions we applied for funding from the European Commission’s Framework V programme. This programme funded only collaborative grants. I had never before applied for a consortium, just for May-Britt and myself. To put together an application that succinctly addressed the criteria of the call, we got enormous help from Bruce Reed, a highly intelligent and knowledgeable advisor quite different from any other grant consultant I have worked with. Unlike most of his colleagues, he gave us feedback on the content of our proposal and helped us shape it into an application that pointed directly to the experiments that so tremendously changed our understanding of spatial representation a few years later. In one of the proposal’s work packages, we aimed specifically to determine the nature of the entorhinal inputs to the place cells, in order to find out how they were generated.  The proposal was submitted in 1999, the reviews were positive, and in 2000 I was suddenly the coordinator of a consortium of 7 groups. Among the members in the group were Richard Morris, our postdoc advisor, and Menno Witter at the Free University of Amsterdam, an expert on entorhinal-hippocampal anatomy whom we had already approached in 1990 as we wrote up our master’s thesis on dorso-ventral gradients in hippocampal function. He wrote a long and helpful reply to our letter in 1990, which encouraged us to maintain contact.  The EU grant came at a time when many funding agencies started to get interested in our work. Just a year later, we applied for ‘strategic’ money from the Research Council of Norway. They had a programme to strengthen research in pre-selected areas, and neuroscience was certainly not among those areas. A group of deans at NTNU was responsible for selecting proposals in the right areas. They chose our proposal, despite the fact that it was completely outside of the Research Council’s pre-selected areas. This group included several people who later became rectors of NTNU, including Eivind Hiis Hauge, Torbjørn Digernes and Gunnar Bovim. They all had confidence in our work from the very beginning. I am very grateful for their ability to see the potential in our proposal at a time when we had little published evidence of scientific excellence.  At about the same time, May-Britt and I moved our lab to the Faculty of Medicine. The Psychology Department had given us exceptional start-up conditions, and we are forever grateful to Sturla Krekling, who saw our potential, but psychology is a diverse field, our work was expensive, and we were too different to remain there. To compensate for the lack of biology-minded individuals at the Psychology Department, we had first met regularly with Arne Valberg, a visual neuro-psychophysicist, and Hanna Mustaparta, a biologist who studied neural coding in insect olfactory systems. Based on these encounters, in 2001, after extensive lobbying by Jon Lamvik, a former Dean of Medicine, we were offered lab space at the Medical-Technical Centre, where most of the Faculty of Medicine’s basic experimental research was conducted. The building was immensely crowded at that time, and we are grateful to Jon Lamvik as well as the Dean in 2001, Gunnar Bovim, for making that space available.  As we moved in, our lab was transformed in many ways. Not only did we get an opportunity to build a lab more suited to our increasing interest in the basic computational mechanisms of the hippocampus, but we suddenly had lots of money – from the EU and from the Strategic Research Programme. In 2002, our success continued. The Research Council inaugurated a new funding scheme where 13 Centres, selected among all fields of science and technology, were given extensive funding for 10 years. This was a new funding scheme meant to boost performance among highly selected research groups. We applied for one of these grants. It was a long application process, involving two stages of selection, and our research plans for the next decade were considerably refined as we wrote the application.  A Christmas and New Year’s visit in 2001 by Carol Barnes and Bruce McNaughton helped improve our application. We talked and wrote, went skiing, and celebrated the holidays together. Bruce even dressed up as Santa for the two girls. In the end our proposal was selected, again before we had much of a track record. But I believe the research plans convinced the committee, as well as the proposal to hire 7 internationally recognized scientists as visiting members of the Centre: Carol and Bruce, Richard Morris, Alessandro Treves, Menno Witter, Randolf Menzel and Ole Paulsen.  The idea was that these researchers would visit the lab once or twice per year to participate directly in experiments. So starting in December 2002, the Centre for the Biology of Memory became a reality and all of a sudden we had enough money to address all of our favourite questions. We could buy equipment, we could recruit just the right number of students, and we had some of the world’s best advisors coming periodically to our lab to help us plan and conduct cutting-edge experiments. From late 2002, we were a group with about 10 motivated and talented students and technicians as well as a wonderful international network (Fig. 5). **The Path to the Entorhinal Cortex** The discovery of grid cells began with the study of intrahippocampal origins of the place cell signal. In the 1990s, it was commonly believed that localised firing emerged within the hippocampus, based on weakly spatial inputs from the entorhinal cortex. This belief was based on several studies showing that cells in the entorhinal cortex had large and diffuse firing fields, very different from those in the CA1 of the hippocampus. Spatial selectivity was thus thought to originate somehow and somewhere in the intrahippocampal circuit. To find out how and where, May-Britt and I joined forces with Menno Witter, one of the members of the EU consortium that I coordinated. Along with Vegard Brun, a talented medical student, we selectively lesioned the CA3 of the dorsal hippocampus, or we used small knife cuts to interrupt connections from CA3 to CA1. With Menno Witter, we used fluorescent tracers to show that after both interventions, intrahippocampal inputs to the CA1 were absent, leaving only the direct connections from the entorhinal cortex.  We expected the lesions to severely disrupt place signals in CA1 but in fact they did not. Despite effective cuts, the cells exhibited localised firing, suggesting that place signals emerged either within the CA1 circuit itself, or were based on spatial signals from the only remaining cortical source – the entorhinal cortex. These findings, published in *Science* in 2002, suggested it was high time to record within the entorhinal cortex itself – a dormant goal in the EU grant that we wrote in 1999.  Until around 2001, the entorhinal cortex had seemed scary but now we were motivated to get started as soon as possible. We needed students. Vegard Brun was an obvious choice but he had medical exams and was only available parttime so we looked around. A year earlier we had recruited Marianne Fyhn. She applied for a position as a technician but we saw her potential and offered her a fellowship instead. For a while she recorded place cells in the water maze but the task was challenging and we considered alternatives. She was the perfect candidate for entorhinal cortex recordings.  In 2002 we got started. Menno Witter was by now a visiting member of the Centre for the Biology of Memory. Based on his early work on dorso-ventral gradients in entorhinal-hippocampal connectivity, which I had read in the finest detail, and based on the many discussions we had in person as we started our collaboration, it became clear that there was an alternative interpretation to the difference between entorhinal and hippocampal spatial selectivity reported in previous *in vivo* recording studies. It turned out that these earlier recordings had all been conducted in the intermediate-to-ventral part of the entorhinal cortex, which is primarily connected to the ventral hippocampus, where place fields are large and difficult to identify when rats run in standard-sized laboratory environments.  We reasoned that it would make much more sense to record in the dorsal part of the entorhinal cortex, from which the dorsal place cells get most of their input. It would also make sense to target the medial part of the entorhinal cortex, considering that much of the visual-somatosensory input reaches this region. Thus, Menno sat down with Marianne and May-Britt and showed them how to access the dorsomedial entorhinal cortex, a chunk of cortex never targeted before in any *in vivo* study, due to its location at the very back of the rat cerebrum, close to the transverse sinus. It was also not easy to localize in standard atlases of the rat brain, which at time mostly showed coronal and horizontal sections, without a sagittal orientation, which is the only suitable one for localizing electrode traces so far back in the brain.  It did not take long before interesting results surfaced. The recordings showed that entorhinal cells had discrete firing fields much like those of hippocampal place cells but each cell had multiple fields scattered all around in the box. The animal’s location could not be inferred from a single cell alone, but collectively the cells provided a pretty good estimate. It was also clear that the multiple firing fields were not arranged randomly. The distance between neighbouring fields was strikingly constant and clearly different from what could be expected by chance. We published these findings in *Science* in 2004, knowing now that the dorsomedial entorhinal cortex provided much of the spatial input to CA1 but without being able to understand the neural code of these inputs.  But we were on the right track. At the end of 2004, we presented our findings at the Society for Neuroscience meeting in San Diego. We knew our results contained much of what O’Keefe and colleagues had searched for in their work on the cognitive map and we changed the title of one of our posters to ‘The Entorhinal Cortex as a Cognitive Map’, in order to highlight the connection to John O’Keefe and Lynn Nadel’s work on hippocampal maps more than 25 years earlier. The poster attracted a lot of attention and excitement from the place cell community and from modellers interested in the neural basis of path integration-mediated spatial representation. We got many insightful suggestions during the poster presentation.  One of the most helpful poster session participants was Bill Skaggs, then at the University of California at Davis. After his many useful suggestions on the poster floor, May-Britt and I invited him for a breakfast meeting in order to discuss how such a pattern could arise, in the context of his understanding of continuous attractor mechanisms for place cells, and we discussed ways to follow up on the findings. Bill clearly suggested how hexagonal firing could arise from an attractor mechanism not too different from the ones he had proposed with Bruce McNaughton for place cells and head direction cells. During the course of a few days, it all became clear to us. We needed to expand the size of the environment, to be sure that the pattern was really hexagonal, the way it appeared to be. We also needed to test animals in darkness, to show that the pattern was path integration-dependent, and we needed to show that the pattern was anchored to visual inputs by testing whether rotation of salient cues also rotated the grid pattern. **Grid Cells** Returning from the Society meeting we had a package of experiments to do, and we again asked Marianne for help, along with her boyfriend Torkel Hafting, who had by then moved to Trondheim. The two of them ran the majority of the experiments, with May-Britt stepping in periodically, working with Marianne in the lab on a daily basis and taking over experiments during weekends or holidays when they were away. My role was to analyse data, write it up, and not least, read, to try to understand. Sturla Molden, the fifth person on the project, wrote code and helped with statistical analysis, including the use of spatial autocor-relation procedures to identify spatial periodicity.  We suspected that there might be something like a hexagonal firing pattern as this was already evident from the recordings in the 2004 paper. However it seemed too good to be true and we needed data from larger environments to be sure that this periodicity was not just coincidental. The turning point was the recording from the circular environment that was two metres in diameter and that we had adopted for this purpose. The arrangement of the firing fields looked strikingly hexagonal – and this became particularly clear when Sturla Molden had finished the autocorrelation program. Within a few weeks, on several occasions, we had multiple Eureka experiences, where it became clearer and clearer that the hexagonal pattern was neither a coincidence nor a technical artefact. The firing fields tiled the entire space available to the rat, in a pattern reminiscent of the holes of a beehive. We had several names for our baby, but because of the grid-like nature of the firing pattern, I suggested we called them grid cells. It was a simple and descriptive term.  The fact that firing fields were so regular despite changes in the animal’s speed and direction suggested that their location was determined by path integration and that grid cells were part of the mechanism for path integration-based spatial mapping – a mechanism envisaged by O’Keefe as early as 1976, but with no evidence for it until now. I was convinced that we had found an important element of the cognitive map – something completely different from anything known elsewhere in the brain. Our journey to this point was aided by important input from the visiting members of the centre. In particular, Bruce McNaughton’s insights in computational neuroscience were really transformative for me. His earlier work on attractor mechanisms inspired me and is still the basis for much of my thinking about how space is represented. With this as a background we felt that we could not only describe a new cell type but we could also put it in a historical and theoretical context. We submitted the paper to *Nature*, the reviews were positive, and in the summer of 2005 the paper was out.  Finding grid cells was exciting because it gave us another piece in the puzzle of how we navigate in space. But the larger significance of the find is that we were able to see how the brain generates one of its own internal codes, with mechanisms that reflect the inner workings of a cortical system, quite independently of any particular sensory inputs. In the past, it had been difficult to make associations between the firing of neurons deep in the higher parts of the cortex and properties of the external world, because as the distance between the sensory input and the neuron increases, the firing of the neurons is triggered by a multitude of converging sensory channels along with intrinsic processes that we don’t really understand.  But with the grid cells, and the place cells that O’Keefe had discovered, we had neural activity that was clearly associated with a feature of the environment, the animal’s location. Here, we think, lies a key to unlocking the mystery of how the brain computes. There is no grid pattern in the external world so the pattern must originate from activity in the entorhinal cortex itself, or in adjacent structures. Having access to data from these cells felt like a great reward, as it might put us on the track of the more general computational operations of the cortex. **From Lab to Institute** When we found the grid cells, we were still a medium-sized research group, and we had only our own group to care for. But soon after, things started to change. Just before the grid cell results were published, the philanthropist Fred Kavli visited NTNU, along with David Auston, the President of the Kavli Foundation at that time. They were in Norway to prepare for the inauguration of the Kavli Prize, which would be awarded for the first time in 2008. At the same time, they used the opportunity to visit research groups in the fields they were interested in. They came to our lab and were totally struck by the grid cell discovery. At the same time, Eric Kandel, who himself was head of a Kavli Institute at Columbia, argued strongly for a Kavli Institute at NTNU. He was tremendously excited about our work.  Soon after they left, May-Britt and I were invited to submit an application, and in 2007, we became the 15th Kavli Institute in the world and the fourth in neuroscience (Fig. 6). In the end, Fred was enormously proud that a Kavli Institute had been established at his alma mater, although it was important for him, to the very end, that the institute had not been established for that reason but only because it satisfied the foundation’s strict criteria for quality. The inauguration of the institute not only gave us funding and support but also opened doors to some of the best neuroscience groups in the world. Many individuals made important contributions to the formation of the institute. In Norway, these individuals include two NTNU rectors – first Eivind Hiis Hauge, and then Torbjørn Digernes, who was the rector during the negotiations – as well as the secretary general of the Ministry of Education and Research, Trond Fevolden, and Arvid Hallén, Director of the Research Council of Norway.  The establishment of the Kavli Institute represented the beginning of a transition from a single-group centre to an institute. Menno Witter was the first new faculty to join us. Menno had collaborated with us almost from the beginning, when we got our first EU grant in 1999. He became a member of the Centre for the Biology of Memory and participated in some of the most important studies in the Centre’s history – studies that led up to the grid cell discovery and several studies that investigated their properties. In 2007, with the Kavli Institute in place, and with the help of the Dean of the Faculty of Medicine, Stig Slørdahl, we were able to offer Menno conditions that convinced him to move his entire research group to NTNU.  A few years later, in 2010, we recruited Yasser Roudi, a theoretical and computational neuroscientist, and a student of Alessandro Treves, who is a visiting member of our institute. In 2013, Cliff Kentros moved from the University of Oregon to set up a group for studies of memory using transgenic mouse technology, and in 2014 we recruited Emre Yaksi to set up a lab for zebrafish studies of the nervous system. Jonathan Whitlock joined the faculty when he received a Starting Grant from the European Research Council. **The Connection to Memory** The discovery of grid cells opened the door on understanding the brain’s system for spatial mapping. However, the brain regions containing place cells and grid cells are also crucial for everyday memory and it was the relation to memory that motivated our first studies in the hippocampus. What could be the link between space and memory? Are the same neurons involved and if so, how can they perform both functions? To understand this relationship, May-Britt and I maintained our interest in memory and conducted a number of studies, in parallel with the entorhinal work, which made it easier to understand how the two phenomena are related.  By 2002, when we moved out of the Psychology Department, we had realized that place cell recording in the water maze was too ambitious. The problem was not primarily the contact with water but rather the complexity of the task. Recording while rats learned to find the hidden platform might reveal activity specifically related to storage of spatial information but the task could be solved in many ways, and it was difficult to rule out the contribution of trivial sensory or motor contributions to changes in firing rates. Thus we were increasingly attracted to simple reductionistic paradigms such as the old open field that we started out with during our work on hyperactive rats with Terje Sagvolden. After a few years in the new lab at the Faculty of Medicine, we made sure that all the rooms in the lab had open fields.  So how could we address spatial memory in an environment with no goal to search for? In the late 1980s, Bob Muller and John Kubie at SUNY Downstate had shown that place cells ‘remap’ between environments. They trained animals in different versions of the same enclosure, in the same place, and found that each enclosure was associated with a different subset of active cells. Along with later work from a number of laboratories, including that of Bruce McNaughton and Carol Barnes in Tucson, they showed that hippocampal ensembles switched between quite different firing patterns as animals moved from one environment to another, and sometimes even when only task factors were changed within the same environment.  It became clear to them, and to us, that remapping might serve as a window on the mechanisms underlying memory storage in the hippocampus. Each environment had its distinct representation, mediated by different combinations of active cells. It seemed like the hippocampus had one map for each environment, operating much like a catalogue for all environments that the animal had encountered. Studying how these representations are formed and how they are segregated from one another felt like an interesting set of questions to pursue.  For our studies of remapping, May-Britt and I recruited Stefan Leutgeb, one of the postdocs who participated in our first EU grant. Stefan shared our interest in neural substrates of memory, as well as computational differences between the hippocampal subfields. We started out by comparing CA3 and CA1 and found, in collaboration with Alessandro Treves, a visiting member of the Centre, that place representations in CA3 cells were much more decorrelated than those typically recorded in CA1. Later work, with Jill Leutgeb, who joined the lab a year later, as well as with Bruce McNaughton and Carol Barnes, showed that CA3 networks had attractor properties, although transitions between representations were not always as sharp as envisaged if the hippocampus contained only discrete attractors.  Our work showed that there are two types of remapping – sharp transitions similar to those seen by Muller and Kubie, which we referred to as global remapping – and more gradual transitions, in which firing rates changed smoothly as external inputs were altered, whereas firing locations remained the same. The latter was dubbed rate remapping. The studies of remapping were possible because we could record large numbers of cells at the same time, using the multitetrode technology that we had learned from Bruce and Carol during our 2001 visit in Tucson.  The use of remapping as a way to understand hippocampal memory begged an obvious question: how was hippocampal memory, expressed through remapping, influenced by inputs from grid cells in the entorhinal cortex? Grid cells are the most abundant cell type in layer II of the entorhinal cortex, and it was very likely, as shown in more recent work from our lab, that they provide a significant share of the projections from the medial entorhinal cortex to the hippocampus.  This led us to compare representations across environments in grid cells, at the same time as cells were recorded in the hippocampus. Again with Marianne Fyhn in the lab, we recorded grid cells and place cells in different enclosures in the same place or in different enclosures in different rooms. With the help of Alessandro Treves, we cross-correlated ensemble maps from each environment to see if relative firing locations and orientations were maintained. The striking finding was that the map structure was maintained in grid cells whereas no similarity was preserved in the hippocampus, suggesting that as information is passed from grid cells to place cells, it is completely transformed – from a single universal map in the entorhinal cortex to a multitude of almost-orthogonal maps in the hippocampus, with apparently one map for each environment.  In this sense, the grid cell map was similar to maps of head direction cells in other areas, which also maintained their intrinsic structure across environments. The data suggested there were two types of spatial maps – a rigid map in the entorhinal cortex that maintained a single metric independent of the nature of the environment, and a much richer map in the hippocampus with representations individualised to each environment, much as one would like for a memory storage system. The relationship between the two maps intrigued us, and with Laura Colgin, we showed that spatial maps in the entorhinal cortex and CA1 are temporarily synchronised via oscillations in the fast gamma range. Between these short moments of entorhinal-CA1 synchronisation, CA1 cells synchronise with CA3 cells possibly involved in the internal storage of spatial representations. Finally, using new molecular and optogenetic tools, we also showed, with Sheng-Jia Zhang and Jing Ye, that grid cells project directly to the hippocampus, as hypothesised by our work on remapping. Thus, by approximately 2012, we felt that we had an improved understanding of how grid and place cells interact, although there remain major questions yet to be answered. **Grid Cells: From Single Cells to Networks** The discovery of grid cells also led us to ask what the intrinsic network of the entorhinal cortex is like. How is the grid pattern formed? How do grid cells interact; what can they achieve together that they cannot do alone? What other cell types are there and how do they all interact?  Since the discovery of grid cells, my fascination with their crystal-like firing pattern and its potential mechanisms has not flagged. In 2005, we were able to record only a few grid cells at the time and it was difficult to infer how they operated at the ensemble level. This has changed. In 2009, Hanne and Tor Stensola, another couple, joined our lab. Hanne had a talent for recording large numbers of grid cells in the same animal and Tor a talent for devising clever analyses to infer their systems properties. They were able to record almost 200 grid cells per animal, enough to demonstrate that grid cells are organised into a small number of functional modules, each with its own unique grid spacing. This result was published in *Nature* in 2012. We found that modules can operate independently in the presence of changes to the geometry of the environment.  Two years later, during the Nobel celebrations in Stockholm, *Nature* accepted a second major finding from their work. We were able to show that grid cells align with borders of the local environment through a shearing-like mechanism that causes both deformation and rotation of the grid pattern. The asymmetry of grid cells is completely predictable by the shearing mechanism that we described.  But what was behind the mechanism of the grid pattern? Early on, Bruce McNaughton alerted us to the significance of attractor network mechanisms in spatial representation. Our interest in these kinds of representations grew as Yasser Roudi joined the faculty to start a theoretical physics group. Shortly after Yasser moved to Trondheim in 2010, Menno Witter’s group had shown that stellate cells – most of which are likely to be grid cells – lacked excitatory recurrent connections. The lack of such connections was a puzzle for attractor theories of grid cells but Yasser and his colleagues showed that hexagonal symmetries could also be obtained by purely inhibitory interconnections.  The attractor model explained some key features of the data. The observed independence of the grid modules, for example, was exactly as predicted. For grid patterns to appear as an equilibrium state in a network of interconnected neurons, and for such patterns to be updated in accordance with the animal’s movement, interconnected cells may need to share both grid spacing and grid orientation. This means that the network must be organised in a modular fashion, with each module corresponding to a semi-independent attractor network. The data have convinced me that grid cells do, to some extent, reflect attractor mechanisms but the detailed implementation of the mechanism is clearly not well understood. Digging deeper into the mechanism of the grid pattern will certainly be among our major goals in the years to come.  Grid cells do not operate in isolation, however. Soon after the discovery of grid cells in 2005, Francesca Sargolini came to the lab. She showed that there are head direction cells in the medial entorhinal cortex, especially in the deeper and intermediate layers, and that they intermingle with grid cells in these layers. Head direction cells are cells that fire selectively when animals face a certain direction, with activity similar to a compass, except that the firing direction is determined by local cues, not magnetic inputs. Head direction cells were discovered by Jim Ranck at SUNY Downstate in 1985, in the dorsal presubiculum, adjacent to the medial entorhinal cortex, but Francesca’s head direction cells were the first in the entorhinal cortex. Many head direction cells were grid cells at the same time. We called them conjunctive cells. The combined spatial and directional signal of these cells obviously pointed to a close link between the metrics for direction and location.  The search for additional cell types also led us to discover border cells in the entorhinal cortex. With Trygve Solstad and others in our lab, we found that approximately one-tenth of our cells fired selectively along walls or edges of the recording environment. They did so in every single environment, and their firing also lined up along small wall inserts within an open field. Border cells were functionally different from their more abundant counterparts, the grid cells. Entorhinal border cells were also observed by Jim Knierim’s group, then at the University of Texas in Houston, and cells with similar properties, referred to as boundary vector cells, had been reported by John O’Keefe and colleagues in the subiculum. The entorhinal border cells were intermingled with head direction cells and grid cells, and they were also present in layer II.  Finally, quite recently, we have shown that grid cells, border cells, and head direction cells co-localise with speed cells, cells that fire linearly in relation to the animal’s instantaneous speed. This is work we have conducted with Emilio Kropff, who worked as a postdoc in our lab. Combined, these many cell types form a network of diverse cells with distinct functions, all embedded in the same network. Understanding how this network of cell types operates to form a holistic representation of space will keep us busy for many years to come. **The Next Decade** After the 10-year lifetime of the Centre for the Biology of Memory ended in 2012, we were awarded another decade of funding. The Centre for Neural Computation, with May-Britt as the Director, will be alive until 2023 and we expect the number of faculty at this centre to increase. The rapid expansion of our activity is the result of generous support from Stig Slørdahl, the Dean of the Faculty of Medicine, who has used every opportunity to help us to further improve and extend the centre. At the same time, the Research Council and NTNU have given us funding for an almost ten-fold expansion of the lab space of the institute, and the Ministry, in collaboration with the Research Council, gave us more or less permanent support for technical and administrative staff – support that is generally not easy to obtain through regular grants. Because of this support, the team has been transformed from a single entity with a strong focus on a single cluster of questions to an entire institute consisting of multiple research groups covering a broad range of systems questions, well beyond the domain of space and memory.  With the new centre funding, we are also establishing new collaborations. One of these is with Tobias Bonhoeffer from the Max Planck Institute for Neurobiology outside Munich. He joined us as a visiting professor in 2014 and works with us on using two-photon imaging to establish the detailed functional organisation of the grid cell network. A student of ours, Albert Tsao, has been working in his lab for almost two years and I have visited Tobias’ lab frequently. At the same time we are setting up imaging technology in our own lab. The collaboration re-establishes a friendship that started almost 50 years ago, when the two of us used to play in a sandbox in a residential area in Tübingen in Germany. I used to spend parts of the summer with my parents visiting my aunt and uncle, Ulrike and Hermann Lange, who lived just a few houses away from the Bonhoeffer house. We rediscovered our friendship when Tobias’s mother told him about the Norwegian boy who came to visit every summer. Today Tobias is the external collaborator who is most strongly transforming our lab, via his help to introduce imaging technology for population studies of grid cell activity. He is not the only one, however. Pico Caroni is also a very valuable member, as is John O’Keefe, who is, and always has been, a thoughtful and forward-looking discussion partner. **The Call from Stockholm** On October 6, 2014, I was on the plane to Munich for an extended research visit to Tobias Bonhoeffer’s group at the Max Planck Institute for Neurobiology near Munich. While I was in the air, working on a manuscript, my life changed dramatically, without me knowing. My first surprise was the encounter with a representative from the Munich Airport who met me with flowers and an airport car at the gate when we landed. She told me I had won a prize but mixed up things and said it was a prize from the Max Planck Society.  It was only when I checked my iPhone that I started to understand (Fig. 7). There was a text message from Göran Hansson, the secretary of the Nobel Committee, as well as hundreds of other emails and text messages. Then Tobias called and congratulated me. A few minutes later I was met by Tobias and his lab, with champagne in the arrivals hall, and an hour later there was a press conference and even more champagne. After an hour or so was I able to connect with May-Britt, who got the call from Göran Hansson two hours before I became aware of the news from Stockholm. On the day after, on October 7, I was back in Trondheim, to celebrate the event with the family, the lab and the rest of the university (Fig. 8).  The subsequent weeks were crazy. It took a while to get organised and find a way to handle the steady flow of requests to lecture, open conferences, and give interviews and comments. In the end I learned to prioritise and life got back to normal, with the brain at the centre. Then, in December, the celebrations started again. The Swedes treated us like kings. Each laureate had his or her own attaché who took care of all appointments and guided us from event to event. The ceremony was moving. Receiving the medal from King Carl Gustaf on the stage, with applause from a packed audience, is imprinted in my memory, as is the Nobel lecture in the new Aula Medica, in front of 1,200 attentive listeners.  It was delightful to share the experience with John, our generous mentor from the 1990s and such a thoughtful scientist. I liked the other laureates. By the end of the Nobel week, we felt we knew all of them a little bit. And I must add that the Swedes really know how to celebrate science. Torsten Wiesel and Eric Kandel had come to celebrate with us, as had numerous colleagues and collaborators. When we left on December 13, I believe everyone in the country knew what a grid cell was. Our research had reached the public and I got the impression that they all celebrated with us. It was a prize not only for systems neuroscience but also for research in Norway and Scandinavia, and everyone was part of it. **Perspective** My journey from Haramsøya – that small island off the coast where I was born – to Stockholm has been quite an adventure. Who would have predicted this when I entered the world from our modest house on that little windy island of farmers and fishermen? I am still not entirely certain what made it possible. The academic interests of my parents certainly contributed, but in the absence of an external intellectual environment, and with no extra stimulation in primary school or secondary school, the fact that I became a successful scientist was perhaps somewhat against the odds.  Even after I knew that I wanted to spend my life doing research, success was far from guaranteed. Finding the right research group is an essential part of any science career, and I can say that my choices were fortuitous. I learned behavioural analysis with Terje Sagvolden but switched to neuroscience with Per Andersen at the right time, when we – and the field – were ready to bring psychology and physiology together.  Since our PhD days, May-Britt and I have been helped by individuals and institutions, all of whom saw the potential in our work and supported us. Perhaps my personality also helped a little bit. I have a strong will and can be extremely focused on a particular goal, even if it is decades away. My slight enthusiasm for mathematics has been useful, as well as my passion for putting together disparate pieces of information. With the help of May-Britt I felt I could sometimes see the whole picture and the path forward. However, it remains for the historians to put it all together.  Let me finally add that my scientific journey did not happen in a vacuum. I have had a wonderful partner and we in turn have two remarkable daughters – Isabel and Ailin. They were born in 1991 and 1995, respectively, and came with us as we travelled the world – to Edinburgh where we worked with Richard Morris, to John O’Keefe in London, and to Bruce McNaughton and Carol Barnes in Tucson. Together we have explored the planet, not only laboratories and conference auditoriums, but also beaches, rainforests, volcanoes, reefs and remote islands. Today our two girls are mature, thoughtful and warm young women who continue to bring happiness to my life (Fig. 9). That is a gift that is even greater than the Nobel Prize. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0525=EM  [Edvard Moser] Hello  [Adam Smith] Hello, my name is Adam Smith calling from Nobelprize.org, the website of the Nobel Prize.  [EM] Oh yes.  [AS] Have you already heard today’s news?  [EM] Yeah I heard the news, I came out of the plane, landing at 12:30 and then there was a respresentative of the airport who came with flowers and picked me up in a car. I didn’t understand anything, and then finally I found out because I saw there were 150 emails and 75 text messages that had come in the last two hours. And then I saw there was one from Göran Hansson, so then, sort of, things started to add up. I guessed what it was, but it took me a little while. But I’m terribly grateful, it’s absolutely fantastic. So … And this year, I mean, I didn’t even know it was today. I really didn’t even think about it. So, even more pleasant when it’s a such a surprise.  [AS] Indeed, well, what a bewildering way to find out.  [EM] Yes, it is. [Laughs]  [AS] And have you managed to speak to May-Britt, your wife yet?  [EM] No, I’ve tried to call three times and I don’t get through, so I hope she will call back sooner or later. But the problem is that the list of incoming phones is so large, so I don’t know if she … but I guess she will find a slot to talk in a few minutes probably.  [AS] I’m sure. Well, I was lucky enough to speak to her a little while ago, and she said she cried when she heard the news and also that the only sadness was that you were on the plane and couldn’t share it at that moment.  [EM] Yeah, yes, it would have been so fantastic to share that moment together. But anyway, I mean the important thing is that it happened and it’s fantastic both for us and for the lab, and for everyone who has supported us, so that’s a lot of people. I mean it is a teamwork, and it is a lot of people who are completely invisible, like all the people at the university, NTNU and people in the research council, for sort of giving us absolutely top conditions for 20 years, which has made it possible to do the research we have done. So, it’s a lot of people behind this.  [AS] It’s interesting that May-Britt made the same point, so you’re obviously in perfect synchrony as a married couple.  [EM] Yeah, yeah, that’s interesting because this is not planned. It’s so unexpected. [Laughs]  [AS] Well, there you are, that’s the proof. And of course you’ve received the Prize with John O’Keefe who I suppose has been something of a mentor at some points.  [EM] Yes, so, yes. I mean in 1996, as probably May-Britt told you, I worked there for three months and she was there for one month, so he trained us to do the type of single cell recordings that we have been doing since. The three months I spent in his lab are the most efficient learning period I ever had. I learnt so much, and he took so much care of me and spent so much personal time on me, which even, I got a desk in his office and I shared the same lab with him. So he has been a fantastic mentor and it’s extremely nice that we can now share the prize together.  [AS] That’s lovely. Have you managed to get away from the airport yet or are you still there?  [EM] No, I’m still at the airport. There’s a lot of people standing here. So they’re trying to get me into the Max Planck Institute, because there’s going to be a press conference at two o’clock. I probably better have to leave. But I saw that there was a number from Sweden so therefore I made an exception and took the call.  [AS] Oh, well, we’re deeply grateful. So enjoy your day in Munich, a strange place to find yourself celebrating.  [EM] OK, thank you very much.  [AS] And thank you so much for speaking to us, thank you.  [EM] Thank you, yeah, OK, goodbye. |
| Interview |  |
| Q23 | Could you please explain your Nobel Prize awarded work for 13-14 year olds? |
|  | Edvard Moser: We have discovered parts of an internal map that we have in our brain, a map that tells the rest of the brain where we are in the room or in the world.  May-Britt Moser: It is like a GPS-system almost.  Edvard Moser: There are different types of cells. O’Keefe, who is the third prize winner, he found a type of cell that is called place cell, which is active only when animals or humans are in one certain place. We found another type of cell that fires active in many places and those places where the cell is active tend to form strictly hexagonal patterns so the many locations in the room where the cell is active form a grid or like a coordinate system that tells the brain where we are.  May-Britt Moser: The animal is walking, and it can be an animal, it can be a human being, then you can record with tiny sensors in the brain and you record the electrical pulses that are released from the cells and you magnify them 10 000 times and then we can listen to one by one cell. And then if we now listen to one place cell and this is the area where the animal is walking around – this is the rat and then it is silent, silent, silent and then suddenly you start to hear: “Po, po, po, po, popo, popo, popopo” and then the rat is moving out again. And whenever the animal is coming back to this place, it is the same thing happening: “Po, po, po, po, popo, popo, popopo” and it doesn’t matter how the animal is coming in, from which directions. And the interesting part is that these place cells, they are located in different areas in the environment. So, one place would be active here, and another here and so on, but then the grid cell that we found doesn’t have one single active field, but it has several ones and they are separate like Edvard said, like each field look like a checkerboard, how do you say? The chess …  Edvard Moser: Like hole in a Chinese checkerboard.  May-Britt Moser: Yes, like a Chinese checkerboard, thank you. So then where the marble should go, that is where the activity field is. And we know that this Chinese checkerboard, they have all these small triangles in between all marbles and that is exactly the firing patterns of the grid cells. Then the grid cells come in different sizes, big fields, big distance between the fields, small and so on. This is the information that goes into the hippocampus, which is the place cell, where John O’Keefe found the place cell. And the interesting part is that, the hippocampus with the place cells, if you lose your cells in this structure, you can’t remember what you had for breakfast, if you had breakfast at all. And if you lose the same cells you can’t find your way in the environment and the input to these cells, that is the grid cells. So, the grid cells are tightly involved in both space navigation and memory. |
| Q1 | What brought you to science? |
|  | Edvard Moser: For me, I was interested in science already when I was a child. I didn’t really know what is was, but I read a lot about scientists and their work and I thought becoming a scientist was like digging dinosaurs, that is what I thought, but I thought that was exciting. And then I read about meteorology and about volcanos and about physics, everything that I could come over, so I nearly knew that I wanted to do this but didn’t really know much what is was like. And then many years later, when I came to university, then … Because I knew wanted to go to university, and then together with May-Britt I then began studies of psychology and then the part of psychology that excited both of us by far the most, was the brain and trying to explain behaviour by the brain and that is an experimental science. And I think I never really had anything else on my mind at least, except perhaps for very short breaks, so I wanted to be a scientist from the beginning.  May-Britt Moser: You wanted to study volcanoes.  Edvard Moser: Yes, I mean the field was open. For a long time I wanted to become a physicist and work on elementary particles, but now I am so glad that I ended up in the brain.  May-Britt Moser: I didn’t read that much as Edvard did but I was extremely curious. And I was curious on humans and animals and I really wanted to understand why they do this and why they don’t do that. And when I became older I knew that I have to go to the university in order to do this, but I didn’t, as Edvard said, I didn’t know how, so when I went to the university finally then I started to study mathematics and physics because those were the topics I loved in the high school, but I didn’t know what kind of job I could get. And then luckily I met Edvard, even though we had been at the same high school, we didn’t know each other that well and then we decided, hm, should we do this together, and then we just made a new path step by step without knowing other things standing star in front of us. We want to understand why the brain or how the brain is working to give behaviour. That is what we’re still doing, and it is fantastic. |
| Q5 | Who is your role model, and why? |
|  | Edvard Moser: I’m not sure there is a single role model.  May-Britt Moser: Me!  Edvard Moser: No, I think it is part of becoming a scientist that you actually have to trust your own judgement as well and go for the really long term goals that no one else has put up, but there are many scientists who I admire but I think it would be kind of wrong to mention one by name because then I always forget the second one.  May-Britt Moser: As you say it is extremely important the support that we have got from other scientists and that they have believed in us and given advice when we needed advice. For example, when we started with our labs just half-year after our PhD:s. That was a crazy decision but still people supported us and said, you can do it if you focus on this and that if you collaborate instead of splitting and trying to build two labs and so on.  Edvard Moser: But since the context is Nobel Prizes, you can always mention a few names at least, so [Eric Kandel](https://www.nobelprize.org/prizes/medicine/2000/kandel/facts/), his work we got exposed to very early and already in the 1980’s was work that we read about and thought was super exciting and then we met him and he has sort of followed us all the way. Another one is [Torsten Wiesel](https://www.nobelprize.org/prizes/medicine/1981/wiesel/facts/), who is also related to Sweden. His work in the 60s especially, was extremely important.  May-Britt Moser: [Hubel](https://www.nobelprize.org/prizes/medicine/1981/hubel/facts/) and Wiesel, it was just like the bible, and the same with Eric Kandel’s book.  Edvard Moser: Defined our field. So those two are at least persons that have meant a lot both for our field and for us personally.  May-Britt Moser: And also for my PhD, then I studied structural changes after different experiences, like living in a enriched environment and then it was so fantastic for me to read about the *Aplysia* work of Eric Kandel because he had shown the same thing in the *Aplysia* when this tiny sea slug is learning. And then I could believe also in my own data because I have read his work. On a lot of different occasions, these people have been important, and also when we were master students. |
| Q16 | At what point did you realise your work was a breakthrough? |
|  | Edvard Moser: I think pretty early actually, when we saw that the firing pattern of this cells forms a strictly hexagonal structure, so very, very regular, almost like a coordinate system then …  May-Britt Moser: That was crazy.  Edvard Moser: … and it was so different from what anyone had expected that we knew that this would be kind of revolutionary, so we worked on really, being sure that there was no mistake in the data. We did lots of control experiments and we sent it to *Nature* and it went right in, so that kind of confirmed our suspicion that it was important. Yet it was of course, difficult to imagine that only nine years later it will be a Nobel Prize. That is perhaps beyond, but still we knew that it was very important from the beginning.  May-Britt Moser: The exciting part of these cells is, like Edvard said, that we tried to do all these controls to find out – is there a specific order, does the rat see something specific that make this grid pattern – and there is none. That means that this pattern is generated by the brain itself and then it’s like going into the brain and detecting the mystery of the brain by studying these cells. And if you start to understand even more how they are generated we understand so much about how the brain is working. |
| Q19 | What were you doing when you heard you had been awarded the Nobel Prize? |
|  | Edvard Moser: In my case, I was actually out flying, so the rest of the world knew about it and I didn’t know anything. So I only got the news when I landed and that was also a bit peculiar because I came out of the airplane and then I was met like a VIP with flowers and name sign at the gate, not after the baggage as usual. I sensed something was strange, but it wasn’t on my mind that this was the day when the Nobel Prize was announced. I would have known it, but I didn’t think about it. And then I asked: “Why all this special attention?” and the lady who picked me up she didn’t know, she knew that it was a prize, but she didn’t know which prize. So she mixed it up with something else and was still not clear and what made it clear to me was when I checked my phone because on that flight to Munich, two hours, then there had been hundreds of calls and then there was a text message from Göran Hansson, the secretary of the Nobel Committee and then I, sort of, finally sensed it. |
| Q19 | And where were you, May-Britt? |
|  | May-Britt Moser: When I heard about the prize, then I was in a lab meeting at a lab and it was such an exciting meeting and it went over time and I was expecting to have another meeting with other people. I got this phone call and I saw it and I said: “No, I don’t recognize this number, I don’t want to speak to this person, I am so busy”. And then I thought, hm, maybe I should take this phone and pick it up and I did, and I heard that it was Göran Hansson and then I was just, hm, why are you calling me? And then I thought maybe this is something serious, I went to my office and then I realized that it was about the Nobel Prize. Then I thought maybe he wants to have some comments about another Nobel Prize winner, just let me sit down and relax and then he said “No, it is you. You and O’Keefe and Edvard who got the Nobel Prize” and I said: “No, I don’t believe you, please can you send me an e-mail so that I can read it because I don’t believe my ears”. And then I got the e-mail and still I didn’t believe it. So it went on and off, I believed it and then I didn’t believe it and then I went to the dean and showed the letter on my phone to the dean and said: “Do you read the same thing as I do?”. He was just: What do you have here?” and then he: “You won the Nobel Prize?”, and it was crazy. So that was an experience, but then I realized that I was so grateful. Especially also about getting this focus on the work that Edvard and I had done and the whole team and also the support that we have got from Norway, from NTNU, from the local university, from politicians abroad, Kavli Institute and it was just “oh wow”, finally we can say thank you to them, that they believed in us. |
| ID | 0526 |
| Biographical | This autobiographical sketch of a life in science mainly focuses on a question I am now often asked – when and how did you know you wanted to be a scientist, and how did you become one? I am also asked by young scientists for advice I could impart from my own experiences and observations. With this in mind, this essay essentially provides bookends of my life until now, and I hope it may be of interest less from the particulars and more from generalizations that may emerge in the eyes of a reader, especially a young scientist. My [Nobel lecture](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2013/rothman-lecture.html) complements this essay, focusing mainly on what happened in between the bookends. **Childhood** From the earliest time I can remember I wanted to be a scientist, especially a physicist. I am not entirely sure where this came from, but at least in part it must have come from my parents (Fig. 1) who deeply valued education, especially in science and medicine. I was really fortunate and owe my parents a lot – they made me feel that I could do anything, and they provided the resources to enable me a privileged education unencumbered by financial needs.  My mother Gloria, with her enormous focus and drive, would in today’s world have been a high-powered executive. But she grew up in an earlier era where women had far fewer options. She ran the home and my Dad’s pediatric practice and taught me how to organize and manage. My father Martin was an intellectually oriented small-town physician who had wanted to do medical research as a young man, but had graduated in the Great Depression and then been caught up in World War II. He was always keen to involve me in the things he did. At perhaps the age of eight (Figure 2, left), I remember accompanying him on nocturnal house calls, at other times to the hospital; assisting him at home by measuring the intervals in his patients’ electrocardiograms; and helping him perform blood analyses in the small lab behind his office.  But I believe that my focus on science came at least as much from the times during which I grew up, and the values that I and other Americans internalized from the society around us. In the 1950s and 1960s science and technology were viscerally understood and applauded by most Americans as mainstays of economic and political power following the victories of World War II. This era began with the polio vaccine eradicating a dread disease and with atomic energy (for better and for worse). It ended with the transistor, the digital computer, and the first men on the Moon.  In such an environment, and with my supportive family, and with an abundance of curiosity and a natural talent for mathematics, it is not surprising that I was designing and building electronics and launching rockets while still in elementary school. Rockets were a big thing for me as a boy (Figure 3). I taught myself basic trigonometry in 7th grade so I could triangulate the height of the rockets, and then calculus two years later so I could better understand the physics involved. As I began to study more advanced physics and mathematics formally in high school, I devoured the subject and challenged myself far outside the excellent curriculum at my secondary school (Pomfret School), so much so that I was graduated after my junior year. Entering Yale College in 1967, I was absolutely committed to theoretical physics. **Yale** Yale provided the perfect environment in which a committed young scientist could develop while also immersed in the broader culture. Yale was big enough to provide every opportunity, yet organized into relatively intimate units (Colleges) small enough to foster the individual. The students had all varieties of interests, and my friends were drawn largely from outside the sciences, providing breadth to complement my personal scientific focus (these friendships continue today with annual summer reunions of the “812 Club,” named after a room in Branford College). I also studied and especially internalized from my friends a great deal about art, philosophy, and history.  As an entering freshman, I was accepted into an “Early Concentration” program which rapidly enabled me to focus deeply on mathematics and physics at an advanced level. Physics taught me how to rigorously analyze the components of a problem by first imagining the form a solution would take. This can be a useful approach when engulfed in the fog that envelopes the uncharted waters of biology.  As I began my junior year, perhaps with fatherly concerns about the poor employment prospects for physicists at that time, my Dad strongly encouraged me to at least give biology a try. I was not especially open-minded, as there was a well-understood intellectual pecking order that every budding physicist was soon informed of. Theoretical physicists were the brightest. Experimental physicists were failed theoreticians, but nonetheless useful for confirming theories. Chemists were not so bright, but still socially acceptable. Biologists were said to be even less bright, and generally not worth mentioning. But, even at the very first lecture in the general biology course, I was amazed that (in contrast to the highly structured field of physics) the research frontier in molecular biology seemed instantly accessible, and yet could be equally rigorous and structure-based.  Thus began a multi-year process in which I gradually learned to think like a biologist, while still retaining the orthogonal way of thinking like a physicist. I believe this mindset was critical not only in my choice of the problem whose solution was recognized by this Nobel Prize, but also in providing me the means to solve it (as elaborated in my Nobel lecture). Therefore, I will devote some detail here to this process of transition from physics towards biology.  The transition came in stages, initially via self-taught physical chemistry (though I never formally studied this subject or many others – in fact, I have completed only one term of college chemistry and biology and most of what I have learned in science and medicine has been self-directed). In physics, I had gravitated to statistical mechanics, probably because unlike quantum mechanics you can visualize it in simple terms. Statistical mechanics served as my intellectual bridge to biology. For example, consider that the three dimensional conformations of polymers (a classic problem in statistical physics and thermodynamics) such as polypeptides are a fundamental determinant of their biochemical mechanisms. A term of research (junior year) with the theoretical chemist Marshall Fixman on the statistical mechanics of polymers equipped me with a fluid way of visualizing individual versus ensemble behavior of molecules that to this day guides my thinking in biochemistry and cell biology.  The next stage in my transition (also junior year) came via Harold Morowitz, introduced by Fixman, a theoretical biophysicist with equal interest in science as in philosophy. Harold was a broad intellectual who has had many interests, but just then he was especially interested in the hotly debated question of the basic structure of biological membranes. His laboratory had just done some influential experiments demonstrating thermal phase transitions in the membrane of microorganisms mimicking the behavior of isolated lipid bilayers. In retrospect, I was attracted by a combination of the familiar (thermal physics and conformational changes of a polymer [fatty acid chain] in the phase transition) and Harold’s personal warmth and charm. Soon I was working in his lab with a postdoctoral fellow, designing and building an instrument to measure the phase transitions, and was deeply engaged.  Harold had a way of collecting interesting people around him, including his former PhD student Donald Engelman. Harold advised me to go to the research seminar that Engelman was to give during an upcoming visit to Yale. This was the first seminar I had ever attended, and as it turned out it was a “job seminar” resulting in Don joining the faculty of Molecular Biophysics and Biochemistry soon thereafter. He spoke about his now classic experiments with Maurice Wilkins (Nobel Prize, 1962) demonstrating the lipid bilayer in biological membranes using an elegant combination of microbiology and X-ray diffraction. I think Harold asked Don to take me under his wing, where in a sense I have been ever since (Don remains one of my closest friends and happily we are both now at Yale). We took on the problem of how cholesterol buffers the fluidity of the lipid bilayer, extinguishing the thermal phase transitions, and my earliest publications came from this. Don taught me by his example how to dissect each morsel of data to get the most from it.  In doing this, I learned another important lesson – the central importance of numbers. My students sometimes seem surprised that there are a lot of numbers that I have at my disposal whenever I may need them; this is true, and it is no accident. From Yale onwards, I have always made a point of remembering key numbers, and I have learned to do this automatically every time I hear a new one. For example, π and e in mathematics; Boltzmann’s constant in physics; absolute zero temperature, the diameter of a hydrogen atom, and the density of various materials in chemistry; the size of proteins and their secondary structure motifs, and the sizes of viruses, organelles and so on in biology; and the rates of fundamental processes (for example, diffusion in water, lipid bilayers; the rate of cell locomotion and so on). Ready knowledge of scale and rates allows one to quickly see if a hypothesis or a result or an experimental design is reasonable.  At that time Yale had an unusual program for a dozen or so seniors called Scholar of the House (sadly this wonderful program has been discontinued). This program allowed me to spend senior year fully in research (with Harold and Don) with no formal course work, and to graduate solely on the strength of a thesis, if it was accepted (if it was not I would need to repeat senior year conventionally). The thesis was evaluated by a committee of Yale’s most eminent scholars drawn mainly from the humanities. With so much riding on this, I was mortified when Harold playfully showed me the evaluation of my work he had written fully in limericks – I was sure I was doomed; but apparently it was just right for the humanists, and I was graduated (with the award for the best thesis).  During that last year at Yale I became a scientist. **Harvard** My father had cnvinced me that I should go to a medical school rather than directly to a PhD program. At that point my knowledge of biology was as narrow as my knowledge of physics was deep, and it would have been impossible to make an informed choice of which discipline in biology to focus on. Therefore, I entered Harvard Medical School (in 1971) with the idea of learning biology and then doing research, rather than ever practicing. I succeeded in the former, ultimately leaving the MD program more or less after the basic sciences (but with enough clinical exposure to gain a lifetime of respect for clinical medicine).  The first year at Harvard Medical School easily proved to be the greatest didactic experience of my life because HMS offered an unencumbered platform for self-directed learning with wonderful access to first-class research professors built on a broad and well-organized curriculum. I still rely on the many things I learned in that first year or so.  In particular, it was as a first year medical student in histology that I first learned about the secretory pathway, at a time when the discoveries of [George Palade](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1974/palade-facts.html) (Nobel Prize, 1974) were still fresh and remarkable. What an astonishing process – how could cells make vesicles from membranes? How could each vesicle know where to go? How could it fuse? It was particularly amazing because at the time it was not even possible to begin to imagine the form a molecular solution might take. This captured my imagination, but not enough was known to productively take up the problem then. But it would ultimately become a lifelong focus when I started my own laboratory at Stanford in 1978.  My PhD thesis (initially as part of Harvard’s MD-PhD program) was with Eugene Kennedy, a master of membrane biochemistry. Kennedy, who was a brilliant intellectual and an original thinker, taught me how to formulate a complex problem in biochemical terms. Some of this work was in collaboration with John Lenard, whom I will soon mention. We established how lipid bilayers in cell membranes are formed by asymmetric biosynthesis, following on the PhD thesis work of [Roger Kornberg](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2006/kornberg-facts.html) (Nobel Prize, 2006), which had at that time just established the basics of the physical dynamics of lipids in membranes.  Harvard, therefore, is where I became an experimentalist and in particular a professional biochemist. Everything that happened afterwards followed from that. **Deep and enduring scientific friendships** A life in research provides many opportunities to meet remarkable people as a student and afterwards around the world. It is hard to over-emphasize the importance of several formative, warm and enduring friendships for my development and success as a scientist. Some evolved from what we would today call mentoring relationships, initially with somewhat older (but still young) scientists who were nonetheless more established than me. Th s group included (in the order of our fi st acquaintance) Donald Engelman, John Lenard, Qais Al-Awqati, Roger Kornberg and Per Peterson. I fi st met each of these extraordinary individuals essentially as teachers. I have already mentioned Engelman.  John Lenard was a young full professor at Rutgers when we met in 1974. He took me into his lab (and his home) while I was still a graduate student so we could understand the topology of lipids in viral envelopes. We worked day and night together and we soon bonded personally. Though we never collaborated experimentally again, many ideas and personal decisions have been subject to John’s wise counsel. We wrote several review articles together over the decades, and in each case he taught me how to improve the framing of ideas and my writing style. Happily, we see each other regularly for dinners, museums, and theatre in Manhattan.  Qais Al-Awqati was my teacher in renal physiology when I was a second year medical student (1972) and he was junior faculty at Mass General. We met again much later (1986) when coincidently we both were at Cold Spring Harbor Laboratory summer lab courses, and we had many lovely evening walks together discussing books and occasionally science. We have been close ever since. Qais is not only one of the world’s best physicians and cell biologists, but without doubt one of the most intelligent and cultured people I have ever met. What a privilege it is to continue to learn from and enjoy him, whether we talk about science or he guides me through the Metropolitan (be it the art museum or the opera).  Roger was an assistant professor in the department of Biological Chemistry at Harvard Medical School and I met him as a PhD student. We had a common interest in membranes, but soon we were discussing ever-widening scientific terrain because of his deep and penetrating mind. He broadened and sharpened my perspective on biochemistry, first as a student and then soon as faculty colleague at Stanford. At Stanford we met many times a week, and I turned to him for criticism and inspiration. After I left Stanford (1988) this of course diminished in frequency, but never in intensity. I also suspect that Roger’s endorsement after “road-testing” me at Harvard somehow figured importantly in the job offer from his father [Arthur Kornberg](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1959/kornberg-facts.html) (Nobel Prize, 1959) and the other faculty to join their Biochemistry department, which came while I was still in the MD-PhD program in 1976.  Per Peterson, as he puts it, “discovered me” at a membrane meeting in Heidelberg (1980). Per is a cellular immunologist, and was at that time the director of the Wallenberg Laboratory in Uppsala (Sweden). As he told me, my findings were good raw material, but needed polishing. Of course, he was correct. He has been trying, with occasional modest success, to improve me ever since. Per has a rare combination of great analytical power with a genuinely sympathetic understanding of human nature. This has enabled him both to contribute centrally to science, and to build and run large and successful organizations, most recently as the Chairman of Research and Development at Johnson & Johnson. During his evolution Per has kept me at his side, and taught me a tremendous amount about the dynamics of industry and approaches to management that have proven very useful to me. He continues to inspire me and help me focus on what really matters.  Other important friendships started on more personal terms but soon evolved into long-term informal intellectual or actual collaborations where new ideas could be debated with absolute intellectual honesty in friendly ways and often in nice settings as well. I met Graham Warren (Figure 4, top) in 1976 when he was a postdoctoral fellow at Cambridge (UK) on an extended visit to Harvard, and we immediately hit it off, his reserve a complement to my exuberance, Graham harboring a well-known (merciless) intellectual rigor salved by his gracious humor. Graham and his family spent a summer at Stanford in 1978, so we could work together (actually starting my lab jointly) on what turned out to be a bold but ultimately ill-conceived hypothesis that we had convinced ourselves was the key to the sorting problem. Although in the past few years, with his responsibilities directing the Max Perutz Institute in Vienna, and mine at Yale, our contact has been less, we have seen each other numerous times every year and many of my best ideas have often drawn on our discussions.  I met Felix Wieland (Figure 4, bottom) in 1985 at Regensburg (Germany) where he was then an assistant professor. He came up to me after my lecture on cell-free reconstitution with the idea of spending two years at Stanford trying to figure out how membrane fusion worked. As with Graham, we also immediately hit it off, though in Felix’s case it was his contagious Bavarian exuberance and humor synergizing with mine. Soon, he was in Palo Alto. Wieland was a real enzymologist who taught me (and the rest of my lab) how the business is really done, having himself learned at the hands of a master (his uncle) [Fyodor Lynen](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1964/lynen-facts.html) (Nobel Prize, 1964). Without Felix, I doubt there would have been NSF, SNAP, SNAREs or coatomer, and even if there were they would not have been as much fun. By 1987 Felix moved back to Germany (at Heidelberg) but we still see each other frequently. I look forward to our annual escapes with our wives to Bad Drei Kirchen (Bolzano), and the Rothman and Wieland children continue their childhood friendships to this day.  Without a doubt the most important, deepest, and most vital relationship is of course with my wife, Joy Hirsch (Figure 5). In addition to the personal side, Joy is also my scientific partner. She is my sounding board on every subject, and has been my critic and supporter through the many early years when my work was not accepted as it is now. Joy comes from a successful farming family in Salem, Oregon and from this very American background is imbued with the Yankee attitude that every problem can be solved if you think about it enough and try hard enough. Joy also lives by this belief in her research. She is also a Professor at Yale, and is gifted scientist who is renowned for her fundamental studies of human cognitive processes and related diseases. **Observations on style from a life in science** As a closing bookend, I will offer some observations that may be of interest to others, especially younger scientists. This is not necessarily to impart specific advice, which would be disingenuous as I rarely followed the advice I was given as a young man; it is more to offer the use of some of my personal experiences as a springboard for generalizations that may apply to the reader. Some of these thoughts will be familiar to several generations of my students, who may recall having heard one or another as a frequently trodden-out aphorism. Some are from my own teachers.  *Science and art.* Science at the edge is an art form as much as a strictly logical development of ideas. The rare artists and the rare scientists capable of performing at the edge have a lot in common. They both have an intuitive vision carrying strong emotional content. Neither is easily discouraged from their work, even with strong obstacles in their path. These are essential traits.  *Choosing a problem.* As a new junior faculty member at Stanford, I asked Arthur Kornberg why he chose to understand DNA synthesis in the early 1950s. He said that the problem was of the greatest importance; that everyone else assumed it could not be done; but that he thought it could be. I listened very carefully when he said this.  *The importance of a clear hypothesis.* I often tell people in my lab “if you want to hit a home run, you have to be in the ball park. If you are outside the ball park you can swing all day but you will never hit a home run.” This idea comes from physics where computationally complex problems are approached by making simplifying “ball park” assumptions so that the main variables can be identified. To do this in biology, you imagine you are designing the system and therefore how you would design it for the required function. This provides a model – a hypothesis – of the form that a likely solution will take. You are now in the ball park, because you can now design specific tests of the model. Your exact model is almost certain to be wrong in detail (evolution rarely works by Cartesian rules) but is likely to be correct in spirit, and this will allow you to get to the truth faster. This process is very basic to my approach to science, as I described in my [Nobel Lecture](https://www.nobelprize.org/uploads/2018/06/rothman-lecture-1.pdf) (Figure 9 in the published lecture).  *Troubles Are Good For You (TAGFY).* The “TAGFY Philosophy” was first enunciated by the master enzymologist Ephraim Racker, and I pass it on. TAGFY has proven true for me over and over again. For example, after Erik Fries and I first published cell-free transport, we had great difficulty repeating our exact results, and it would have been easy to be discouraged. But TAGFY meant that we were really about to discover something basic that we had no idea about. Indeed, in resolving the “trouble” we found that we had reconstituted intra-Golgi vesicular transport, a process not previously known to exist (as documented in the Nobel Lecture). TAGFY can give you strength in hard times.  *If you are hitting your head against a brick wall, find a new wall.* It is so human to try that experiment one more time hoping for a better result. It almost never pays. Try a new approach. Remarkably, most people don’t.  *It is much harder to stop a project than to start one.* To do so takes real intellectual honesty and a complete disregard of ego. Worse, stopping involves a huge sunk cost of time and emotion, but if you don’t, then the next phase (which may hold success) will be only further away.  *Don’t be afraid to be “stupid.”* If you don’t understand it, it is probably unclear. If you don’t know how to do something, ask. It is far better than losing days in the lab because you didn’t. It is amazing how many people don’t ask. I always did and it made a difference.  *Smart is good; lucky is better.* Eugene Kennedy always said this, and he was right. In other words, in spite of any and all, don’t over-think and be open to chance. **Additional personal history** In addition to me (1950) my parents Gloria Rothman (née Hartnick, born 1923) and Martin Rothman (1915–2005) had two children, Richard (1953) and John (1955). My brother Richard is an MD-PhD who recently retired from the NIH after many years as a leading researcher in neuropharmacology, and is now in practice in Psychiatry. John is a successful attorney specializing in mediation. I am married to Joy Hirsch (Figure 5) who is an eminent professor at Yale in Neurobiology and Psychiatry. She is a graduate of the University of Oregon (BS) and Columbia (PhD). We reside in New York and New Haven. I am always dazzled by her beauty and elegance but equally by her brilliance and compassion. Joy is the glue that holds together our wide circle of personal and scientific friends, and our extended family. She has also been an exceptional stepmother to our children, and we are very proud of their accomplishments. Matthew (1977; Figure 6) graduated from Yale (BA) and Columbia (MBA) and is a senior executive in a major investment firm. He is married to the former Sarah Levinson, a senior executive in a national public relations firm. Sarah and Matthew are superb parents to our two delightful grandchildren, Alexandra (2010) and George (2012). Lisa (1982; Figure 6) graduated from Yale (BA) and Columbia (MD) and soon will start her residency in Dermatology at NYU. She is married to the former Jeannie Chung, an attorney in a major Manhattan law firm. **Curriculum vitae** James Edward Rothman was born on November 3, 1950 in Haverhill, Massachusetts (U.S.A.). He went to public schools in Haverhill, Massachusetts for elementary school through 8th grade, and then to Pomfret School (Pomfret, Connecticut) in 1964, from which he graduated in 1967. He then matriculated at Yale College, graduating *summa cum laude* in 1971 with a B.A. in Physics, having been Scholar of the House. Rothman then matriculated at the Harvard Medical School as an MD student, then joined the MD.-PhD program there. Ultimately, he graduated with a PhD in Biological Chemistry (thesis advisor, Eugene P. Kennedy) in 1976. He then joined the laboratory of Harvey F. Lodish in the Department of Biology at M.I.T. as a Damon Runyan postdoctoral fellow (1976–1978). In 1978 he joined the Department of Biochemistry at Stanford University as an assistant professor, and was promoted to associate professor with tenure (1981) and then full professor (1984). Rothman moved in 1988 to Princeton University in the Department of Molecular Biology where he held the E. R. Squib Chair of Molecular Biology. In 1991 he moved to the Memorial Sloan-Kettering Cancer Center where he founded and chaired the Cellular Biophysics and Biochemistry department, served as a Vice-Chairman of the Sloan-Kettering Institute for Cancer Research, and held the Paul Marks Chair. In 2004, Rothman joined the Columbia University College of Physicians and Surgeons as a professor in the Department of Physiology and Cellular Biophysics, where he also directed the Columbia Genome Center and held the Clyde and Helen Wu Chair of Chemical Biology. Then, in 2008 he returned to Yale and at the time of this writing is the Wallace Professor of Biomedical Sciences and Chair of the Department of Cell Biology and a Professor of Chemistry.  Prior to the Nobel Prize, Rothman’s contributions to cell biology, biochemistry, and neuroscience were recognized by numerous prizes and honors. These include: the Eli Lilly Award for Fundamental Research in Biological Chemistry, U.S.A. (1986); the Passano Young Scientist Award, U.S.A. (1986); the Alexander Von Humboldt Award, Germany (1989); the Heinrich Wieland Prize, Germany (1990); election as Member, U.S. National Academy of Sciences (1993); the Rosenstiel Award in Biomedical Sciences, U.S.A. (1994); election as Fellow, American Academy of Arts and Sciences (1994); the Fritz Lipmann Award, U.S.A. (1995); elected as Member, Institute of Medicine, National Academy of Sciences, U.S.A. (1995); Honorary Degree, University of Regensburg, Germany (1995); elected as Foreign Associate, European Molecular Biology Organization (1995); the Gairdner Foundation International Award, Canada (1996); the King Faisal International Prize in Science, Saudi Arabia (1996); the Harden Medal of the British Biochemical Society, U.K. (1997); the Lounsbery Award, National Academy of Sciences, U.S.A. (1997); the Feodor Lynen Award, U.S.A. (1997); honorary MD and PhD degrees, University of Geneva (1997); the Jacobæus Prize, Denmark (1999); the Heineken Prize for Biochemistry, The Netherlands (2000); the Otto-Warburg Medal, German Biochemical Society, Germany (2001); the Louisa Gross Horwitz Prize, U.S.A. (2002); the Lasker Basic Research Award, U.S.A. (2002); elected as Honorary Member, Japanese Biochemical Society (2005); the Beering Award U.S.A. (2005); elected as Fellow, American Association for the Advancement of Science (2007); the E.B. Wilson Medal, American Society for Cell Biology (2010); the Kavli Prize in Neuroscience, Norway (2010); and the Massry Prize. U.S.A. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0526=JR  [Unknown] Hello.  [Adam Smith] Oh good morning, my name is Adam Smith calling from Nobel Media in Stockholm, would it be possible to speak to James Rothman please?  [U] Yes, it is, just a moment.  [James Rothman] Hello  [AS] Oh good morning, Professor Rothman?  [JR] Speaking.  [AS] My name is Adam Smith calling from Nobel Media in Stockholm, we have a tradition …  [JR] Yes, Göran warned me that you’d be calling (laughs), and he also said you would kind enough to give me ten minutes to take a shower, and I’ve done that, so I’ve collected myself.  [AS] Perfect, gosh. You haven’t had long to do so. What were you doing when the call came from Göran?  [JR] I was sleeping actually, not surprisingly.  [AS] And what was your first thought on hearing the news?  [JR] At this time, on this day, I was completely shocked and surprised.  [AS] Marvellous, marvellous.  [JR] The truth is that anyone, almost anyone, who receives the Nobel Prize, has some indirect knowledge of one sort or another that they may be a candidate. And so at some level it’s not a complete surprise. But that it actually happens, it’s an out-of-body experience.  [AS] And do you think you’re going to relish the onslaught of press attention that follows this?  [JR] I’m not … no actually not. But the opportunity to be a spokesman for the field and for medical science, I do welcome that.  [AS] Yes, I imagine, that’s the big opportunity. It really highlights the field you work in, cell biology in general.  [JR] Have you talked to Randy Schekman yet?  [AS] Not yet, no. I just tried calling …  [JR] Actually, I was just on the phone with him, he gave me a call. I want to say that I’m absolutely delighted to share this award with Randy Schekman and Thomas Südhof. Absolutely and genuinely delighted.  [AS] Together you are credited with taking the field of vesicle trafficking from a descriptive to a mechanistic level. And the citation describes, it uses the word machinery to describe vesicle traffic. Is that how you think of it, when you think of the cell, moving molecules around in vesicles? Do you think of it as a machine?  [JR] That is a perceptive question. That is exactly how I think about it, machinery. And the reason is that one of the major lessons in all of biochemistry, cell biology and molecular medicine is that when proteins operate at the sub-cellular level they behave in certain way, as if they were mechanical machinery. It’s absolutely fascinating. When you … when we study chemistry, the rules of chemistry, electrons and so on, they operate at an even smaller level of atoms and molecules. But when you get to the sort of level of the nanoscale, you find that these objects start behaving as if they were mechanical. Exactly how I think about it, and always have.  [AS] It’s a beautiful picture.  [JR] My orientation originally was in physics. I was trained as a physicist as a young man. And what so attracted me about molecular biology is the opportunity to find the simplicity through that very simple concept … guided me. Funny you should ask that on the outset. It’s very perceptive of you.  [AS] Thank you, and in a week or two’s time, when things have quietened down, I hope we can have a longer conversation where we can dig into this more. But one question, what gave you the courage to embark on this idea in the first place? Because the initial experiments, it wasn’t clear they’d work at all.  [JR] No I don’t know, you probably have the benefit of the press release?  [AS] Uh-huh.  [JR] Which I do not. So I don’t quite know how the committee has written the story. But yes, in the earlier years when I started this project, at Stanford University, everybody told me it was nuts to go and try to reproduce the complexities, the mysterious complexities that occur in a whole cell, in a cell free extract. And … my courage came from three sources I would say. The first, in all seriousness, was youth. Because there’s a certain arrogance in youth, I don’t if I’d have had the courage to do that today. The second was the fact that, you could in those days, in the United States you could do adventurous things with very little, no more preliminary data, and you can still get support from the NIH to do it. And so in today’s environment I doubt very much I would have had the freedom or the opportunity to truly pursue this. And the third, frankly, was that I was inspired by a man named [Arthur Kornberg](https://www.nobelprize.org/prizes/medicine/1959/kornberg/facts/). And Arthur Kornberg is a name that should come up in your interviews because Randy Schekman was Arthur’s PhD student.  [AS] Indeed, yes.  [JR] And Arthur as you know, unfortunately died a few years ago, was one of the great biochemists of the century, of the 20th century. And he was the reason why I was Stanford in the first place, why I left medical school, and the opportunity to be in his department and have the lab next door. And the reason why Arthur was such an inspiration, is that in his own time he had conquered an unbreakable barrier for enzymology, as he called it, which was the synthesis of DNA, so I frankly got a lot of courage, encouragement from being in that environment and watching what Arthur and the others could do. And that’s … my answer to your question.  [AS] It’s a beautifully succinct answer, thank you very much indeed. Well as I say, I will schedule a longer interview with you in the coming week, but for now, I just should let you get on with what will be an extraordinary day (laughs).  [JR] Good luck with your interviews with the other Laureates today, and I’ll look forward to speaking with you at greater length on another occasion.  [AS] Thank you very much indeed. Pleasure to speak with you, and once again congratulations.  [JR] Thank you so much.  [AS] Thanks. Bye bye. |
| Interview |  |
| Q23 | Could you explain your Nobel Prize awarded work to young students? |
|  | To the young teenagers and other students when you study science and you start thinking about the human body. One of first things that you are taught is that the body has a lot of parts, we have our brain, we have our muscles and we have the various parts inside the body, the so-called organs. They teach you a lot about these different parts of the body, but one of the most important things is how the different parts of the body talk to each other. How does the brain talk to the muscle to tell you to move an arm, for example? We call that synaptic or neuronal communication. How does your stomach talk to your pancreas to cause hormones like insulin to control the sugar that you are eating and make sure that the right amount of sugar goes throughout your body and then to your brain so your brain can be thinking in a way because I hope you are right now if you are listening to this. It is those very basic questions of cell to cell communication in the body that professors Südhof, Schekman and I have helped to understand. |
| Q1 | What brought you to science? |
|  | You know there are some scientists who … they sort of get into science accidently, they met somebody, or they saw somebody or whatever their story is. In my case I can’t ever remember not wanting to be a scientist. I think I briefly flirted with the idea of driving a locomotive train when I was probably two or three. I was very fortunate to come from a family that was very focused on education. My father was a doctor in a small town, but education and especially science and medicine were an important part of the sort of family culture and so I also grew up in the United States of America. I was born in 1950, the significance in that was that after world war two America was really at that time seen it was becoming and it already was a very powerful country. It was taking on global responsibilities including scientific research, but also in a major competition with the Soviet Union as everybody knows, the so-called Cold War. When the Soviets developed the nuclear bomb and when they also were the first to put satellites into space, quite frankly it scared the wham out of certainly Americans, but certainly a lot of the world. It caused an energy … the whole enterprise of scientific research especially the physical sciences, but also biomedical sciences got energized. So that’s the environment that I grew up in and in that environment scientists and medical doctors doing research and so on, we are really prized by society. I am not entirely sure that’s so true today, but it was certainly true then and we were seen as assets, very little in the liability call, so you know as a young boy your hero might have been a baseball player, but it might also have been a physicist like Oppenheim or [Einstein](https://www.nobelprize.org/prizes/physics/1921/einstein/facts/). |
| Q5 | Who is your role model, and why? |
|  | Sometimes I get asked the question, who is my role model? I guess the answer to that is it probably depends at what age. When I was really young and probably did have role models that affected me, I didn’t know the concept of a role model. I actually think that the role models that we have that really help determine our character. I mean of course there are our parents and our friends, made a family, but I don’t think we really think about that at the time when it has the most effect. Later on in life, as you are an adult, you have your teachers and I have had mine, but I guess I feel like I have had many, not just one and I have been very fortunate for that reason. I think people who are successful in life have the wonderful accident of having had, whether intentional or not, sometimes you find the person who you admire, that’s a skill, but the ability to have that skill to seek out a role model is something that probably is acquired through role models that we don’t seek out.  As a young scientist there was a great biochemist who was very influential to me and also, I have to say when you interview Randy Schekman I am sure you hear the same name. His name was [Arthur Kornberg](https://www.nobelprize.org/prizes/medicine/1959/kornberg/facts/). Arthur Kornberg was one of the great biochemists of the twentieth century, possibly the greatest biochemist of the second half of the twentieth century. He was my hero as I was learning biochemistry and I actually left medical school without finishing my medical doctor’s degree in order to take the opportunity to work in a laboratory next to professor Kornberg. My first job as an independent scientist was as a young professor at Stanford University and Arthur was the chief of the department really and actually was a great inspiration to me. The work that was recognized in this Nobel Prize, my contribution to it, began during that period and I don’t think that I would have been as successful in doing what I did if it were not for the kind of scientific environment that he fostered and the type of science that he represented which we called enzymology. He was without a doubt the master of enzymology of his era and for me to have the opportunity to take that discipline to a new level under the watchful eyes of the master was quite an extraordinary experience. He won the Nobel Prize by the way many years ago and I believe 1959. |
| Q16 | At what point did you realize your work was a breakthrough? |
|  | It’s always difficult to know at any one time as a basic scientist whether what you are doing at that time is going to have some monumental significance. I am not sure my work has monumental significance, but it certainly has been recognized as having some significance. The thing about basic science is that we any one day, any one experiment, you never really know, you try your best every single day. I tell my students every day that you work in the lab is a day that you will never have again, so think very carefully to do the most important thing that you can do every day. But the nature of science is such that if you are doing real research on the frontier where nobody has ever been, it doesn’t always work. The hardest thing about being a scientist is you have to be prepared to fail most of the time. A Nobel Laureate might be a scientist who fails only 99% of the time, maybe everybody else is a little bit less luckier or whatever fails 99.9% of the time. By definition what you are doing at any one time, it’s a little hard to know if it’s the most important. On the other hand, when it does happen, and it’s happened to me actually twice. I have had very special moments and I kind of understood and everybody around me kind of understood that it was a special moment. We celebrated some of the basic discoveries at the time they were made with my co-workers. With scientists, it’s also very important for students especially, to understand that science these days is not a solo enterprise, it’s the work of a team. It’s students, professors and we all contribute, not everyone gets recognized with the Nobel Prize, but there are a lot of people who contribute. |
| Q19 | What were you doing when you got the message of being awarded the Nobel Prize? |
|  | The experience of getting a telephone call from Stockholm at 04.30 in the morning is absolutely singular. I was of course sleeping when it came, but not for long and woke up rather abruptly. I went to sleep actually quite late the night before and perhaps had a little too much to drink and but my wife Joy of course woke up at the same time and said: “This might be it!” and of course I was thinking the same thing and sure enough it was and there was a voice not entirely unfamiliar to me, professor Hansson, I had met on a couple of meetings, didn’t know him well, but it was wonderful news. |
| Q15 | Is basic research important? |
|  | It’s a terrific honor to be recognized by a Nobel Prize. This year we have three Nobel Laureates in Physiology or Medicine and the emphasis, as the Nobel Committee mentioned in their announcement, is on the physiology, but also the medicine. This is a basic science prize and it recognizes fundamental research whose medical implications are not immediate, they will happen, some of them are already happening, but what it really does is it celebrates the importance of understanding the life process in and of itself. That focus on the importance of fundamental research, in this case in the life sciences, is something that the Nobel Prize contributes importantly to, because oftentimes this type of work goes less noticed than the next momentary medical advance or clinical trial and funding for basic science research around the world is in serious jeopardy, particularly in the United States, but not only in the United States and certain parts of Europe, even here in Sweden. Although there is good funding for basic research, it could be better and so it’s really important that the type of work that we represent and what we represent is just a tip of an iceberg and there are many of tips and it’s great when these tips of the iceberg are recognized from time to time. |
|  |  |
| ID | 0527 |
| Biographical | **Ancestors** The Russian Revolution and the growing influence of the Soviet empire stimulated a migration of Jews to America and Israel. My father’s father, Norman, followed his brother Nathan to Massachusetts where he enlisted in the British foreign brigade to fight in Palestine. He returned to the US and settled in Minnesota, along with a growing Jewish community in the Twin Cities. He met and married my grandmother, Rose, after whom I was given the name Randy, or Ruvain in Hebrew. My grandparents raised their children, my aunt Helen, my father Alfred, born in 1927, and my uncle Arthur in St. Paul. My grandfather had several careers; one I recall hearing about was as a traveling salesman selling clothing to farmers in the agricultural areas around the Twin Cities. My grandmother Rose died tragically of a stroke just as my father met and dated Esther Bader, a young high school student living on the north side of Minneapolis, then an enclave for Jewish immigrants from Eastern Europe. They married in 1947 at the tender ages of 20 for my father and just 18 for my mother.  My mother’s parents, Raymond and Ida, grew up in a village in Bessarabia, which at the time was part of Romania, but which is now Moldova. My grandfather became a tailor, my mental image of which will always be fixed by the character Motel from “Fiddler on the Roof.” He was drafted onto the Romanian Army as a tailor and then by some stroke of good fortune won a lottery to immigrate with my grandmother to the US in 1927. Most of the members of their families were slaughtered in the Nazi takeover of Eastern Europe in the early years of WWII, but some managed to escape to Israel where a branch of our family lives today. My grandparents landed in Providence, Rhode Island and found their way to New York City. My grandmother was uncomfortable in a big city, so they sought out an adopted member of my grandmother’s family who had previously migrated to Minneapolis, where they ultimately settled and had two daughters, my aunt Mary and then one year later in 1929, my mother Esther. The family struggled to get by in the Depression, made worse by the illness of my grandmother who contracted tuberculosis and was taken to a sanitarium for a couple of years, during which time my mother and her sister were sheltered in an orphanage so that my grandfather could work as a tailor to cover the family expenses. Many decades later, years after my mother died, I learned from Rodney Rothstein, a fellow yeast geneticist, that his mother had befriended my mother and aunt during their years in the orphanage. I had the surreal experience of meeting Mrs. Rothstein at a special occasion where Rodney was honored and she recounted her memories, some 70 years later, of my mother during that time in the early 1930s. I will never forget embracing Mrs. Rothstein as a living memory of the mother I so cherished. **Early years in Minnesota** My parents took an apartment in St. Paul and I was born a year later in 1948. We then moved to another small apartment on the north side of Minneapolis, probably so that my mother could be closer to her parents. My sister Wendy was born in 1950 and my earliest memories are of the two of us as infants in cribs in that small apartment. My sister and I occupied the one small bedroom and my parents slept in the living room, which doubled as the dining room. My aunt Mary married Marshall Kopman, and for two years they lived together in the second bedroom of my grandparent’s home, probably no more than a mile away from our family apartment.  My oldest cousin Michael was born around that time and I am told – but do not recall – that I walked by myself to my grandparent’s home to see him, much to the horror of my parents. In the first years of my life, it was clear that I was shorter than my peers so my mother, who was quite combative as a child, decided that I needed to learn self-protection. She claimed, but again I do not recall, that she tried to teach me to hold up my fists in a threatening gesture, but it may have backfired when I resorted to the use of the top of a garbage can when I fought with a local child.  We remained in that apartment for several years. My father then designed and had built a small three-bedroom home of less than 1000 sq. ft. a couple of miles away, but still in the north side area just a block away from a home my uncle Marshall had built for his family. During the six years we lived on Upton Avenue, the Schekman family grew with two more boys, my brothers Murry and Cary, and the Kopman family grew with two girls, Jodi and Robin. We were a close knit family with daily activities revolving around playtime with my cousins and friends from the neighborhood, school at the Jewish community center and John Hay Elementary School, and afternoon Hebrew lessons at a religious school just down the block from my grandparents. The regular highlights were Friday evening Sabbath dinners at my grandparents’ home, holidays at the synagogue, a conservative congregation that my grandparents joined. My fondest memories are of drives to the countryside for an ice cream cone, occasional sleep overs on the porch at my grandparent’s home, but most of all, our annual trips to a cottage on a lake in Northern Minnesota, where my grandfather would take us fishing in a boat in pursuit of sunfish, walleye, crappie and the special treat of early morning trolling for northern pike. We lived and associated exclusively with other Jewish families and I was unaware of anti-Semitism until one day on my way to the Jewish Community Center, an older kid slugged me in the stomach when he learned where I was headed.  I have fewer memories of my father’s family. We would occasionally see his father and new wife, Evelyn, a dear woman who was sweet to the children and whom I grew to love in later years on a high school trip to Florida where she and my grandfather moved for retirement, and then later, after my grandfather died, on a visit to her sisters and their families in the New York area. My father’s younger brother Arthur lived with us briefly in the Upton Avenue house. We had more social occasions with Arthur and my aunt Carol and their children, Scott, Ronnie and Lorrie when they moved to Southern California in the 1960s. My father’s sister Helen moved to Columbus, Georgia and raised a family of five boys, whom I am sorry to say we almost never met for family events, other than one trip with my wife and son and my parents to a meeting in Atlanta in 1987.  I have only vague memories of any particular academic interest during those years in Minnesota. My father was a mechanical engineer working at General Mills. He was drafted after the war, but never left the country after boot camp and had attended the University of Minnesota on the GI bill. My mother worked part time in a department store during and after high school, but did not attend college. It was clear that the family valued learning and college for all the children was always an expectation, but any particular professional goals beyond college never entered my mind. I remember a casual interest in astronomy and I still have some electron microscope (EM) pictures of bacterial viruses that my father took which were used in particle size calibration at work. My casual reading was almost always of boy’s adventure stories.  I briefly belonged to a troop of cub scouts, but that sort of regimented activity had little appeal. Correspondingly, my most unpleasant memory of that time was of a military outfit that my parents bought for one of my birthdays. **Westward to California** In 1959, my father answered an ad for an engineering position in Southern California. On returning home from Los Angeles he announced that we would move at the end of the year to the great frontier of the Golden State. Neither of my parents had known anything other than Minnesota and yet my father somehow knew his future lay in the burgeoning computer industry of Southern California. My mother was traumatized by the move. She was emotionally dependent on her parents and could not bear the thought of such a geographic separation. For years after the move, she was inconsolable – when visits to Minnesota and/or of her parents to us in Southern California came to an end.  For me however, the move was a great adventure. We packed up the car and drove off in the deep cold of December 1959, traveling through snow flurries in the Midwest over the 2,000 miles to Los Angeles. The weather delayed our excursion and when we finally arrived on December 31, the reservation my father had made at a motel was cancelled and we had to scrounge for a single unheated room where the children bundled into one bed for warmth on New Year’s Eve. Still, Southern California was a dream with the network television studios just down the block from the motel we occupied for several weeks before moving to a rental home in Pacoima. I still recall with awe my first glimpse of the vast Pacific Ocean and the maze of freeways, not yet impassable with the choked traffic of today.  In 1960, my father purchased a new tract home in Rossmoor, then a new development in western Orange County, just adjacent to Long Beach. I had the privilege of my own bedroom where I hung out for long hours listening to the daily radio broadcasts of the LA Dodgers and their famous – and still active – announcer Vin Scully. My hero, indeed the hero of the entire Jewish community, was Sandy Koufax, the greatest pitcher of his generation. Those great World Series championships, especially the shutout of the Yankees in the 1963 World Series, are cherished memories that an impressionable child can never forget. On the other hand, although I have now lived in the San Francisco Bay Area for most of my life, I can never forgive the Giants and their infamous pitcher Juan Marichal who took a bat to the head of the Dodger’s great catcher Johnny Rosboro during a tense moment in a game at Chavez Ravine in 1965. I was a baseball nut but not at all athletic. My one year in little league ended ignominiously with a strike out on a bad pitch that I never should have swung at.  My father expected his children to be industrious and to work for extra money. I baby sat for the children of my parents’ friends, mowed lawns and held a paper route delivering news for the now defunct *Los Angeles Examiner*. My memories of school are not particularly strong. I remember the expectation of academic performance instilled by my parents, but until around 7th grade, I recall no particular interests or ability at the end of elementary and beginning of junior high school. That began to change when I received a toy microscope and collected a jar of pond scum from a local creek. I recall with amazement the rich microbial life seen in a drop of that pond scum, even just from squinting into the plastic lens of that toy. **The microbial world** In the spring of 7th grade, I attended the school science fair and was captivated by the dozens of projects that the older students had assembled. The vivid memory of that simple event resonated somehow in a way that nothing else in my experience in school ever had. Here were simple but clearly individual efforts on display for recognition by fellow students, teachers and parents. In retrospect, this may have been the single event in my youth that fixed my path in science. In the following year, I spent countless hours looking into or projecting an image onto a sintered glass screen of paramecia and rotifers gliding or crawling across my field of view. I built a science project display based on my simple observations for my first entry in 8th grade, and although I recall no particular recognition for that work, I was nonetheless hooked, and the annual science fair became my one abiding academic passion through junior and high school.  Another revealing moment came that year when I recounted my excitement about these protozoa in a family conversation at the dinner table. My father, perhaps recalling his own experience with EM images of bacterial viruses, was dubious that anything of value could be seen in my toy microscope. At that point, I resolved to save and buy a student professional microscope using the money from my odd jobs.  Time went on, but I never seemed to reach my goal of $100 because my mother would borrow the money for family expenses. One Saturday I became so upset that after mowing a neighbor’s lawn, I bicycled to the police station and announced to the desk officer that I wanted to run away from home because my mother took my money and I couldn’t use it to buy a microscope. My father was called in and words were exchanged behind a closed door, the net effect of which was that we purchased my microscope at a pawnshop in Long Beach that afternoon! That microscope became my treasured possession for the rest of my years at school, but it was inevitably put aside as I went ahead to college and graduate school. Fortunately, my parents saved it and sent it up to my current home in the San Francisco Bay Area, where it languished in the dust for decades until the call from Stockholm at which point I realized it might be more interesting to visitors at the Nobel Museum. My old microscope is now on display, together with the tale of how it was acquired in a fit of childhood pique.  In 9th grade, a friend of my parents who worked in a hospital lab in Long Beach took an interest in my budding passion for microbes. She provided me with simple training in the classification of bacteria and valuable assistance in acquiring simple ingredients I would need to grow bacteria at home. I assembled a homemade incubator whose temperature was controlled by a light bulb hooked to a rheostat. I purchased simple supplies of glass petri plates, flasks and agar. Through my friend at the hospital, I was given units of spent human blood, which proved to be a rich source of nutrients for the growth of bacteria that were the subjects of my science fair projects over the next several years. I used my mother’s pressure cooker to sterilize and melt the agar and stored the spent human blood and my fresh medium in her refrigerator. In truth I didn’t really know what I was doing most of the time, but it certainly stimulated my reading of as many books on the microbial world as I could lay my hands on.  Just before I entered high school, my future biology teacher, Jack Hoskins, introduced himself as I stood in front of my project at the county science fair. Jack became my mentor during the next three years, and though his knowledge of experimental science was limited, he became a valuable source of encouragement outside of my family, who had much less knowledge of or interest in science. Indeed, we remained in contact through all the years since then – through to the morning of the Nobel Prize announcement when he sent a congratulatory message, expressing delight that he had lived to see this day. Back in high school, the peak of my effort was a fifth place prize in the senior life science division at the California State Science Fair, and an on-TV interview by Vin Scully, whose velvet voice of the LA Dodgers had entertained me for so many years.  As I dreamed of my future in college, I read such books as *The Microbial World* by Adelberg, Doudoroff and Stanier, and *Bacterial Viruses* by Gunther Stent. Indeed, as I explored the annual catalogue of courses at UC Berkeley I recognized the authors of these books as faculty members and wondered what opportunities I might have to learn directly from such individuals. The cost of college was foremost in the mind of my mother who thought it would be good enough if I lived at home and attended the local State College in Long Beach. However, I was certain that I wanted the more vigorous experience and peer group of a selective University, so I compromised on distance and applied to just one school, UCLA. In truth, UCLA also appealed because of the great basketball teams coached by John Wooden who had just recruited the best high school player of all time, Lew Alcindor (now Kareem Abdul Jabbar). **Stirrings of the life of a scholar** In the fall of 1966, I drove my motorcycle the 30 miles to UCLA where I took up residence in the student co-op dormitory along with my high school buddy Peter Wissner. The timing was perfect because just one week earlier my mother had given birth to my youngest brother, Tracey, and as hectic as college was, it would have been even more disruptive with a new baby back home. I threw myself into my studies and spent every waking hour in class or in study in a library. My courses were generally wonderful, particularly freshman chemistry then taught by a brilliant lecturer, Kenneth Trueblood, who received a standing ovation at the end of the term. I did well enough in that course to be admitted to an honors section for the third term, a course taught by [Willard Libby](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1960/libby-facts.html), a Nobel Laureate who had won the prize for C14-radiodating of ancient materials.  The students in this class were clearly a cut above the others in my courses, and as a result I enjoyed my first taste of serious scholarship. Although it was inspiring to be taught by such a renowned chemist, Libby was not the effective lecturer we had experienced in Trueblood. But what made this class special was that each student was assigned to work in a Chemistry Department lab for the term. By chance, I was assigned to the lab of a new assistant professor, Michael Konrad, who had worked as a graduate student with Stent at Berkeley. Konrad assigned me to read a new book just off the press, entitled *The Molecular Biology of the Gene*, by [James Watson](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/watson-facts.html). The book was a revelation to me and I read its paragraphs and chapters as though they came from a new bible of life. My project in the Konrad lab was simple enough: I hydrolyzed a sample of DNA and determined the base composition by chromatographic separation and UV absorption.  Although I had started UCLA with an aspiration to attend medical school and become a pathologist, the experience of my first year changed my outlook completely. I was disappointed that most of my pre-medical classmates were more interested in getting high marks than in the science itself. In contrast, the one term experience in Konrad’s lab combined with Watson’s book convinced me that my future lay in experimental science, preferably as an academic in a research university. The summer after my first year in college I worked with my father at his computer data firm. He had hoped to enthuse me about writing computer code, but I found it boring and my mind turned to how to pursue a basic molecular biology research project when I returned to UCLA for my second year. I cooked up an idea to look at the effect of a mild organic solvent, DMSO, on the uptake of viral DNA by bacterial protoplasts. After a couple of disappointing approaches to various faculty members, I found another new assistant professor, Dan Ray, of the then Zoology Department who was willing to gamble on me. **A path to discovery of molecular mechanisms** Dan had trained with Phil Hanawalt at Stanford studying bacterial DNA repair and then with Peter Hofschneider in Munich studying the replication of a small circular chromosome of the phage M13. I puttered around for a term trying to learn how to perform the experiments necessary to test M13 phage DNA uptake into *E. coli* protoplasts. Dan took me under his wing and gradually turned me to the interests he had in the mechanism of replication of the duplex form of M13 in cells infected with the phage. I was captivated by the idea that an experimentalist could use physical techniques such as velocity and density gradient separation of chromosomes extracted from infected cells to test models of chromosome strand inheritance during replication. Dan offered me a summer job and then generously listed me as a co-author on two papers he had prepared for publication.  Not many UCLA undergraduates worked in a research lab during that time, but I was happy to work alone well into the evening. Although my coursework was also going well, I increasingly began to feel that I was perhaps misplaced at UCLA, and that I might benefit by transfer to a school such as the University of Chicago that had a reputation for serious scholarship at the undergraduate level. James Watson himself had been an undergraduate at Chicago. Indeed, in the fall of 1967 I read Watson’s *The Double Helix*, which as much as his textbook had steeled my determination to live the life of a scholar in pursuit of a basic understanding of life. But as a simpler and much less expensive alternative, I learned of the University of California education abroad program and I applied and was accepted for a year at the University of Edinburgh.  I was excited to travel to Britain – I had never been out of the US – and in anticipation I asked a professor who taught a graduate course in genetics whom I might approach on the faculty in Edinburgh. I learned that the prominent bacterial geneticist William Hayes, had just started a new Medical Research Council unit in this research topic. I wrote to Hayes and he welcomed me to join the new unit, though he mistakenly believed that I would spend the year as a sabbatical visitor. I arrived to find that I had been listed on the opening program as a visiting faculty member from UCLA and was assigned my own laboratory space. They quickly realized their error but graciously provided me an opportunity to learn bacterial genetics from a Lecturer, John Scaife. I managed also to continue my studies on M13 phage and took the biochemistry course in the medical school in downtown Edinburgh. The year provided a wonderful opportunity to travel on the continent during the term breaks. However, I was ill prepared for the British style of examination that consisted of one comprehensive exam followed by an interview with the Biochemistry faculty. I survived by the skin of my teeth, but was appropriately upbraided by the faculty who relished the opportunity to take an arrogant Yank down several notches in my exit interview.  The most enduring influence of my year in Edinburgh was my acquaintance with Leonard (“Len”) Kelly, a graduate student in the lab next door in the Molecular Biology Department. Len shared correspondence with his brother Regis (“Reg”) who was then a postdoctoral fellow in the laboratory of Arthur Kornberg, whom I knew to be the leading DNA enzymologist of this era. Reg had discovered that the DNA polymerase was capable of removing thymine dimers from UV-irradiated DNA in a repair-like replication reaction. The work was elegant and precise in a way that I had not experienced; I resolved to learn biochemistry from a master such as Kornberg.  In the months before I left Edinburgh to return to the US, I considered summer opportunities in the US prior to my senior year at UCLA. One possibility was the Undergraduate Research Program at Cold Spring Harbor (CSH). I would have relished the total immersion of that program, and the timing could not have been better with the discovery of the *E coli* DNA polymerase mutant by John Cairns who was then the director of the CSH lab. However, the summer stipend they offered was just enough to live on and I had to save money to pay for my remaining year of college. Instead, I took a summer position with David Denhardt in the Biological Laboratories at Harvard. The ferment of the Bio labs was intense with the [Walter Gilbert](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/gilbert-facts.html) and James Watson labs just down the hall. But the bickering and contentiousness of the atmosphere left me with a bad feeling about what it would be like to do PhD work in such a hypercompetitive environment. Nonetheless, I had a wonderful time in Denhardt’s lab and learned much to affirm my resolve to pursue a more biochemical approach to the study of DNA replication in graduate school. I left having done enough work to publish a first author paper in the *Journal of Molecular Biology* the following year. **Personal growth, loss and challenges in college and graduate school** My last year at UCLA brought emotional highs and lows. On the upside, I had the opportunity to meet [Arthur Kornberg](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1959/kornberg-facts.html) and to discuss my interest in the biochemistry of DNA replication and then in the spring of the next year, I was admitted to Kornberg’s department at Stanford for graduate school. But before that, just as I returned home from my summer at Harvard, I was greeted by my mother at the Los Angeles airport with the news that my sister Wendy had been diagnosed with acute leukemia and was given just months to live. Wendy’s rapid decline and our family’s anguish at her loss left a scar that is never far removed from my thoughts, even 45 years after her death. My mother was tortured by the loss of her one daughter and never fully recovered from the emotional blow.  Perhaps in reaction to this trauma in my life, I threw myself into the work back in Dan Ray’s lab at UCLA and didn’t bother with many of the lectures in classes that I had to complete in order to graduate. As a result, my grades declined and I was placed on academic probation for the second of the three terms of the year. Indeed, I failed German twice and left UCLA without actually having graduated. The registrar at Stanford took a dim view of this gap in my record and it was not until a sympathetic Dean back at UCLA waived that requirement – thus allowing me to graduate – that I was able to look ahead to my graduate career.  My personal life at Stanford was also a mix of highs and lows. Although I was thrilled to be in such an exciting environment, my immaturity led to personal isolation. Most of my fellow PhD students came from elite private universities and I felt insecure as one of the few students from a public university. Kornberg once asked me why I hadn’t enrolled in a “better” school, to which I responded that it was the best my family could afford. But looking back at what I was able to accomplish then, and now after nearly 40 years at UC Berkeley, I can state with confidence that I had the best preparation and that our great public institutions, the University of California in particular, offer educational and real life experiences that are second to none.  After a period of personal decompression (I was placed in small lab room by myself as penance for my obnoxious behavior), I slowly developed great friendships that have lasted a lifetime. Costa Georgopoulis, a postdoctoral fellow in Dale Kaiser’s lab, took pity on me and invited me to join a group for a camping trip in a nearby state park. Costa deflated my ego by calling me a turkey, a term of endearment that seemed to fit and which stuck for some years. But my greatest friendship came when Bill Wickner joined the Kornberg lab in 1971. Although we were in a somewhat competitive situation in the first months of his time at Stanford, I will never forget the favor he did me when, after I made an aggressive remark, he lifted me from the floor by the front of my shirt and told me to settle down!  But Bill did more than that for me. After a few more months of intense and close cooperation, he could see that my personal life was going nowhere so he and his wife Hali conspired to find a suitable mate for me. After one failed effort at matchmaking, Bill had a call from a former girlfriend, Nancy Walls, whom he had dated in Boston. Nancy had completed her training as a nurse at Massachusetts General Hospital and decided to make a clean break to the West Coast. Feeling lonely herself, she called Bill at Stanford but learned that he had in the meantime married Hali, but he had a lab partner who needed distraction. I still remember our first date at a Greek restaurant in San Francisco and our first kiss goodnight. Nancy and I grew close quickly as these things happen when you are young. We moved into a small duplex home in Palo Alto and Nancy took a job as a nurse at Stanford Hospital. We would meet for a goodnight kiss while she was on a night shift and I worked into the wee hours of the morning in the lab. Nancy and I married in a ’70s style outdoor wedding in Huddart Park in Woodside, near the Stanford campus. Our years at Stanford were fulfilling in every way. I grew emotionally secure in a loving relationship and even with the intense and sometime acrimonious battles I had with Kornberg, I left graduate school equipped with the intellectual and technical skills that made my subsequent career possible.  Nancy took classes at a local community college with the goal of obtaining a BA in nursing. As we considered our next move for my postdoctoral training, she felt we should remain in California where her course credits would be recognized by a state school. I arranged a postdoctoral position with SJ Singer at UC San Diego and we moved south for what would be a short two-year stay in San Diego. In spite of the issue of course credit, Nancy enrolled at private school, the University of San Diego, and completed the requirements for her BA degree. She worked as an intensive and coronary care nurse, but we both missed Northern California, so when the opportunity came for a position at Berkeley, we moved back north and have remained ever since. **Family life and career at Berkeley** We settled into a family life in El Cerrito, a bedroom community just north of Berkeley. Nancy took a job at Alta Bates Hospital in Berkeley and we saved as much as possible to afford a home which we purchased in 1977 – and where have lived to this day. Our son Joel was born at Alta Bates in March of 1978, and our daughter Lauren was born in Basel, Switzerland in November 1982, during a sabbatical year in Basel that Bill Wickner, I and our wives had arranged for the year after I was granted tenure at Berkeley. Both of our children inherited a talent and taste for classical music from Nancy, who had played the saxophone in school and her mother Beatrice, who played the violin, so it seemed natural to expose the children to piano and other forms of musical training. The years of our family life sped by, enriched by the music of our talented children who filled our home with beautiful sound. Joel took up the clarinet and never let go. His passion grew into a career as a classical musician, currently in the Grand Rapids, MI Symphony Orchestra. Lauren sang in youth choirs that traveled the world, but she found more of a calling in economics, management and the business world, though she remains active in a semi-professional choir where she lives in Portland, Oregon.  Nancy worked full-time and then part-time when the children were young, and she may have remained active in nursing, but life intervened and at the relatively young age of 48, she was diagnosed with Parkinson’s Disease (PD). In her case, the disease progressed quite slowly and was effectively controlled by medication, but inexorably the physical symptoms worsened. In 2009, she had neurosurgery to implant electrodes in a treatment called Deep Brain Stimulation. This procedure worked remarkably well, and together with medications, her physical symptoms are unusually mild for someone now 18 years post-diagnosis. Unfortunately, this awful disease comes with other disabilities and in her case, dementia set in, which has slowly but inexorably sapped her memory and independence. Two years ago, her dementia was diagnosed as an atypical form of PD called Diffuse Lewy Body Disease for which no effective treatment exists. Life continues and we remain devoted to each other after nearly 42 years of marriage, but I fear for the future as her condition worsens year by year.  My parents rejoiced in the birth of my children, their first grandchildren, and our occasions together were filled with pride in the musical accomplishments of Joel and Lauren. As my career flourished, my parents tagged along to every special event and award ceremony and they fully expected to include a trip to Stockholm at the end of the rainbow. But in 1996, my mother was diagnosed with an inoperable brain tumor, which took her life two years later at the age of 69. This loss struck my father even more deeply than the loss of his daughter / my sister. However, with time he recovered and with the help of a support group he met a wonderful woman, Sandy, who had lost her husband to heart disease. They were married within two years and continue to live happily together in a new home in Southern California.  Sandy and my Dad were the first people I called on that fateful early Monday morning of October 7, 2013. Among the many thrills of our memorable trip to Stockholm, I will never forget having my father rise to receive my appreciation in front of the thousand people who attended my Nobel Lecture. He never faltered in his certainty that I would someday receive that recognition. In honor of my sister and mother, I donated my Nobel Prize funds to create an endowed chair, the Esther and Wendy Schekman Chair in basic cancer research at UC Berkeley. **An appreciation** In my Nobel essay, I described in detail the contributions of my students and postdoctoral fellows that led to our dissection of the secretory pathway in yeast and the many molecular insights that developed from our discovery of the *SEC* genes and their protein products. I had the good fortune to attract some of the finest young scholars from around the world to join in that effort. But I owe at least as much to the many colleagues at Berkeley who taught me how to be a constructive citizen of science. Among them, I wish to offer a special tribute to Dan Koshland, Howard Schachman, Bruce and Giovanna Ames, Bob Tjian, Jeremy Thorner and Mike Botchan. They offered counsel and friendship that has enriched my life as a scholar and teacher.  During that nearly 40-year adventure, I observed a sea change in the attitudes and acceptance of women as scholars in the academic community. Gone are the days when women were relegated to “adjunct” status in couples seeking academic appointments. Instead, I found women who joined our department and my laboratory who had the highest standards and drive for achievement. Several who stand out in my experience are Susan Ferro-Novick, who was and continues to be as ambitious as they come, Linda Hicke, whose experiment I detailed in my Nobel Lecture as one of the most memorable in my experience at Berkeley, Nina Salama, who completed the detection and purification of the COPII proteins, Sabeeha Merchant, who came for a brief sabbatical and has remained a best friend and confidant ever since, and Liz Miller, who solved the mystery of cargo selection by the COPII coat. Science will never be the same now that women have taken a proper role in creative scholarship.  It is hard to believe that nearly 40 years has elapsed since that first day when I walked into the Biochemistry building to begin my career at Berkeley. The memories of all those years could fill a book, but I must bring this biography to a close with an appreciation of all that my family, friends, students and colleagues have done to make this a “Wonderful Life”, as the director Frank Capra so movingly captured in the movie of that title. I am not a religious person but I feel that I have been blessed with opportunities and people who have enriched my life immeasurably. This essay is dedicated to those who have passed on and to the love of those who now sustain me. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0527=RS  [Adam Smith] Oh hello, may I speak with Randy Schekman please?  [Randy Schekman] Speaking.  [AS] Oh hello, this is Adam Smith from Nobel Media in Stockholm, we have this tradition of recording very short interviews with new Laureates, would you be willing to talk for a few minutes?  [RS] Of course.  [AS] Thank you very much indeed. Well, first of all congratulations on the award of course.  [RS] Thank you, thank you.  [AS] What were you doing when the call came?  [RS] Well, I was sleeping (laughs). It was a quarter after one in the morning here. And I just came back from Frankfurt yesterday, where I spent a week at a meeting, so I was quite exhausted. But of course I was aware of what happens in the morning. So as soon the phone started ringing, my wife yelled out, ‘there it is, there it is’ and I sized up things and picked up the phone and there was Göran Hansson. It was a thrill, a real thrill.  [AS] Lovely, what was your first action after the call?  [RS] After the call? Well, I danced around with my wife and repeatedly said ‘oh my god, oh my god’.  [AS] (Laughs)  [RS] Then I called my father, my 86-year old father, who had been hoping for this for many years. He was shaken but thrilled. I called my two children, Joel and Lauren, got them out of bed and they were excited.  [AS] That’s lovely, now they are celebrations all over the country.  [RS] Yeah.  [AS] People always joke that the award of a Nobel Prize always get’s you a parking space at Berkeley, do you think that will happen?  [RS] (Laughs) Right. That’s … In fact, when I was the Chairman of the biochemistry division, I negotiated with two young faculty, who were moving from MIT, and who were very concerned about their opportunity to have parking permits for themselves as Assistant Professors, and in the formal letter of offer I assured them that they not only could pay for parking but if they happened to win a Nobel Prize, they’d get their parking for free. And they claim that was part of the contract that really sealed the deal for them.  [AS] (Laughs) It’s an unusual incentive to work hard.  [RS] Yes it is.  [AS] So you are credited with doing the initial work that took our understanding of vesicle traffic from a purely descriptive to the beginning of a mechanistic understanding. And that understanding has taken a lot of time to achieve.  [RS] Yeah, yeah, yeah. So well, to begin with I want to credit [George Palade](https://www.nobelprize.org/prizes/medicine/1974/palade/facts/) who really pioneered the field of cell biology by developing the techniques of electron microscopy to visualise membranes within human cells, and it was his genius to realise, to appreciate how proteins that are going to be exported from cells are assembled, in a kind of assembly line process inside the cell. And when I began my laboratory in 1976, really around the same time when Jim Rothman began his laboratory at Stanford, we conceived of very different approaches to try to identify the machinery responsible for this mechanism. And I used the technique of classical yeast genetics, to make mutations in yeast cells, that define the pathway, and Rothman used a very complementary biochemical process to reconstitute the pathway *in vitro*. Over a period of years as we compared notes, sometimes collaboratively, sometimes competitively, it became clear that he and I were working many of the same proteins, many of the same genes and proteins. So that synthesis between the two sets really convinced us that we were on the right track, the project on, as I did.  [AS] Last question, how do you feel about the onslaught of press attention that’s about to arrive?  [RS] The onslaught of?  [AS] Of attention that’s about to … that will follow the announcement?  [RS] Yeah, well, I don’t what to expect. Of course around this time of the year I’m always reminded that this could happen. In fact, I just returned from Germany, where I got another award the [Otto Warburg](https://www.nobelprize.org/prizes/medicine/1931/warburg/facts/) Prize. The whole time people were saying, we’ll see what happens on Monday. So I guess I was sort of primed for this today, although I came back from Europe yesterday, so I’m pretty jetlagged.  [AS] Yes, but I imagine you’ll be living on the high of it for some time to come.  [RS] Oh yeah, I’ll stay awake today.  [AS] Ok, well I wish you a really splendid day and once again congratulations. Thank you for talking to us and I look forward to talking to you again soon.  [RS] Thank you, thank you.  [AS] Ok, bye bye.  [RS] Bye. |
| Interview |  |
| Q23 | Could you explain your Nobel Prize awarded work to young students? |
|  | My work involves studying how protein molecules, which are the machines that operate life, how some of them are shipped outside of a cell, Almost all the cells in our body produce most of the proteins that act inside the cell and do the chemistry of life, but about 10% of the proteins on average are special proteins that have to be incapsulated and then sent by export out of the cell and these are proteins that everyone knows about, insulin, growth factors , hormones, all of the proteins in your blood are actually manufactured inside of a cell and then have a special machinery for their export. This pathway was first understood by using the electron microscope to peer inside of a human pancreatic cell and the Nobel Prize in 1974 was given to a pioneer by name of [George Palade](https://www.nobelprize.org/prizes/medicine/1974/palade/facts/) who understood how the machinery inside of the cells conveyed molecules outside of the cell. What he didn’t understand, because of the technics available at the time, was how these machines operate.  When I started my career at Berkeley I chose to study baker’s yeast which is not a traditional system to evaluate protein secretion but they still, that’s how they grow and divide, they actually secret and assemble their membrane using this process and secretion. My first graduate student, one of my first students, Peter Novick and I developed a genetic approach that allowed us to isolate mutations that cripple this process and when we did so we were able to see that these cells use a process that’s essentially the same as human cells and as a result the biotechnology industry was able using yeast as a vehicle for the production of useful human proteins in fact. One third of the world supply of human insulin is made secretion and yeast so we what we did which was just very basic turned out to have quite practical application. |
| Q1 | What brought you to science? |
|  | My dad was an engineer so there was some interest in science. My own interest developed when I was very young. I had a toy microscope and I was fascinated with life forms that I could see in pond scum. I saved up my money and I brought a professional microscope when I was a young teenager and I have actually just today donated that microscope to the Nobel Museum. It’s really very important in my early development of an interest in microbiology and that just sort of naturally evolved and when I got to university I continued to study viruses and microorganisms and that interest has continued to this day. |
| Q19 | How did you learn that you had been awarded the Nobel Prize? |
|  | At 01.20 in the morning on October 7 I was fast asleep. The phone rang, I am not sure I heard it, my wife yelled out: “This is it!” so I stumbled out of bed, still half asleep, got to the phone and I think I was trembling at this point, but I am pretty sure I knew what it was, and I was greeted by a nice Swedish accent on the other side, Göran Hansson. At that point I think I said: “Oh my god” and then he assured me after congratulating me that it was not a hoax and then the fog lifted so I sort of decided how I had to proceed for the next hour or so before the press conference. The first person I called was my father, 86 years old, who has been hopeful for years about this, so he was ecstatic. I called my kids, I called my best friend and then I called the press officer at Berkeley because I was warned years ago that I had do this and as result there were two press officers in my home at 02.30 in the morning lining up the TV-camera crews and since then my life has not been the same. |
| Q5 | Who is your role model, and why? |
|  | I had many people who were inspiring models, two of them stand out though, one was my graduate adviser [Arthur Kornberg](https://www.nobelprize.org/prizes/medicine/1959/kornberg/facts/) who had the very highest standards in science and scholarship of anyone that I had ever met, really rigorous, very demanding, tough guy, but I learnt I great deal from him how to do science. And at a very different level, another great scientist, Daniel Koshland was the chairman of the biochemistry department at Berkeley when I was hired as a beginning faculty member. He had in additional to great scientific qualities a concern for science as a leader of scientists. He was chairman of the department, he was very collegial, concerned about promoting the university and promoting public higher education and I have taken his example in doing the many other things that I do. I value him as highly as I value what I learnt from Kornberg. He was the editor of the *Proceedings of the National Academy of Science*, then he became the editor of *Science* magazine and I followed in his footsteps. I was for five years the editor in chief of the *Proceedings of the National Academy*, but then more recently I have taken on a new role as an editor of a new online journal called *e-Life* which is journal sponsored by Howard Hughes Medical Institute, the Wellcome Trust and Max Planck Society. We feel very strongly that there’s a need for another journal at the very high end where the decisions are made by active scientists and where the limitations impose by the print model do not apply so we accept papers and publish full length papers and we don’t have artificial restrictions based on some feather fashion so this is a journal that I am promoting. Actually, from here in Stockholm I will be speaking to journalists about his. |
| Q16 | Have you ever had an eureka moment? |
|  | There is a eureka moment that happened early on in the work that Novick and I were doing. He isolated the first mutant and he could see, using simple assays, that the enzymes that normally are secreted outside of the yeast cell in this mutant now build up inside the cell. But the most dramatic moment came when he looked, using the electron microscope, at sections of this cell. He called excitedly up to my office from down in the basement where the electron microscope was and I went down and I had a look. It was revelation to see a cell that ordinarily has only a sort of sparse collection of organelles but which instead in this mutant had, it was just dying of overload of the vesicles that were being produced, but couldn’t be delivered to the cell surface and so the cell has just accumulated lots of vesicles. That image stands in my mind as really the beginning of my career and I knew from that moment that I would be consumed for at least the next 20 years trying to figure it all out, so that was really a lucky break. |
| Q7 | Do you know how you are going to spend your Nobel Prize money? |
|  | Unfortunately in my lifetime the funding of public higher education has gone down dramatically so for instance when I was a university student at UCLA I could work a summer job and pay fees and room and board and books for the rest of the year. My father had five kids and they all went to public institutions; he never had to pay anything. Now in US students have to assume the responsibility for their higher education themselves. They go into tremendous debt, there’s a trillion-dollar debt just owed to educational institutions in the US that just didn’t exist when I was growing up. I think this is a wholesale change in the political atmosphere that is I think really damaging, so I feel very strongly about this and as the result, the one action that I could do is that I donated my Nobel Prize money for the creation of an endowed chair at my institution so we can be as competitive as the private institutions and brining the best young scholars to Berkeley.  [Watch the interview](https://www.nobelprize.org/prizes/medicine/2013/schekman/interview/) |
| ID | 0528 |
| Biographical | **Upbringing** I was born in Göttingen on December 22, 1955. At that time, the aftermaths of the Second World War were still reverberating. Mine was an anthroposophical family; my maternal grandparents had been early followers of Rudolf Steiner’s teaching, and worked for Waldorf schools when Hitler assumed power and banned the anthrophosophical movement. Waldorf schools were forced to close, and my grandfather was conscripted to work in a chemical munitions factory – it was a miracle he survived the war. My uncle was drafted into the army out of school, and when I was born, he had just returned from the Soviet Union after 10 years as a prisoner of war. I was the second of four children. My parents were physicians, with my father pursuing a career in academic medicine, while my mother cared for our growing family. My father’s training led him to the United States during the time I was born; as a result, he learned of my arrival by telegram as he was learning biochemical methods in San Francisco, close to where – by a twist of fate – I now live.  I spent my childhood in Göttingen and Hannover, and graduated from the Hannover Waldorf School – resurrected after the war – in 1975. My strongest childhood memories were those of my maternal grandmother telling me stories about the time during the war, how she was reading Dostoyevski while trying to escape the bombs in underground shelters and hoping that my grandfather would survive. She imbued me with the importance of Goethe and detested Kant, whom I learned to love. I learned from my grandmother how important an intellectual life is under any circumstance, and that values are spiritual even if you are an atheist.  My father was a successful doctor who managed an entire hospital district and wrote countless books on general internal medicine; he worked very hard, and was continuously frustrated by what he felt were the inadequacies of the medical care system and the academic world. However, when I was in high school, my father died of a heart attack, brought about by inattention to his health, and my mother had to cope with life alone with four children – a difficult and sad but an also partially liberating experience for her, as she explained to me later. Her strength was an example to me, her ability to accept what happened without giving up, and to concentrate on what was important to her.  I had been interested in many different subjects in high school, in fact all subjects except for sports which I found primitive – now ironic to me as I have become addicted to regular exercise. Early on, I became fascinated by classical music. After unsuccessful attempts at playing the violin, I gave this instrument up to the delight of everyone around me who had to listen to me trying. However, I then decided to learn to play bassoon, which I pursued with a vengeance, motivated by a wonderful teacher (Herbert Tauscher) who was the solo-bassoonist at the local opera house, and who probably taught me more about life than most of my other teachers. I credit my musical education with my dual appreciation for discipline and hard work on the one hand, and for creativity on the other. I think trying to be marginally successful in learning how to be a musician taught me how to be a scientist: there is no creativity if one does not master the subject and pay exquisite attention to the details, but there is also no creativity if one cannot transcend the details and the common interpretation of such details, and use one’s mastery of the subject like an instrument to develop new ideas.  I did not know what to do with my life after school, except that I was determined not to serve in the military. More by default than by vocation, I decided to enter medical school, which kept all avenues open for a possible career in science or as a practitioner of something useful – as a physician – and allowed me to defer my military service. I thought that music, philosophy, or history were more interesting subjects than medicine, but I did not feel confident that I had sufficient talent to succeed in these difficult areas, whereas I thought that almost anybody can become a reasonably good medical doctor. **First Experiments** I studied first in Aachen, the beautiful former capital of Charles the Great, and then transferred to Göttingen, the former scientific center of the Weimar republic, in order to have better access to laboratory training since I became more and more interested in science.  Soon after arriving in Göttingen, I decided to join the Dept. of Neurochemistry of Prof. Victor P. Whittaker at the Max-Planck-Institut für biophysikalische Chemie as a ‘Hilfswissenschaftler’ (literally an ‘assisting scientist’, but more accurately a kind of ‘sub-scientist’). I was attracted to Whittaker’s department because it focused on biochemical approaches to probe the function of the brain, following up on Whittaker’s development of purification methods for synaptosomes and synaptic vesicles in the two preceding decades. Moreover, when I entered his lab, Whittaker had become increasingly interested in the cell biology of synaptic vesicle exo- and endocytosis, which I thought were fascinating. However, I never got a chance to work on the brain or synaptic vesicles when I was in Whittaker’s lab. As a lowly ‘Hilfswissenschaftler’, I was assigned to the task of examining the biophysical structure of chromaffin granules, which are the secretory vesicles of the adrenal medulla that store catecholamines. Although my project developed well, I started exploring other questions in parallel as I became more and more familiar with doing experiments, while simultaneously studying medicine at the university. A helpful factor was that my supposed supervisor, a senior US scientist who worked with Whittaker, departed soon after I started in Whittaker’s lab, leaving me completely alone in my experiments since Whittaker was not really interested in that work. I am infinitely grateful to Victor Whittaker for giving me complete freedom in his department in pursuing whatever I thought was interesting. I continued working in his department after my graduation from medical school in 1982 until I moved to the US a year later in 1983.  Among the work I performed during my time in Whittaker’s department in Göttingen, the most significant is probably the isolation and characterization of a new family of calcium-binding proteins that we called ‘calelectrins’ because we had initially purified them from the electric organ of Torpedo marmorata, although we also identified them in bovine liver and brain. ‘Calelectrins’ were among the first identified members of an enigmatic and evolutionarily ancient family of calcium-binding proteins now called annexins. Annexins were at the same time discovered in several other laboratories, and I am proud of the fact that we contributed to the first description of this intriguing protein family, although to this date their function remains unknown. **Postdoctoral Training** After finishing medical school, I decided to become an academic physician, along the mold of my deceased father. Although my time in Whittaker’s laboratory had taught me to love doing science, I wanted to do something more practical, exciting, and immediately useful than what I had seen in the Max-Planck-Institut in Göttingen. The standard career for an academic physician in Germany was to go abroad for a couple of years to acquire more clinically oriented scientific training before starting her/his clinical specialty training. Upon surveying the scientific landscape, I decided to join the laboratory of [Mike Brown](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/brown-facts.html) and [Joe Goldstein](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/goldstein-facts.html) at the University of Texas Southwestern Medical School in Dallas for postdoctoral training. Brown and Goldstein were already famous for their brilliant cell-biological studies when I made this decision. They were equally renowned for using cutting-edge scientific tools to address a central question in medicine, namely how cholesterol in blood is regulated. When I announced my decision to go to Dallas instead of the more conventional Boston or San Francisco, my friends and family were disappointed, but it was the best professional decision I ever made.  While in Joe Goldstein’s and Mike Brown’s laboratory, I cloned the gene encoding the LDL receptor, which taught me molecular biology, revealed to me the beauty of sequences and protein organizations, and opened up genetic analyses of this gene in human patients suffering from atherosclerosis. I also became interested in how expression of the LDL receptor is regulated by cholesterol, and identified a sequence element in the LDL receptor gene called ‘SRE’ for sterol-regulatory element that mediates the regulation of the LDL receptor expression by cholesterol. During my time in their laboratory, Joe Goldstein and Mike Brown were awarded the Nobel Prize (in 1985), which I still consider one of the best Nobel Prizes given. After I left, discovery of the SRE led to the identification of the SRE-binding protein in Brown and Goldstein’s laboratory, which in turn identified new mechanisms of transcriptional regulation effected by intramembrane proteolysis.  The contrast between Göttingen and Dallas could not have been bigger. When I arrived in Dallas, Texas was not yet the extremely conservative bastion of religious fundamentalism that it is now, but a vast state with an optimistic ‘can-do’ culture that was very different from the culture to which I had been exposed in Göttingen. The difference in scientific environment was even more extreme. In Dallas, scientific life was teeming with enthusiasm and energy, work was a pleasure, and excitement was pulsating through every experiment because the importance of the goals was self-evident. In Göttingen, as I realized when I was in Dallas, although the approach was very scholarly in the sense of pursuing knowledge, much of that pursuit was without regard to the importance of the subject. As a result, people often asked uninteresting questions, and possibly even wasted their time. To this date, I find it one of the hardest challenges in science to achieve the right balance between trusting my own judgment and listening to others. If I only rely on my own judgment, there is no corrective for mistakes, no adjustment of unreasonable impressions. However, if I listen only to the ‘world’, I will only follow fashions, will always be behind, and often will be just as wrong. Among the many things I credit Brown and Goldstein with for teaching me, the realization of this challenge and their example of how to deal with this challenge is among the most important. This challenge resembles that of composing music in which pure harmony is boring and meaningless, but pure dissonance is unbearable, and it is really the back and forth between these extremes that creates meaning. **Early Years of the Südhof Lab** In 1986, at the end of my postdoctoral training, I faced the choice of resuming my clinical training, or of establishing my own laboratory. Probably the best advice Brown and Goldstein gave me was now: they suggested I forego further clinical training and do ‘only’ science, and they backed up this advice by providing me with the opportunity to start my own laboratory at Dallas. This I did, and ended up staying for another 22 years, interrupted only by a short guest appearance as a Max-Planck Director in Göttingen (see below).  When I started my laboratory at Dallas in 1986, I decided to attack a question that was raised by Whittaker’s work, but neglected since: what are synaptic vesicles composed of, and how do they undergo exo- and endocytosis, i.e., what is the mechanism of neurotransmitter release that underlies all synaptic transmission? We had learned from Whittaker’s work that synaptic vesicles could be biochemically purified, but nothing was known about the molecular mechanisms guiding synaptic vesicle exo- and endocytosis. Our initial approach, performed in close collaboration with Reinhard Jahn, whose laboratory at that time had just been set up in Munich, was simple: We set out to purify and clone every protein that might conceivably be involved, and worry about their functions later. This approach was initially criticized for being too descriptive, but turned out to be more fruitful than I could have hoped for, and has arguably led to a plausible understanding of neurotransmitter release.  In the nearly three decades since I started my laboratory, our work, together with that of others, led to the identification of the key proteins that are involved in synaptic vesicle exocytosis. In particular, this work shed light on the molecular mechanisms underlying membrane fusion during synaptic vesicle exocytosis, explained how calcium signals control these mechanisms, and described the molecular organization of the presynaptic terminal that allows fast coupling of an action potential and the ensuing calcium influx to neurotransmitter release. Some of the proteins whose function we identified are now scientific household names and have general roles in eukaryotic membrane fusion that go beyond a synaptic function, while other proteins are specific to synapses and in part account for the exquisite precision and plasticity of synapses as elementary computational elements in brain. I feel fortunate to have stumbled onto this overarching neuroscience question at a time when it was ready to be addressed, and it has been tremendous fun to work our way through the various synaptic proteins and their properties that shape the functions of these proteins.  It is important to note, however, that the nature of our studies was not revolutionary. In my career, no single major discovery changed the field all at once. Instead, our work progressed in incremental steps over two decades. I think this is a general property of scientific progress in understanding how something works – a single experiment rarely explains a major question, but usually a body of work is required. In contrast, scientific progress in developing tools normally advances in spurts, and often a single flash of genius creates a completely new method (e.g., see monoclonal antibodies, patch clamping, PCR, or shRNAs, to name a few).  The closest our work came to inducing a radical change in the field was probably the identification of synaptotagmins as calcium-sensors for fusion, and of Sec1/Munc18-like proteins (SM-proteins) as membrane fusion proteins, but both hypotheses took decades to develop and to become accepted by the field – in fact, the SM-protein hypothesis was only recently adopted by others, 20 years after we proposed it, and is still in flux. Thus, our work in parallel with that of others (Reinhard Jahn, James Rothman, Jose Rizo, Randy Schekman, Richard Scheller, Cesare Montecucco, and Axel Brunger come to mind) produced a steady incremental advance that resulted a better understanding of how membranes fuse, one step at a time. As a result of this combined effort, we now know that SNAREs are the fusion catalysts at the synapse, first shown when SNAREs were shown to be the substrates of clostridial neurotoxins, that SM-proteins in general and Munc18-1 in particular are essential contributors to all membrane fusion events, that a synaptotagmin-based mechanism assisted by complexin underlies nearly all regulated exocytosis, and that synaptic exocytosis is organized in time and space by an active zone protein scaffold containing RIM and Munc13 proteins as central elements.  The work in my lab would have been impossible without the contributions of many brilliant postdoctoral fellows who have now gone on to successful careers on their own. Ever since I started my laboratory, I have found the pleasure of working with others the best part of my life. The continuing friendship of my former trainees has been one of the major satisfactions of my career. Among these were Mark Perin with whom I cloned synaptotagmin, Yutaka Hata who discovered Munc18, Martin Geppert who performed the initial mouse genetics experiments in my lab, Nils Brose who identified Munc13, Harvey McMahon who identified complexins, Yun Wang who isolated RIM, and many others who made essential contributions. Complementing these great co-workers, I had the best collaborators I could possibly wish for. Besides Reinhard Jahn (who had moved to Yale after Munich, and then on to Göttingen), the most important of these collaborators were Jose Rizo in Dallas with whom we worked out the atomic structures of many of the proteins we studied, Bob Hammer in Dallas who helped us with the mouse genetics, and Chuck Stevens at the Salk Institute who introduced us to the beauty of electrophysiological analyses. **My German Intermezzo** Ten years after I started my laboratory, while the work described above was progressing, I was offered the opportunity to return to Germany and to organize a Department of Neuroscience at the Max-Planck-Institut für experimentelle Medizin in Göttingen, my home town. I enthusiastically took on the challenge, planned and oversaw the building of a new animal facility, hired scientists, and organized the renovations and equipment of a suite of laboratories. However, after a few years the leadership of the Max-Planck-Society changed. It soon became clear that the Max-Planck-Society’s new president, Prof. Hubert Markl, developed doubts about my recruitment, and wanted to rebuild the institute that I was recruited into in directions that were quite different from what I had been promised. In a personal discussion, Prof. Markl suggested I resign my position at the Max-Planck-Institut and look for a future in the U.S., which I did.  I have never regretted my work for the Max-Planck-Institut in Göttingen, which laid the foundation for much of what happened there subsequently, including the subsequent recruitment of one of my postdoctoral fellows (Nils Brose) as a new director who has done a much better job than I could have done. However, I have also never regretted following Prof. Markl’s suggestion and returning to the U.S., where the breadth and tolerance of the system allowed me to operate in a manner that was more suitable for my somewhat iconoclastic temperament. Overall, my work as a director at the Max-Planck-Institut in Göttingen was a very positive experience that shaped my thinking when I subsequently had the opportunity to help build the Department of Neuroscience at the University of Texas Southwestern Medical Center in Dallas. **Maturity** Soon after I returned full-time to UT Southwestern at Dallas in 1998, I accepted the position of director of the Center for Basic Neuroscience, which was later transformed into the Department of Neuroscience. Building a Center and Department of Neuroscience partly occupied the following ten years, and was a lot of fun. Southwestern had a free-flowing and unbureaucratic environment that was extremely supportive. It was a pleasure to hire young people and see them develop, and I greatly appreciated the support of my colleagues in every respect.  Scientifically the 10 years between 1998 and 2008 were even more important. The flurry of discoveries of the 1990s created the impression that everything was already solved in membrane fusion and neurotransmitter release, but nothing could have been farther from the truth. I decided to continue to work on these questions, and believe that some of the most important observations in the field came out of our work during that time period.  For example, it was well established in 2000 that SNAREs ‘do’ fusion and that they ‘do so’ by pulling membranes together, but it was unknown whether SNAREs were just nanomachines that acted as force-generators in approximating membranes, or whether they actually catalyze the fusion process, possibly by their transmembrane regions. Similarly, although we found that the SM-protein Munc18-1 was absolutely essential for fusion, Munc 18-1 appeared to bind to a form of the SNARE protein syntaxin-1 that was ‘closed’ and was thought to block fusion, whereas the yeast homolog Sec1p, as shown in elegant work by Peter Novick, bound to assembled SNARE complexes. How could the same protein be essential for fusion and inhibit SNARE-complex formation? Comparably puzzling questions surrounded the role of synaptotagmin as a calcium sensor in neurotransmitter release. Furthermore, a major question in understanding synapses had never been addressed, namely how the presynaptic machinery is organized in a manner that allows tight coupling of calcium-influx to the calcium-triggering of release. The significance of this latter question is often underestimated outside of the esoteric realm of neurophysiologists, but this tight coupling is the most important prerequisite for the speed and brevity of neurotransmitter release – in essence this coupling is what makes a synapse precise.  In the years after 1998, my lab and the labs of others, foremost those of my former postdoctoral fellows Nils Brose, Harvey McMahon, and Matthijs Verhage, of Christian Rosenmund, of Peter Novick, and of Jim Rothman, established several key points that address these questions. The most important was the demonstration that synaptotagmin is truly the calcium-sensor for release by showing that point mutations in synaptotagmin that change its calcium-affinity change release accordingly. Maybe equally important was the finding that Munc18 acts by binding to SNARE complexes after assembly, not by binding to one SNARE protein before assembly. Other significant findings of these years included the demonstration of the priming function of Munc13, the discovery that complexin acts as a ‘sidekick’ to support synaptotagmin function and that both synaptotagmin and complexin clamp minis in addition to the major action as activators of release, and that multiple synaptotagmins generally function as calcium-sensors in release. Moreover, in these years we identified specific chaperones that support the proper folding of SNAREs, opening up a new perspective on how SNARE function is maintained in neurons, an important issue because the loss of these chaperone activities were found to cause neurodegeneration. These were very productive years that did more than complete the stories we had begun in the 90s – they extended these stories into new directions, including an explanation of at least some forms of neurodegeneration. The one major issue that remained unresolved was how calcium-channels are recruited to the active zone, a question that was really only resolved after I moved to Stanford in 2008. **New and Old Directions** The currently final chapter in my career began when I moved my laboratory from UT Southwestern to Stanford University in 2008. After 10 years as a chair of a Neuroscience Center and then Department in Dallas, I felt that I wanted to devote more of my time to pure science, and to embark on a new professional direction, with an environment that was focused on academics. Moreover, I decided to redirect a large part of my efforts towards a major problem in neuroscience that appeared to be unexplored: how synapses are formed. Thus, in this currently last chapter of my work, I am probing the mechanisms that allow circuits to form in brain, and to form with often nearly magical properties dictated by the specific features of particular synapses at highly specific positions. I am fascinated by the complexity of this process, which far surpasses the numerical size of the genome, and interested in how disturbances in this process contribute to neuropsychiatric diseases such as autism and schizophrenia. This is what I would like to address in the next few years, hoping for at least some interesting insights.  As early as 1992, my laboratory had identified a family of cell-surface proteins called neurexins whose properties suggested that they may be involved in synapse formation. Neurexins were discovered because they are presynaptic receptors for the black widow spider venom component *α*-latrotoxin which paralyses small prey by causing excessive neurotransmitter release. However, the importance of neurexins and their ligands – such as the neuroligins, cerebellins, and neurexophilins which we and others identified – only became apparent in recent years when we started to analyze mouse mutants of these proteins.  Apart from these new directions, at Stanford we followed up on two ‘old’ questions about release: how calcium-channels are recruited to active zones, and what mediates the calcium-triggered release that remains in synapses which lack fast synaptotagmin calcium-sensor isoforms. Both questions had haunted me for decades – I was convinced of their importance but could not solve them. Only in the last few years did we develop answers to these questions in identifying the scaffolding proteins RIMs and RIM-BPs as the organizers of calcium-channels in the presynaptic active zone, and another synaptotagmin isoform (synaptotagmin-7) as a calcium-sensor for the remaining release in synaptotag-min-1 deficient forebrain neurons. Fittingly, this last observation was submitted a few weeks before the announcement of the Nobel Prize, and published coincidently with the award ceremony! **Life Lessons** After nearly 60 years of life and nearly 40 years as a scientist, I would like to draw the following personal conclusions, none of them very original. First, being a scientist, although socially a privilege and luxury, is not socially rewarding – for personal happiness, this profession is only worth it if a person obtains individual satisfaction in doing science. A scientist has to have the attitude of an adherent to Philip Spener’s pietism in Lutheran Germany in the 18th century – what counts are not outward successes, money, and social decorations, but the conviction of truth obtained from personal inspection of the evidence. After a glorious period of ascendance in Western Europe from Bacon’s England over Courvoisier’s France to Boltzmann’s Germany, the scientific method is now increasingly being challenged based on ideological grounds. In the most powerful country of the world, the United States, the majority of the governing elite at present feels free to dismiss some established scientific facts as fantasy, even suspecting evolution or climate science as communist conspiracies at a time when there is no communism left anywhere. At this stage – different from previous centuries – the only reason to pursue a career in science is an enormous curiosity to know what is really true.  Second, I at least have learned most from personal contacts, not from reading the literature or listening to talks. Although reading books or papers provided me with an indispensable background of facts, I learned how to think, how to assess a subject, and how to value a perspective from insightful comments of others. Thus, for a scientific career the most important elements are good teachers and mentors, and a great environment – not only during early years as student and postdoc, but throughout the entire career of a scientist. Now at an arguably rather advanced stage of my career, I need mentors and teachers more than ever – I need people who know better than I to tell me when I am wrong, and to make me aware of my mistakes! As an immediate consequence of this realization, I would advise everybody to make career choices primarily based on the people involved, not on the geographic location of a place or the fashionableness of the subject or the techniques. I believe this is true for all stages of a career.  Third, once a scientist has the opportunity to choose what to work on (increasingly a rarity in our world where political prescriptions of what scientists are supposed to discover are becoming more and more prevalent), he/she should make sure that whatever the choice of subject is, it is both important and tractable. I am personally often amazed about the choice of subject by some of my colleagues, possibly because I simply fail to recognize the importance of the subject. However, if one looks at the history of science over the last 50 years or so, I think one can argue that some approaches and goals have proved to be highly productive whereas others have not. For example, investments into bacterial and bacteriophage genetics early on eventually led to the golden age of molecular biology that all of science, but particularly cellular neuroscience, has benefitted from, whereas the parallel large investments into systems neuroscience has only recently started to bear some fruit after the tools developed by molecular and cellular neurobiology were beginning to be applied.  Finally, quantity doesn’t matter very much, nor does the place one publishes – in the end what counts is discovery which is often not immediately apparent. Most articles in “high-impact journals,” although highly cited initially, are soon forgotten. Especially in our time, when it is basically the editor of a journal and not the reviewers who decides what gets published – an editor who often has limited knowledge of the subject but knows what is ‘exciting’ – the major journals publish many papers that are composed of true data with contrived interpretations and very little long-term import. As scientists, we have to intellectually dissociate ourselves from fashion and journals, and focus on what is the actual content of a study, what the data really say (not what the abstract says!). We can then take pride and pleasure in work that reports an actual advance – I feel that this is the most important ability I tried to learn from my mentors, and I am trying to teach my students. **Thank You** Throughout my career, I have been generously supported by the Howard Hughes Medical Institute and the National Institute of Mental Health. I am grateful to both for their unflinching support. I have received several recognitions, all of them unexpected, among which I particularly cherish the Alden Spencer Award from Columbia University in 1993, the von Euler Lectureship from the Karolinska Institutet in 2004, the Kavli Award in 2010, the Lasker~deBakey Award in 2013, and – of course – the Nobel Prize. I am not sure I deserve any of these awards, as conceptual advances in science always represent incremental progress to which many minds contribute, but I immensely appreciate receiving them. Finally, I feel indebted beyond words to my family, my wife Lu Chen and my children Saskia, Alexander, Leanna, Sören, Roland, and Moritz, without whom I would be barren and rudderless, and who have been more considerate of me than I deserve, and finally to my ex-wife Annette Südhof who greatly supported me in earlier stages of my life, and to my brothers Markus and Donat Südhof and my sister Gudrun Südhof-Müller whom I appreciate more the older I get. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0528=TCS  [TCS] Hello.  [AS] Hello Professor Südhof?  [TCS] Yes.  [AS] This is Adam Smith calling from the Nobel Prize website in Stockholm, where it has just been announced that you have been awarded the Nobel Prize, together with Jim Rothman and Randy Schekman.  [TCS] Are you serious?  [AS] I am serious, yes, my name is Adam Smith and I work for Nobel Media, which is the media company of the Nobel Foundation, and the announcement has just been made, just a very few minutes ago, here in Stockholm.  [TCS] Oh my god (laughs).  [AS] I just had the pleasure of speaking to your wife in California who I’m afraid I probably woke up, and she very kindly gave me your phone number.  [TCS] Oh (laughs), oh poor Lu (laughs).  [AS] She seemed …  [TCS] Let me just stop for a moment here because I’m driving in the middle of Spain somewhere.  [AS] (laughs)  [TCS] I was actually thinking that my friend was calling me, because I’m a little lost. Em. Okay. Em. I’m sorry (laughs). It’s a little unexpected.  [AS] (laughs) Well your wife seemed very happy to be woken up with the news and …  [TCS] (laughs) It is quite an amazing … gosh  [AS] It’s a time of awards. I mean, just a couple of weeks ago you were in New York receiving the Lasker Award  [TCS] Yes, yeah but you know … I mean there has been a lot of speculation about this, but I never thought I would be … I would get it, but anyway  [AS] (laughs)  [TCS] (laughs)  [AS] And I imagine it’s also very nice to be awarded together with James Rothman and Randy Schekman  [TCS] Oh it’s wonderful; it’s wonderful, I am actually extremely happy about that, because I think that that’s incredibly fair, and you know, everybody has their own view of who deserves what and one tends to overestimate oneself but I think that, I mean, its more than fair.  [AS] You’re renowned for your productivity. What gives you the drive to work so hard?  [TCS] (laughs) My wife thinks I’m crazy, I don’t know. I am incredibly driven. I didn’t think I was when I was young, I thought I was normal, but as I got older and I see the other people around me, and I feel sometimes that I just … that’s the way I am. And … I still have to digest this, I’m sorry.  [AS] Of course, of course. And I guess now you have a choice, because you’re on your own in a car in the middle of Spain somewhere. You have the possibility of running off and being on your own, or facing everybody who wants to talk to you (laughs).  [TCS] Well, I’m supposed to give a talk this afternoon, so that will be quite interesting (laughs).  [AS] (laughs) Yes. Lucky institute that has you for the afternoon.  [TCS] And its … I cannot tell you how much I enjoy what I do, so I will always consider it an enormous privilege to be a scientist, and … of course, this honour is very … incredibly beautiful. (laughs)  [AS] So, my …  [TCS] Thank you very much.  [AS] My very sincere congratulations, thank you. Bye bye.  [TCS] Thank you very much, okay.  [AS] Pleasure. Bye bye |
| Interview |  |
| Q23 | Could you explain your Nobel Prize awarded work to young students? |
|  | To actually explain that one has to sort of introduce the subject in little broader terms. A person, I think most people would agree, is a person because of in the end of a person’s brain, which is where people think, plan and where all perceptions are collected and processed. I am a neuroscientist, I work on how the brain works which is an unbelievable big challenge because it’s a really quite amazing organ. In principle how the brain works is easy enough to explain. Billions and billions of nerve cells that constantly talk to each other and by talking to each other process information and at some point, come to some decision of doing something. What we have been doing over decades now, ever since I started in science, trying to understand how nerve cells in the brain communicate with each other so our contribution to science in a broad sense was to shed light on how a nerve cell speaks to another nerve cell and the way a nerve cell does that is via the specialized connection that is formed between these cells and the brain and that connection is called a synapse. And a synapse transfers information and processes information from one nerve cell to the next. It is a specialized junction between nerve cells that is not only there to relay information but also to change information, its own little nano computer. if you want to call it that. What we have done is to try to understand better how one cell sends out the information to the next cell at the synapse and ideally how also it processes that information and our major contributions I believe was in figuring out the basic fundamental molecular processes that govern this ability of a nerve cell in all brains, in all cells and in all animals. |
| Q23 | So basically, the communication is in the brain? |
|  | Fundamentally our work deals with trying to understand how brain cells communicate, yes. How exactly, what is the molecular basis, what are the genes, how do they work? What is the atomic structure? How are they regulated? How does their activity effect the overall brain? And how does that change in disease? |
| Q19 | What were you doing when you got the message of being awarded the Nobel Prize? |
|  | The question of what I was doing when I got the Nobel Prize call, a question that has been asked a thousand times. I think many people have listen to the call that was recorded and which I didn’t know and put on the website and I was driving in the middle of Spain trying to find a small city where I was supposed to go for a conference. Most people who live in the United States, if they have the fortune or luck or both to get such a call, most people are sleeping except if they expect it, and the usual procedure is as I understand, that you first get the call and then you are called and the recording is only done for the time you are called again, so most people are prepared. They know what they are going to do and my co-laureates already had showered when they got the call, so the situation was a little different for me because the first call never reached me. Adam Smith, who is part of Nobel Media I understand, was actually the one who called me and my first thought was quite honestly skeptic, skepticism, I was skeptic about the call, I felt that there was something not quite … It didn’t sound right that somebody with high-English accent would call you about that, so I was a little cautious, I was also a little sleepy because I hadn’t slept the night before of course, I was flying. I had to gather my wits and try to figure out whether that was actually a truthful call or a prank call. |
| Q16 | At what point did you realize your work was a breakthrough? |
|  | The question of sort of a major discovery point or single event is often asked. Most Nobel Prizes are given, I believe, for technical advances or because such moments are identifiable in the discovery of techniques, monoclonal antibodies, patch clamping and so on. Much fewer Nobel Prizes are actually given for discoveries of how something works, which is because, in my personal view, most discoveries of how something works are not discoveries that can be incapsulated in a single moment. The discoveries that require an incremental advance over many different experiments. If you want to understand the process, you can’t understand it in a single experiment. You have to approach it from many different angles. In my personal case the work that we performed that I think led to this prize was actually work that initiated 25 years ago and there were a lot of important observations, but in the end the promise of these observations only materialized or became more concrete very recently because continuing experiments in our lab backed them up, expanded them, explained them and gave them substance. I actually don’t think that there was any single eureka moment in my career, there were many small eureka moments, but not just one discovery, it’s in fact the whole question I am working on and I think that our work has contributed to understanding a process that involves or necessitates, more than understanding one little thing or one big thing, but understanding really how it works. |
| Q5 | Who is your role model, and why? |
|  | There is many people who have inspired me during my career. When I grew up I was probably most inspired by some of the teachers who I most admired, like music teachers for example, not science teachers I am afraid. I greatly admire and was tremendously influenced as a role model if you like by my mentors [Joe Goldstein](https://www.nobelprize.org/prizes/medicine/1985/goldstein/facts/) and [Mike Brown](https://www.nobelprize.org/prizes/medicine/1985/brown/facts/) who were my mentors in my post-doctoral training and who are Nobel Laureates. I think I have always admired people who have had the ability yo actually make discoveries that allow us to understand something and not only to discover a new approach and a new technique and I see this with Brown and Goldstein. I can also see that for example in the work that [Bert Sakmann](https://www.nobelprize.org/prizes/medicine/1991/sakmann/facts/) did after he won the Nobel Prize, which he won as you probably know for patch clamping, but afterwards he became a true, well actually he developed neuroscience in a way that I found very inspiring and so those are people I could mention here. |
| Q7 | Is there anything else you would like to share with us? |
|  | The one thing that I always feel I would like to always express is that what I appreciated about the Nobel Prize in particular and what I think is absolutely essential for science, not only science, but for our societies and maybe even for civilization in a broad sense is that science operates purely or should operate purely by the idea of figuring out what the truth is about real things, but it is done by humans and humans are by their very nature never always truthful. I really appreciate about the Nobel Prize that historically it is has always been unbelievably well done, in the sense that the selection was … I can’t say this about my own case, but about previous cases were really based on scholarship and I think that is an enormous achievement. I think that that’s really what constitutes the value of the prize and I can only really congratulate the Nobel, I don’t know actually who does this, but I can only congratulate them on doing such a wonderful job. |
| ID | 0529 |
| Biographical | **Family Background** John Bertrand Gurdon (JBG), born 2 October 1933, was brought up in a comfortable home by his parents (fig.1) on the Surrey/Hampshire border in a village, Frensham in South England, endowed with a large amount of National Trust heathland and ponds. His mother, Marjorie Byass, was from an East Yorkshire farming family. Brought up on a farm, and educated in that region, she became a physical training teacher working for some time in an American private school. When her son and daughter (Caroline, who trained as a nurse) had been raised, she gave much time to the regional administration of the “Women’s Institute,” a voluntary organisation for educating women.  His father, William Gurdon, was from a longstanding Suffolk family whose ancestors go back to 1199 (fig. 2; Muskett, 1900; Cunnington, 2008); with the family motto “*virtus viget in arduis*” [virtue flourishes in adversity].  Many of them had distinguished careers in government and as regional administrators, including Sir Adam Gurdon [Muskett, 1900]. JBG’s ancestors lived in a stately home, Assington Hall, in West Suffolk (fig. 3).  His grandfather had to leave the family home through lack of money to maintain it, due to repeal of the Corn Laws (1846) so that tenant farmers could no longer pay their rent, because of foreign imports. Assington Hall was requisitioned by the army during World War II, and was burnt down in a supposedly accidental fire in 1957. The remaining part of the house was partly restored and part of the original home, including its minarets, is still present in Assington. One of JBG’s ancestors married again after his first wife died and the outcome of a second marriage yielded a distinguished lawyer who accepted the hereditary title of Baron Cranworth. JBG’s father left school at the age of 16 and took a position in a rice broking firm in Burma. He was an early volunteer in the First World War and was decorated with the Distinguished Conduct Medal (DCM) before being commissioned to an officer rank. After that he led a career in banking in Assam and East India. He retired, in his forties, and in retirement, he gave much time to the transcribing of professional textbooks (especially legal) into Braille for the blind as voluntary work.  World War II started in 1939 when JBG was aged six. It was a time of austerity. Limited rations of food were managed by his mother, and the garden was used to raise chickens. He did not see luxuries like a banana or an orange until well after the end of the war. At the age of eight he was sent to a local private school, Frensham Heights. In an intelligence test at that age, he was asked to draw an orange. He started drawing the stalk by which the orange would hang from a tree, reasoning that an orange would not exist in space. The teacher tore up the piece of paper and reported to his parents that he was mentally subnormal and would need special teaching. The teacher meant to say, draw a circle. He was moved to another private school in the village, namely Edgeborough, where he thrived. At that age he had an intense interest in plants and insects. In most of his spare time he collected butterflies and moths and raised their caterpillars. **Education** At the age of 13, he started school at Eton as a boarder. He found life there intensely uncomfortable, because senior boys acted as despots, administering punishments for trivial misdemeanours. As a means of survival, he took up squash, and as a result of hard work rather than ability, he became eventually the school captain in this sport. While at school he continued his interest in Lepidoptera, raising large numbers of moths from their larval stage.  It was during his first term of being taught Science at the school, at the age of 15, that he received a totally damning report from the Biology master (fig. 4). This report resulted from JBG being placed in the bottom position of the lowest form in a group of 250 students of the same age. The report, sent to his housemaster, resulted in him being taken off any further study of Science of any kind at the school. For the rest of his school days, for the next three years, he was given no Science teaching and was placed in a class which studied Ancient Greek, Latin and a modern language, a course intended for those judged to be unsuited for studying any subject in depth.  Entrance to University was a problem: having sat the Entrance examination in Latin and Greek, the Admissions tutor at Christ Church Oxford University told JBG that he would be accepted for Entrance on condition that he did not plan to study the subject in which he took the Entrance (Classics). Later the Admissions tutor admitted that he had under-filled the college and had his mind on other things; he was Hugh Trevor-Roper, later Lord Dacre, and author of *The Last Days of Hitler*. In due course it emerged that JBG’s acceptance for Christ Church involved a complicated arrangement between JBG’s uncle, at that time a Fellow of Christ Church, JBG’s school housemaster and a friend of his uncle, Sir John Masterman, who was Master of Worcester College, Oxford and in charge of the wartime Enigma operation at Bletchley, agreeing to accept the housemaster’s son. Such a manoeuvre, and admission to Oxford on those terms, could never happen now. At that time, 1952, it was not very easy to fill a college with paying students. Before entering University, JBG had to take a year off to learn elementary Biology with a private tutor, generously funded by his parents who had already paid several years of Eton fees. He was told that he could formally enter the Department of Zoology course at Oxford if he passed the elementary exams in Physics, Chemistry and Biology in a preliminary year. He survived this and started the course in Zoology at Oxford in 1953. The course was extremely oldfashioned, by today’s standards. A major part of the teaching involved learning Palaeontology, and the names of skeletal parts of dinosaurs. JBG later became a personal friend of Sir Alister Hardy, the Head of that department, through his Oxford aunt (see later). **Graduate Student Work** As the Zoology course came to an end, JBG enquired about the possibility of doing a PhD in Entomology, in accord with his continuing interest in insects. While still a student, he had got permission to go to Oxford University’s nature reserve, namely Wytham Woods, with his butterfly net. No butterflies were to be seen, but he caught the only moving thing, which was a kind of fly. He used the taxonomic reference works to try to identify this “fly.” Having realised that the fly was a Hymenopteron, he was still unable to identify it. He therefore went to the Natural History Museum in London for help. They pronounced that it was in fact a species of sawfly new to Britain. This must have been intensely irritating to the Professor of Entomology, whose main research project was to identify animals and plants in Wytham Woods. JBG was later rejected for PhD work in Entomology. This was a great blessing because the work he would have done in Entomology was not well regarded and had very little, if any, analytical component to it. By his immense good fortune, he was invited to do a PhD with the Oxford University lecturer who taught Developmental Biology, Dr Michael Fischberg.  Fischberg was born in St Petersburg, Russia, in 1919. He was educated in Switzerland and was a PhD student of E. Hadorn. Hadorn in turn was a student of F. Baltzer, who was a student of H. Spemann, himself a student of T. Boveri. This German-Swiss lineage of eminent Developmental Biologists turns out to be the background of a great many of the successful Developmental Biologists of the mid-1950s. Most of those that did not have this background can trace their own training back to R. G. Harrison (1870–1959) of the USA, who pioneered cell culture. Having finished his PhD with Hadorn, Fischberg took a position in the Institute of Animal Genetics under Waddington in Edinburgh, from where he accepted his appointment in the Oxford Zoology department, headed by Professor Sir Alister Hardy, an eminent marine biologist [Royal Society memoirs].  Starting his PhD work in 1956, Fischberg suggested to JBG that he should try to carry out somatic cell nuclear transfer in *Xenopus*, a procedure for this having been recently published by Briggs and King (1952). The advisability and technical problems that arose at this point are described in the accompanying papers (Gurdon 2013 a,b). Once these technical obstacles had been overcome, largely as a result of good luck, JBG’s work proceeded extraordinarily fast; strongly motivated by early success, he became an intensely hard worker. By the end of his PhD he had succeeded in obtaining normal development of intestinal epithelium cell nuclei transplanted to enucleated eggs of *Xenopus*. When these tadpoles had eventually reached sexual maturity, he was able to publish a paper entitled “Fertile intestine nuclei.”This was the first decisive evidence that all cells of the body contain the same complete set of genes. This answered a long-standing and important question in the field of Developmental Biology. However it also showed very clearly, as was commented on in JBG’s papers at the time, the remarkable ability of eggs to reprogram somatic cell nuclei back to an embryonic state. Eventually this phenomenon attracted increasingly large interest, and led to the idea of cell replacement using accessible adult cells, such as skin. A key future discovery was that of [Martin Evans](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2007/evans-facts.html) (Nobel Prize, 2006) that a permanently proliferating embryonic stem cell line could be established from mouse embryos. Under appropriate conditions these cells could be caused to differentiate into all different cell types. The combination of somatic cell nuclear transfer and the derivation of embryonic stem cells in mammals made it realistic to think of cell replacement for human diseases. A huge boost for this idea was later provided by Takahashi and Yamanaka (2006), with their discovery that the overexpression of certain transcription factors can also yield embryonic stem cells from adult somatic tissue. The accompanying [Nobel lecture](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/gurdon-lecture.html) provides more detail of the later scientific part of JBG’s career. **Post-Doctoral Work** A visit by the Nobel Laureate [George Beadle](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1958/beadle-facts.html) to the Fischberg Group in the Oxford Zoology department in 1960 led to an offer from the California Institute of Technology (CalTech) (previous chairman George Beadle) for JBG to do postdoctoral work there. Fischberg very wisely advised JBG to accept the CalTech offer of postdoctoral work rather than offers from other nuclear transplant labs. Stimulated by his mother’s adventurous spirit, JBG decided to buy a secondhand Chevrolet in New York and drive across the USA to California, using the famous Route 66 (now replaced). He gave lectures as he travelled across the USA and stopped at laboratories of Briggs and King, Alexander Brink (paramutation) etc. He had hoped to become a post-doctoral student of [R. Dulbecco](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1975/dulbecco-facts.html) at CalTech (Nobel Prize), but the chairman of that department advised against this because JBG had no training in virology. Therefore JBG did his postdoctoral work with Robert Edgar on Bacteriophage Genetics. JBG found he had no aptitude at all for Phage Genetics and decided to return to Britain after one year at CalTech. Nevertheless, that year at CalTech was extremely formative because it provided some acquaintance with Molecular Biology, which had so far entirely escaped his training. During that year he met Sturtevant, a student of Morgan, who pioneered the whole field of *Drosophila* Genetics. He also got to know [Ed Lewis](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1995/lewis-bio.html) (future Nobel Laureate). Thanks to James Ebert (director of the Department of Embryology, Carnegie Institute of Washington, in Baltimore) JBG visited various labs in the USA at the end of his post-doctoral period and met Donald Brown in Baltimore on that visit. Meantime, the success of the nuclear transfer work in Oxford had led to Michael Fischberg being offered a head of department professorship in Geneva, Switzerland. JBG was offered the teaching position in Oxford vacated by M. Fischberg. JBG returned from California to England via Japan and many other countries over a two-month period. One month of that time he spent in Japan and met Tokindo Okada and made other friends in Japan, including M. Furusawa and subsequently Koichiro Shiokawa.  While doing graduate and postdoctoral work in Oxford, JBG made other contacts and friendships. His mother’s sister lived in Oxford, and he spent much time at her house and visiting famous gardens, fostering a lifelong interest in plants. Through that connection he met Miriam Rothschild, and became a lifelong friend of hers (Van Emden and Gurdon, 2006). This friendship contained, through Miriam Rothschild’s generosity, ski mountaineering holidays based in her house in Wengen. JBG had achieved the British ski club’s Gold standard ski medal, again through relentless practice rather than any natural ability. Also, in accord with his interest in the open air and dogged determination, he became a reasonably accomplished ice figure skater. **Assistant Lectureship in Oxford, Department of Zoology** On starting the job, JBG was immediately asked to do 24 lectures on Development. From then on his allocation of student lecturing duties went down progressively during his career until, in the end, he was only asked to do two such lectures per year. But the lectures seemed to go well because he attracted, almost immediately, some of the best students to do PhD work with him. Notable among these were C.F. Graham (later FRS) and R.A. Laskey (later FRS, Royal Medal and CBE). During his time in Oxford when he started his own research group, he was able to interact with many very senior scientists in other departments, notably [R. R. Porter](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1972/porter-facts.html) (Nobel), H. Harris and J. L. Gowans.  On return to Oxford, as an Assistant Lecturer in the Zoology department JBG was accorded a privileged position, at his Oxford College Christ Church, as a Research Fellow. He was given only minimal teaching duties, so that he could establish his own research group. At that time, he was fortunate to meet his future wife (fig. 5), Jean Elizabeth Margaret Curtis, eldest daughter of Mr H.J. Curtis who owned a successful business in Oxford in property and gravel. With his wife he had two children; his daughter Aurea has two of her own children. His son, William, did not marry and has no issue.  At fi he lived with his wife and children in a brew-house in Christ Church Oxford (fi . 6), then in a house they had built in his father-in-law’s land.  At this time he made, with his father-in-law, a crossing under the town of Oxford in a disused drain, the Trill Mill underground stream – now permanently closed (fi . 7).  On moving to Cambridge, he was able to acquire, largely through a successful property business of his wife, a large property with a 16th century house in the village of Whittlesford (fig. 8). **Career Moves** After nearly ten years (then 1972) as lecturer in the Zoology department, Oxford, JBG was given a very generous research grant by the MRC of four positions (3 Sci + 1 Tech). At the same time, [Max Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/perutz-facts.html) of Cambridge MRC Molecular Biology lab offered him a position. Max Perutz had empty space that had (by MRC rules) to be filled externally. JBG accepted, and planned to move to Cambridge, very reluctantly by his wife because of our house and her family in Oxford). But senior professors in Oxford persuaded him to decline the offer, notably Rodney Porter (Biochemistry), James Gowan and H. Harris (Pathology). They tried hard to persuade his own (Zoology) Professor Pringle to give JBG the space needed for a now enlarging MRC “unit.” But JBG said he could not manage with the very dispersed space offered. So JBG (eventually) accepted Max Perutz’s offer, and moved to Cambridge LMB. After a few years, Rodney Porter (Biochemistry) offered JBG the Chair of Genetics in Oxford, a sub-department of Biochemistry, a position vacated by Professor Bodmer. By then JBG’s wife and family were very settled in Cambridge and they decided not to move back to Oxford. **Wellcome CRC Institute** After a further ten years (then 1982), Sir Gabriel Horn (Head of Zoology, Cambridge) offered JBG and Ronald Laskey professorships in his department. We both decided (RAL had by then also moved to LMB, Cambridge) to accept jobs in Zoology Cambridge, if they succeeded (as they did) in obtaining substantial support from the Cancer Research Campaign for a joint “unit” in Zoology, Cambridge. They were accommodated, very generously, by Professor Horn, in Zoology, Cambridge. At this time the Wellcome Trust had, thanks to Sir Roger Gibbs, become a major national funding agency. Ron Laskey and JBG were encouraged by the Wellcome Trust to bid for a small Institute to be built in Cambridge for their”unit” and to accommodate some other scientists. It was agreed that the Wellcome Trust and CRC would jointly fund an Institute costing £4M to include some two groups and four others for which we chose: Martin Evans, Janet and Chris Wyllie and Michael Akam. A new building was designed by Laskey and Akam, and they decided, generously, to have JBG as Chairman. We attempted to follow the administrative style of Max Perutz, whose LMB was widely regarded as the most successful research institute internationally. Our Institute thrived, and most particularly because Gabriel Horn, extremely generously, made our new Institute independent of his Zoology department. This arose, importantly by proposing that Group Leaders in our Institute should be affiliated with several different departments in Cambridge, and not all with Zoology. Their new appointments included Azim Surani, Daniel St Johnston, Steve Jackson and Tony Kouzarides (all later FRS). In the 1990s, the Institute had the chance to bid for a new building and more space. They were awarded a Wellcome Trust and CRUK building (£23M), located next to the new Biochemistry department in Cambridge (now 2000).  JBG was succeeded as Chairman by Jim Smith, and then, by Daniel St Johnston. By 2012 the Institute had 17 Group Leaders and had been joined by Anne McLaren. Its tally: one Dame, two Knights, two Nobels, four CBEs, eight FRS, importantly four home-grown. **Cambridge College Appointments** Soon after moving from Oxford to Cambridge in 1971 JBG was offered, on the recommendation of Professor Richard Keynes, a research fellowship at Churchill College. With no obligatory teaching duties, this was a very appealing college connection. Being a large college with over 100 fellows, this was a very welcome opportunity to meet a wide range of Cambridge academics. In 1985 JBG was offered by Lord Braybrooke, the College Visitor, the Mastership of Magdalene College. He accepted this position and this was a major blessing. Compared to two other colleges for which he had been unsuccessfully interviewed, Magdalene accepted that he would wish to keep his laboratory activities going while acting as Master of the College. He chose to decline the usual emolument of a Master so that it could be used to hire a professional fundraiser, thereby releasing JBG for his own laboratory work. The college required only minimal time and spared him much of the committee work normally expected. His wife took to the Master’s wife job like a duck to water. She chose to entertain every undergraduate, every year, in the college to a sit-down Sunday lunch prepared and cooked by herself. She invited 20 students to lunch every Sunday in term. She got to know all the staff in the college and her complete involvement was enormously appreciated. With no internal frictions that he was aware of, the college seemed a happy place and a privileged existence for JBG and his family.  For other administrative jobs for which JBG had been proposed, fortunately he was not selected. In retrospect, any of these would have destroyed his remaining research career. He did however serve for 15 years as a Fellow (Governor) of Eton College where he met some outstanding individuals, including most notably Sir John Smith, the founder of the Landmark Trust, and also a benefactor to JBG’s research. JBG also served for a long time on the Cancer Research Campaign (subsequently CRUK) research grant committee. Compared to many others this committee was very well run and promoted a very happy relationship among its members. This connection opened the door for eventual funding by the CRC/Wellcome Trust for a new Institute for him and his colleague Ron Laskey in Cambridge. JBG also served for a few years as a “Governor”(Board member) of the Wellcome Trust, under the chairmanship of Sir Roger Gibbs, who, as it later turned out, had in earlier years almost as undistinguished career as JBG at the same school. **Other Activities** JBG sees himself as the ultimate non-intellectual. He prefers to do things himself rather than watch others. He never goes to the theatre or musical performances, and hates reading books. With the time thereby saved, he likes to take exercise, in earlier years through skiing and squash (later tennis). Throughout life he has travelled widely, with a special interest in going up mountains and seeing alpine plants. He has been to the top of many of the 14,000ers in Colorado, USA, the highest point in New Guinea, etc. **References** Muskett, J.J. (1900), *Suffolk Manorial Families*, Wm Pollard & Co., Ltd, North Street, Exeter. Cunnington, B. (2008), *The Gurdon Family*, Cunnington, Bronwen. Beechwater, Australia, 3747.  Briggs, R. & King T.J. (1952),”Transplantation of living nuclei from blastula cells into enucleated frogs’ eggs.” *Proc. Nat. Acad. Sci*. 38:4 55–463.  Van Emden, H.F. and Gurdon J.B. (2006), “Dame Miriam Louisa Rothschild CBE 5 August 1908–20 January 2005.” *Biogr. Mems Fell. R. Soc*. 52: 315–330.  Gurdon, J.B. (2013a),”The egg and the nucleus: A battle for supremacy.”*Development*, 140: 2449–2456.  Gurdon, J.B. (2013b) “The cloning of a frog.” *Development*, 140: 2446–2448.  Takahashi, K. & Yamanaka S. (2006) “Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors.” *Cell* 126: 663–676. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0529=JG  [John Gurdon] Hello  [Adam Smith] Hello, may I speak to Sir John Gurdon please?  [JG] Yes, this is John Gurdon speaking.  [AS] Oh hello, my name is Adam Smith. I’m calling from the Nobel Prize website in Stockholm.  [JG] Oh yes.  [AS] We have a traditional of recording extremely short interviews with new Laureates. Would you mind talking to me for just a very few minutes?  [JG] No, that’s fine. Can you hear me now?  [AS] I can hear you beautifully, yes.  [JG] Okay, we’ve got a new phone and it is a little bit erratic. But I can hear you now, and if whoever will be speaking to me can speak in this way.  [AS] Yes, I shall. I shall try and speak clearly.  [JG] Thank you very much.  [AS] Well, thank you. And of course, first, our sincere congratulations on the award.  [JG] Well, I am immensely grateful of course. What more can one say?  [both laugh]  [AS] May I ask what you were doing when the call from Stockholm came?  [JG] Yes, I was in my, I get into lab early and leave a bit early too. So I like to have an hour or two before everybody comes in. So I was in my lab, doing things, dealing with the usual sort of emails before you get down to lab work, which I still do.  [AS] And, do you recall your initial reaction to the news?  [JG] Well, yes. Of course, the first one is this is amazing, if it’s really true. Could it be someone is pulling your leg? And that has happened before. You know, people somehow hear the date when the announcement’s made and decide to tell you that news that is totally incorrect. So you have to be a little bit cautious in believing that the person you are speaking to is actually the right person.  [AS] [Laughs]  [JG] But he sort of said he was the secretary of the Foundation and mentioned things that made me think it probably was real. But your initial reaction must always be, is it someone teasing you?  [AS] I imagine the Swedish accent helps make it sound convincing.  [JG] Yes, that helps too. But you have to be a bit cautious, I think.  [AS] Quite, quite. It has been, it is indeed the fiftieth anniversary of that 1962 publication of yours. So it has been a long time.  [JG] Yes, well, that’s perfectly true. The major publication, on which no doubt the award was made, was actually fifty years ago. And the experiment was done a bit before that. So I’m fortunate, of course, to survive long enough to have this amazing honour.  [AS] I suppose it says something about the progress of science and how expectations shouldn’t be too great that things are going to yield benefit immediately.  [JG] I think that’s right, yes. And, of course, one is always looking for therapeutic benefits. I would say when that when the work was done there was virtually no expectation of any immediate therapeutic benefit, so the recognition as it were of the early result, one can understand has to wait. And indeed there was quite a period after the early work when people did not believe the results. So it took nearly 10 years for the major result to be accepted.  [AS] Well quite, because it was fifty years ago and you were just a graduate student at that point?  [JG] I was indeed a graduate student when the major result was obtained. That’s absolutely right, and that was in 1958 and then I took a post-doc job in California, working in a completely unrelated field. So I left my frogs, which I had grown, with my supervisor who had moved to Geneva and he and a technician grew them up. So by 1962, they were adults and one could publish a paper to say that these animals, derived from nuclear transfer, really were absolutely normal. So it took a little time to get through.  [AS] Now one looks at it as an established fact. But at the time, it must have been quite difficult flying in the face of established opinion and major figures in the field.  [JG] It was, and the people who pioneered the technique of nuclear transfer were called Briggs and King and they had developed the technique and they found, before I started work, that they got the opposite result to me. In other words, they found that when they tried to (I don’t know if you know the field) transplant nuclei from specialised cells it was not successful. So the conclusion drawn was actually opposite to what was indicated by the results that I was getting. So it’s entirely reasonable for the sceptics to say, well these well-established people have already done this experiment and here’s a graduate student from Europe who is disagreeing with them, why should we pay attention to that? Briggs, himself, was a wonderful person. He’s sadly no longer alive. But he was extremely generous and in every way reasonable. So it was just the sceptics who felt the results must be wrong. So one had to go through a few years of, in a sense, letting the results sink in and people decide if they really were correct.  [AS] That is how science should work, exactly.  [JG] That’s how things work.  [AS] And 1962 also happens to be the year that Shinya Yamanaka was born.  [JG] [Laughs] He told me that, isn’t that funny? Yes, that’s rather amazing isn’t it? [Laughs] Extraordinary coincidence, yes.  [AS] Actually, I was just speaking to him. And he was saying repeatedly how important it was to him that the two of you are tied. That his work, indeed, builds on yours and it’s only because of your work that he was able to do his work. So he was expressing his very great pleasure that the two of you are the recipients of this year’s Nobel Prize.  [JG] Well it’s extremely generous of him to take that view. And, of course, the actual key experiment he did had nothing to do with nuclear transfer at all. So I think it’s very generous of him to give credit for the very much earlier, preceding work. He’s very generous that way and always very polite and supportive. So I am, of course, extremely grateful to him for taking that positive view.  [AS] But in his work, he was, I think, looking for factors that could turn cells back …  [JG] Yes.  [AS] And that was based on the principle of gene conservation in differentiation that you had established. So I suppose the fundamental …  [JG] I think that’s correct. From the early point that almost all cells of the body have the same genes, I think it was reasonably clear that given time it should be possible to achieve a complete reversal, though things take time to do. Once the principle is there, that cells have the same genes, my own personal belief is that we will, in the end, understand everything about how cells actually work. So if the genes are there, it seems to me, it must have been in principle possible to achieve a functional reversal. But it depended a lot on all the technical advances that have occurred in the meantime, to make these things possible.  [AS] Some might find that a remarkable assertion, that we will understand everything about how cells work…  [JG] Yes, that is rather presumptuous isn’t it? I’ll tell you why I like to think that. I should say, I think that, I cannot immediately see the route by which we should really understand memory and the workings of the brain. But if we take the earlier stage, that is how you get from an egg to an adult functional animal, forgetting for the moment the brain. I would have thought it would, I would have guessed that in the next 20 years or so, we would really understand in detail how all that works. In other words, we’d identify all the molecules in an egg, how they interact with others, their concentration and location. I can’t see that not becoming evident. And if that is evident, I would have thought that would explain how you would go from an egg to an adult animal. But, I can’t imagine for the moment how one can expect to fully understand things like memory and aspects of the brain. So this rather presumptuous expectation is based on, really, morphology. You know, the functional adult rather than how its brain might work.  [AS] But it does underline that all this work is fundamentally about understanding. Application is lovely, but understanding comes before application.  [JG] I think that’s exactly right. I would agree with that view. And of course it very much relates to the question that’s always being asked, which is, should basic science be supported if there isn’t an immediate benefit to health? And, of course, I am biased but I would hope that basic science would be supported. Because so often it happens that the practical or therapeutic benefit comes along quite a long time after the initial discovery.  [AS] Well, luckily, when you come to Stockholm in December, we have a chance to interview you at a greater length about all this.  [JG] Thank you very much. I understand the dates for that are early December and I look forward to hearing the programme so that I am prepared. At the moment, my thoughts are one of amazement and not had time to entirely absorb this amazing event. But, thank you anyway for talking to me a bit about it.  [AS] I wish you the very best for the rest of this, what will turn out to be, an extraordinarily busy day, no doubt.  [JG] Well I’m sure it will. And thank you very much indeed for calling.  [AS] Okay, my pleasure. Bye bye. My congratulations again. |
| Interview |  |
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| ID | 0530 |
| Biographical | I was born on September 4, 1962, in Osaka, Japan. My father, Shozaburo, ran a small factory in the city of Higashi-Osaka manufacturing components for sawing machines, which he took over in his early 20s after my grandfather passed away. Higashi-Osaka is well known for its cluster of highly skilled small and midsize manufacturers. Like other owners of small companies in the area, my father was an engineer who designed new products and made them by himself. My mother, Minako, helped him run the business, raising their two children, me and my older sister, Yumiko. Looking back on my childhood, I can see now that my father exerted a great influence on me. He did not force me to do or be anything, but, by showing diligence in his work, he taught me silently how meaningful it is to create something from the drawing board, and how interesting it is to seek for oneself a better way of achieving a goal.  SCHOOL DAYS I remember that when I was a child, I found it very exciting to dismantle clocks and radios into small pieces and then try to assemble them again, though most of the time I ended up breaking them. Maybe I just copied what my father was doing. My childhood dream was to become an engineer like him. Science was one of my favorite classes at school. I liked reading a monthly scientific magazine for elementary school children. This magazine came with various kits for children to do experiments. I remember one time I was doing an experiment with an alcohol lamp that came with the magazine. It dropped onto a *kotatsu* heater table and the quilt over it caught fire. I was severely scolded by my mother.  I was educated at the Tennoji Junior High School/High School attached to Osaka Kyoiku University and received an excellent education, with many unique friends and teachers. Entering the junior high in 1975, I joined its judo team as my father recommended me. He thought I was too skinny and should become stronger. I devoted myself to judo and continued practicing it for several years until I quit it due to a serious injury in my second year at college. At the high school, there were some teachers who often told students that we should try to become a superman or superwoman, meaning that we should not only study hard but also try to experience many activities such as sports and activities in the student association. Inspired by them, I formed a folk song band with my classmates, called “Karesansui” (‘Dry Garden Style’), and performed at the school’s student festivals. I played the guitar and was a vocalist. I also committed to the school association as a vice president.  Throughout my school years, I was good at mathematics and physics. Thinking about my career, I considered studying basic sciences in college but decided to go to medical school, partly because my father used to advise me to become a physician instead of taking over his business. I don’t know why that was his wish, but he may have thought that I was not cut out for business or may have wanted me to have a job more stable than running a small business that is easily affected by the economic climate. A book also pushed me to become a medical doctor. I was deeply inspired by Torao Tokuda, a physician who founded a hospital group in the 1970s that tried to revolutionize the Japanese medical care system. In 1981, I succeeded in my ambition of being accepted at Kobe University’s School of Medicine. There again, I enjoyed playing judo and rugby, and suffered many broken bones while doing sports. In addition, I often suffered from severe pain in my legs due to over-training. These experiences made me interested in sports medicine and I decided to become an orthopedic surgeon.  RESIDENT AT A HOSPITAL After receiving an M.D. from Kobe University in 1987, I served as a resident at the Osaka National Hospital for two years. During this period, two major events happened to me. I married Chika, whom I first met as a classmate at junior high school. She became a dermatologist and now runs a clinic in Osaka. The other unforgettable event was my father’s death. He had long suffered from diabetes and also had hepatitis caused by a blood transfusion he had received a few years earlier to treat an injury. During his last two years, as a medical student and resident I gave him injections and administered intravenous drips, and he seemed happy to receive such treatments from his son.  Working at the hospital, I found that my surgical skills were not as good as I expected. One time it took me two hours to do a surgical operation which could have been completed in 30 minutes by other surgeons. My supervisors were very tough on new residents like me, and I lost confidence in my ability. In addition, treating many patients with intractable diseases and injuries such as rheumatoid arthritis and spinal cord injury, I realized that there were many diseases that even talented surgeons and physicians cannot cure. Even now, I recall clearly one female patient who had severe rheumatoid arthritis. There was a photograph of a cheerful woman on her bedside cabinet. I though it must be her sister or something. Learning that it was herself only a few years back, I was shocked that the patient looked totally different because of the disease. Painful and unforgettable bedside experiences finally drove me to switch my goal from becoming a surgeon who would help free patients from pain to becoming a basic scientist who would eradicate those intractable diseases by finding out their mechanisms and ultimately a way of curing them.  FROM SURGEON TO SCIENTIST As the first step toward my new goal, I became a Ph.D. student in pharmacology at Osaka City University Graduate School of Medicine in 1989, working in Kenjiro Yamamoto’s laboratory. During the next four years, I learned the essentials about how to design and conduct experiments and analyze data from my direct mentor, Katsuyuki Miura. The first instruction he gave me was to read as many papers as possible to help me think about a research theme. A few months later he assigned me to perform an experiment to study the role of a blood lipid named platelet-activating factor in lowering blood pressure in dogs. Miura’s hypothesis was that administering an inhibitor of another lipid, thromboxane A2, which is activated by platelet-activating factor, would prevent the blood pressure from going down. But my experiment showed a completely opposite result. I was so excited with the unexpected outcome that I became totally fascinated by basic science. Miura was also enthusiastic about the findings even though they were against his hypothesis. This study later became my Ph.D. dissertation, published in *Circulation Research* in 1993. There was an eye-opening moment when Miura told me that scientists have to compete with researchers around the world. When I was a resident, my rivals were other residents at the same hospital. As a scientist, I could win global recognition in a scientific field, albeit a small one, if my findings were published in high-profile journals. His words made me pay keen attention to research abroad.  POSTDOCTORAL FELLOW AT GLADSTONE At the time, I was astonished by mouse transgenesis and gene targeting, which specifically induce or delete a single gene of interest, because no pharmacological agents could perform such miracles. After finishing my Ph.D. work in 1993, I applied for as many postdoctoral positions as I could in labs doing mouse molecular genetics because I wanted to obtain postdoctoral training and further skills including techniques to make knockout mice. However, it was very natural that a failed surgeon with little experience in molecular biology had a hard time finding a position. A turning point came when I got a fax from Thomas Innerarity at the Gladstone Institute of Cardiovascular Diseases in San Francisco. After a short telephone conversation, Tom was brave enough to give me a postdoctoral position in his lab! Working at Gladstone was one of the best decisions I ever made in my life. Gladstone provided an almost perfect environment for an ambitious new researcher like me thanks to its skillful technicians and the provocative discussions about science I had with enthusiastic colleagues.  When I joined Tom’s lab, he had a hypothesis that forced expression in the liver of APOBEC1, the ApoB messenger RNA-editing enzyme, would lower plasma cholesterol levels and thus prevent atherosclerosis. To examine this hypothesis, I generated transgenic mice overexpressing Apobec1 in their livers. To our surprise, however, the transgenic mice developed liver tumors. We learned that Apobec1 is a potent protooncogene. Naturally, Tom was disappointed, but I became very interested in the molecular mechanisms of this totally unexpected result. Tom, despite the finding being against his hypothesis, encouraged me to continue studying the APOBEC1-mediated oncogenesis. Thanks to his support, I identified a novel target of Apobec1, Nat1, which was aberrantly edited in the transgenic mouse livers. I decided to generate Nat1-knockout mice to study the gene’s function. Robert Farese at Gladstone and his research associate Heather Myers kindly taught me how to culture mouse embryonic stem (ES) cells and make chimeras.  Gladstone also provided me with the opportunity to acquire presentation skills and to learn a key idea for success as a scientist. One day, Robert Mahley, the then president of Gladstone, gathered about 20 postdocs and said that “VW” was a magic word to make us successful scientists. What he meant was that scientists need to have a clear vision and work hard toward it. I found myself not having a clear vision, although I was confident that I was one of the most hard-working postdocs at Gladstone at the time. I have since set my vision as being “to contribute to the development of new cures for patients through basic research.” I still have the “VW” lesson in mind and often quote it to my students in my lab.  In 1996, my wife Chika and our two daughters, Mika and Miki, who were living in San Francisco with me, returned to Japan to enroll Mika in an elementary school in Osaka. About six months after they left, I went back to Japan as I missed them so much. Back in my home country, I eventually got an assistant professor position in the department of pharmacology at Osaka City University Medical School. Tom kindly let me continue the Nat1 work and shipped three chimeric mice I had made to Japan. The then chairman of the department, Hiroshi Iwao, was very supportive and allowed me to work on Nat1, which seemed to have little value in pharmacology. I found that Nat1 is required for early mouse development. More importantly, I found that Nat1-null embryonic stem (ES) cells proliferate normally but cannot properly differentiate. These surprising findings changed the meaning of mouse ES cells for me from a research tool to a research subject. I became intrigued in how ES cells maintain their differentiation ability while rapidly proliferating.  POST AMERICA DEPRESSION In Japan, however, I found myself suffering from Post America Depression or PAD. The environment for researchers in Japan was quite different in many ways from that in the U.S. At the medical school, very few scientists showed interest in the basic biology of mouse ES cells, and there was little thought-provoking discussion with my colleagues. Some of my colleagues advised me to work on something more related to medicine. Furthermore, I could not get enough funding and had to change the cages of the numerous mice by myself every week. What was worse, the Nat1 work was being rejected by many journals. I felt lonely and depressed, and I was about to give up my career as a scientist and return to the path of physician.  Fortunately, two events rescued me from PAD and from giving up on science. First, James Thomson of the University of Wisconsin-Madison and his colleagues announced that they had succeeded in generating human ES cells in 1998. His success taught me that ES cells have enormous potential in medicine and encouraged me to continue my research. Second, in December 1999, I got a new position as an associate professor with my own laboratory for the first time in my career at the Nara Institute of Science and Technology (NAIST ) in Nara Prefecture. This institute has brilliant investigators in basic and applied sciences, an excellent research environment and competent Ph.D. students. I was fortunate that several talented colleagues and students joined my laboratory.  RESEARCH AT NAIST At NAIST, I was expected to establish a knockout mouse core facility. It was a difficult task, but thanks to an excellent technician, Tomoko Ichisaka, and to funding from NAIST, we were able to establish it within a few years. The first gene that we knocked out was Fbxo15, which we identified as a gene specifically expressed in mouse ES cells. One of my first Ph.D. students, Yoshimi Tokuzawa, with the help of Tomoko, successfully targeted the gene. However, we did not see any phenotypes in mice or ES cells lacking Fbxo15. We were disappointed, but this knockout mouse line turned out later to be useful in the generation of induced pluripotent stem cells or iPS cells.  As a principal investigator, I needed to set a long-term goal for my laboratory. Because of my interest in ES cells, because of the successful generation of human ES cells and because I had to use ES cells anyway in the knockout mouse core facility, I decided to list “ES cells” in the title of my lab website. At the time, most researchers focused on differentiating from ES cells into somatic cells. Human ES cells are associated with two major hurdles – ethical issues regarding the use of human embryos and immune rejection after they are transplanted into a human body. The use of human embryos has been an obstacle to the promotion of ES cell research in many countries, including the U.S. and Japan. To overcome these major hurdles, I decided nuclear reprogramming would be the goal of my lab. More precisely, I set my lab’s goal as being to generate ES cell-like pluripotent cells from somatic cells, without using embryos.  Nuclear reprogramming was first proved by Sir John Gurdon in 1962, the year I was born. He reported the generation of new frogs by transferring tadpole intestine cell nuclei into enucleated eggs from the African clawed toad, *Xenopuslaevis*. Then, in 1997, Sir Ian Wilmut’s team unveiled Dolly the sheep, the first cloned mammal created using a nuclear transfer method. These achievements showed that the genome DNA of mature cells theoretically have all the information needed to develop animals. A further advance came in a 2001 report by Takashi Tada of Kyoto University, who demonstrated that thymocytes acquire pluripotency upon electrofusion with mouse ES cells, which indicated that ES cells also contain factors that induce pluripotency in somatic cells. However, I knew that making pluripotent cells from somatic cells would be extremely difficult, and when I started this project with my lab members at NAIST, I was not sure if the goal could be achieved in my lifetime.  My initial hypothesis was that factors that maintain the pluripotency of mouse ES cells might induce pluripotency in somatic cells. With the great help of the initial members of my lab – Tomoko, Yoshimi, and two other students, Kazutoshi Takahashi and Eiko Kaiho, and then Assistant Professor Kaoru Mitsui, my lab identified many factors that either are specifically expressed by or have important roles in mouse ES cells. Among them was the transcription factor Klf4, identified by Yoshimi. By 2004, with our own work and that of other groups, we had collected 24 initial candidate genes that might be able to induce pluripotency in somatic cells. We then needed a simple and sensitive assay system to evaluate these candidates, and the Fbxo15-knockout mice turned out to be such a system. Instead of simply deleting the gene, we knocked the neomycin resistant gene (neoR) into the Fbxo15 locus. Somatic cells derived from these mice do not express neoR and are sensitive to the antibiotic G418. Somatic cells that become ES cell–like pluripotent cells after transfection with some of our candidate genes should express neoR and become resistant to G418.  THE DISCOVERY OF IPS CELLS In 2004, I moved to the Institute of Frontier Medical Sciences at Kyoto University as a professor. The major reason for the change was that I wanted to conduct experiments using human ES cells. NAIST did not have a medical school and a hospital attached, and therefore had no institutional review board to examine a study plan using human ES cells. At that time, Kyoto University was the only institute in Japan that had succeeded in culturing human ES cells. I came to Kyoto with the 24 candidate genes, the Fbxo15-neoR knock-in mice and many members of my lab, including Tomoko and Kazutoshi. I asked Kazutoshi to test the 24 candidates using the Fbxo15 knock-in mice. He was pleased to take over this very risky project and did a remarkable job. When Kazutoshi introduced each candidate into the Fbxo15-neoR reporter fibroblasts using retroviral vectors, no G418-resistant colonies emerged. However, when he introduced the mixture of all 24 genes via retroviral vectors, we observed several drug-resistant colonies in a Petri dish. These cells were similar to ES cells in morphology, proliferation and gene expression. When transplanted into nude mice, they formed teratomas containing a variety of tissues from all three germ layers, showing their pluripotency. Among the myriad combinations of the 24 factors, Kazutoshi found that four transcription factors – Oct3/4, Sox2, Klf4 and c-Myc – are essential.  In 2005, we succeeded in generating ES-like cells with the four factors, and I named the resulting cells “induced pluripotent stem cells or iPS cells.” I was anxious about whether they were really the pluripotent cells that we were looking for because the method used to generate the iPS cells was much simpler than I had expected. In addition, after hearing about a big scandal involving a Korean researcher who falsely reported the successful generation of human ES cells by cloning at around that time, I thought we should repeat our experiments to make sure of the result so that no researcher could cast doubt on our findings. In 2006, we published a paper in *Cell* on the successful generation of mouse iPS cells using the four factors. Some researchers seemed surprised at the finding that only four genes are needed to reprogram somatic cells into the embryonic state. But in the following months, a few labs at MIT and Harvard demonstrated that they had been able to produce mouse iPS cells using our protocol, and an increasing number of researchers have since started working on the new technology.  Right after we generated mouse iPS cells, my team began to work on reprogramming human somatic cells. In November 2007, we reported the generation of human iPS cells from human fibroblasts by introducing the same quartet of genes via viral vectors. On the same day, Thomson’s lab announced in *Science* that they had also succeeded in making human iPS cells using a different set of four factors – Nanog, Lin28, Oct3/4 and Sox2. I remember that I worked day and night to publish our paper as quickly as possible after I heard a rumor in the summer that a U.S. group had submitted an article on the successful generation of human iPS cells. My lab members continued to improve the induction and selection methods. Keisuke Okita, with the help of Tomoko, succeeded in making iPS cells that are competent for production of adult chimeras and germline transmission. Masato Nakagawa and Michiyo Koyanagi then showed that iPS cells can be generated without c-Myc, an oncogene. Takashi Aoi showed that iPS cells can be generated not only from fibroblasts but also from adult mouse hepatocytes and gastric epithelial cells.  With the ability to differentiate into virtually all types of cell and to grow robustly like ES cells, iPS cells have enormous potential for pharmaceutical and clinical applications. Patient-specific iPS cells can be used to produce disease model cells in which the pathological process can be studied. Thousands of chemicals and natural products can be tested on such cells, some of which we hope will become new effective medicines for intractable diseases.  CENTER FOR IPS CELL RESEARCH AND APPLICATION The Ministry of Education, Sports, Science and Technology of Japan has since supported iPS cell research in cooperation with other government agencies by providing sufficient funding. Encouraged by this support, in January 2008, about two months after we reported the generation of the human iPS cells, Kyoto University founded the Center for iPS Cell Research and Applications (CiRA), the world’s first organization solely focusing on iPS cell technology, under the auspices of the Institute for Integrated Cell-Material Sciences (iCeMS). I was appointed as the Director of CiRA. I had given up my career as a physician, but I had found a powerful tool that could help develop new cures for disease. This center is designed not only to progress with basic research to improve fundamental iPS cell technology but also to use the technology in clinical applications. In April 2010, CiRA became independent of iCeMS as a full-fledged institute in a newly opened research building. At the inauguration ceremony for the new CiRA research building, I publicly pledged to achieve four goals over the first ten years:  CiRA’s Goals for the First 10 Years  1. Establish basic iPS cell technology and secure intellectual property. 2. Create an iPS cell stock for clinical use in regenerative medicine. 3. Conduct preclinical and clinical studies on such diseases as Parkinson’s disease, diabetes and blood diseases. 4. Contribute to the development of therapeutic drugs using patient-derived iPS cells.  Since the discovery of human iPS cells, I have seen iPS cell technology advancing at an amazing speed. Owing to its simple and reproducible method, numerous laboratories inside and outside Japan are now working on iPS cell research, and protocols have been developed for direct reprogramming, whereby somatic cells are directly converted into mature cells of a different type. My lab developed a method to generate safer iPS cells without integrating viral vectors into the cell genome, which was one of the major safety concerns. Now CiRA is promoting the iPS cell stock project, in which we make clinical-grade iPS cell lines from blood cells donated by healthy HLA-homozygous individuals. The iPS cell lines will be distributed to other institutes so that they can differentiate them into various types of cell for use in transplantation therapy. Scientists at CiRA have succeeded in recapitulating a number of abnormalities in the cells of patients with such diseases as amyotrophic lateral sclerosis (ALS) and chronic infantile neurologic cutaneous and articular (CINCA) syndrome, which I hope will contribute to development of new therapeutic drugs. I have a small laboratory at Gladstone since I was offered a senior investigator position in 2007 and the lab members are also working hard. Working for Gladstone is a great pleasure for me as it means I can make some contribution to the institute where I received excellent training as a young scientist.  Running CiRA with some 250 staff, I have come to spend less time discussing their data with my colleagues and students, and have been absorbed by my duties as the “chief executive officer” of CiRA, including devising strategies to advance both basic and applied research and to obtain sufficient funding. Anxious about the lack of financial resources for the future to allow us to continue hiring research support staffers, I even ran the full Kyoto Marathon in 2012 to raise online donations from the public. It was hard but helped us raise more than 10 million yen. Now I hope that receiving the Nobel Prize in Physiology or Medicine will consolidate long-term support from the government and the general public for iPS cell research nationwide.  THANK YOU FOR YOUR SUPPORT! Looking back at my life, I have been very fortunate that I have encountered many talented students and colleagues who have supported and encouraged me on many occasions, including my lab members in the past and the present. In addition to my direct mentors, I also owe much not only to the great scientists who made breakthrough discoveries in biology but also to countless predecessors who have contributed to the development of nuclear reprogramming and stem cell biology. I am deeply thankful to my wife and our two daughters, who have supported my hectic life as a scientist for years. Finally I am grateful to my parents. I was glad that my mother was able to take part in the award ceremony of the 2012 Nobel Prize in Stockholm. My father wanted me to become a physician who helps a lot of patients. Although I gave up my career as a surgeon, I still hope to help people suffering from serious diseases and injuries. With iPS cell technology I will continue to work hard together with my colleagues to achieve this goal as quickly as possible. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0530=SY  [Shinya Yamanaka] Hello  [Adam Smith] Hello, may I speak to Professor Yamanaka please?  [SY] Yes, speaking.  [AS] Oh hello, this is Adam Smith calling from the Nobel Prize website in Stockholm. We have a tradition of recording very short interviews with new Nobel Laureates. Would you be able to speak for just a very few minutes?  [SY] Okay.  [AS] Thank you. First of all, our sincere congratulations on the award of the Nobel Prize.  [SY] Oh, thank you very much. It is a tremendous honour to me. Especially I heard that I am going to share the prize with Dr. John Gurdon, so I feel more honoured, because I respect him a lot.  [AS] He established the principle of gene conservation in differentiated cells, half a century ago. And so there was this very long run up then very rapidly you have transformed the field by creating induced pluripotent stem (iPS) cells.  [SY] Yes, well I was able to initiate my project because of his experiments fifty years ago. Actually, he published his work in 1962. And that was the year when I was born. So I really feel just great, feel honoured.  [AS] There’s a lovely symmetry about that. And it shows the progress of science, and one can’t be too rushed in expecting things to happen.  [SY] Indeed.  [AS] And indeed, it’s the fiftieth anniversary of your birth and of his publications.  [SY] Oh yes exactly. Yes. I just turned out to be fifty.  [AS] Congratulations on that also, then.  [SY] Thank you very much.  [AS] May I ask, what were you doing when the call from Stockholm came?  [SY] Well actually I was at home. I was doing some housework. So I was very surprised.  [AS] So you were actually doing some housework, you were cleaning the house or something?  [SY] Yes, exactly. So I didn’t expect at all.  [AS] Can you recall your initial reaction to the call?  [SY] Well, so I was kind of alarmed by my secretary, who is still at my office. So she got a call from Stockholm, and asked about my phone number. So she kind of gave me an alert. But still, you know, I was not sure at all. So when I received the call, I was surprised. Almost, you know, I just thought wow, it’s very … a phonecall from Stockholm. I just couldn’t believe it.  [AS] That’s lovely. That’s very nice. Indeed it hasn’t been long. It was only in 2006 that you created the first iPS cells, so it hasn’t been long.  [SY] So I strongly feel that this is, that I am able to receive this award because of John Gurdon and also many other researchers in the field. This field has a long history, starting with John Gurdon. So I feel very lucky. I may have played some important role in this long history, but it was not myself who initiated this field. So that’s my feeling right now.  [AS] I understand and it’s so nice that the two of you are tied together by the award and will be in Stockholm together in December to accept it.  [SY] Yes, that’s great, yes.  [AS] When you come to Stockholm we have a longer chance, happily, to interview you and so talk more.  [SY] Okay  [AS] But I just wanted ask you one final question, which was what your greatest hopes for stem cells technologies are at the moment? What do you hope will be the first benefit?  [SY] Well, I will bring this technology to clinics. I really want to help as many patients as possible. As you may know, I started my career as a surgeon 25 years ago. But it turned out that I am not talented as a surgeon. So I decided to change my career, from clinics to laboratories. But I still feel that I am a doctor, I am a physician, so I really want to help patients. So my goal, all my life, is to bring this technology, stem cell technology to the bedside, to patients, to clinics.  [AS] Thank you. And I understand that iPS cells will, in fact, be going into the clinic for trials next year for the first time.  [SY] Yes, indeed. Yes.  [AS] Okay. Well, thank you very much indeed. And I wish a lovely evening of celebration.  [SY] Okay, thank you so much  [AS] It was a pleasure to talk to you. Thank you. Congratulations again.  [SY] Thank you very much. Bye bye.  [AS] Bye. |
| Interview |  |
|  |  |
| ID | 0531 |
| Biographical | One of the happiest days of my life It was 2:30 a.m. on October 3, 2011, and I was at home, in my small condominium in San Diego, CA. I was sleepless, having recently returned from a trip to Hong Kong. There I had shared the Shaw Prize in Life Sciences: one of a series of prizes in recent years. The previous afternoon, as we visited our mother in La Jolla, my brother Earl had remarked that the Nobel Prize in Physiology or Medicine would be announced the next day. He also had asked if I was going to win it this year. This was on my mind as I lay awake.  Bleary-eyed, I looked at my cell phone to see if there was any email. There was a message: just one. The title line seemed to be “Nobel Prize.” I reached for my glasses, looked again, and found I was correct. Nobel Prize. Perhaps this year the Committee had made a mass e-mailing of the announcement to members of various National Academies? I opened the message and read the first lines of a letter from Göran Hansson …  *“Dear Dr Beutler, I have good news for you. The Nobel Assembly has today decided to award you the Nobel Prize in Physiology or Medicine for 2011. You will share the Prize with Drs Jules Hoffmann and Ralph Steinman. Congratulations!”*  I was too excited to read more at that moment, and hurried downstairs. I called Betsy Layton, my longtime colleague and Administrative Manager. She was in Dallas, preparing the way for our relocation from the Scripps Research Institute to UT Southwestern, where we had earlier done some of our most important work. She had worked with me over the past 25 years, and had played an important part in finding the Lps mutation for which the Prize was awarded. I woke her from a sound sleep. “Bets,” I said tentatively, “I think I won the Nobel Prize!” She was ecstatic, but I cautioned her that I had to confirm it, and kept her on the line.  I tried to access the website Nobelprize.org, but found I couldn’t; there was too much traffic. Then I went to news.google.com. I searched for my name, and within a minute or two, began to see it in reports emanating from all over the world. It was true. I told Betsy so, and she was so happy she began to cry! Yet still I was somehow disbelieving and only over the days and weeks that followed did the new reality settle in my mind.  Nadia Krochin, my dear friend and companion of many years, called me from the east coast before I could call her, and left a message on my voice mail that was almost incoherent with joy! I called my brother Earl; then my brother Steve; then my sons; then my friend Ari Theofilopoulos. I waited until about 4 a.m. to call my mother. Each person, though awakened abruptly, was nearly as happy as I had been.  By this time, my cell phone was ringing almost constantly, and it didn’t stop ringing until late afternoon. Mostly reporters were calling, and I attempted to respond immediately to a few of them, hearing a constant beeping of incoming calls in the background as I did. Among those to whom I spoke during those first hours was a National Public Radio anchor, and it was on NPR, driving to work in various parts of the country, that many of my friends soon heard the news, along with my initial reaction. Emails were arriving every few seconds, and by the end of the day, I had more than a thousand of them. I realized it was hopeless to reply to them, and instead, via Betsy, I advanced my pre-existing plans to fly to Dallas. While waiting for my 10 a.m. flight, I went for a haircut earlier scheduled for 8 a.m. Hannah Andrusky, a charming lady who had cut my hair each month for several years, agreed to meet me an hour early that morning. I was her first client of the day, and she, too, knew of the Prize. She was as delighted and proud of me as everyone else had been. The haircut was free.  In Dallas I was greeted as a hero. A press conference was arranged for the next day, and after introductory speeches by the Dean, President, and Past President of UT Southwestern Medical Center, I stepped to the podium, met by a warm standing ovation. I spoke for several minutes from the heart, without slides, notes, or preparation of any kind. I felt a sense of self-confidence I hadn’t known before. After all, I was a Nobel Laureate. Everyone present was elated and wished me well. I talked a bit about my life, about the steps that had brought me to the Nobel Prize, and also about some of the struggles and strains this entailed.  My background All of my grandparents immigrated to the United States to escape persecution as Jews, and I was reminded of this often from an early age. World War II had ended only 12 years before I was born, and recollections were fresh. My father was born in Germany, my mother in America to immigrant parents. My siblings, my cousins and I were always strongly conscious of our European origins, and of the extreme anti-Semitism that had recently prevailed in Europe. Probably we all felt a need to excel partly because of these facts; to show that we were as good as the other children in our schools.  My mother’s parents, Aral (“Harry”) Fleisher (1895–1953), and Miriam (“Mary”) Fleisher, née Krasne (1893–1966), were both from Kiev, and moved separately to the USA near the turn of the century, settling in Chicago where they met and married in 1922. Harry initially worked in the insurance business. However, he was persuaded to join the company of Mary’s father, Louis Krasne (L. Krasne and Sons). Mary and her brother Isador traveled to the west, ultimately settling in Tulsa, Oklahoma where they established a branch of L. Krasne and Sons that traded in “Leather and Findings.” My mother, Brondelle May Fleisher, was born in Chicago but raised in Tulsa from the age of 11. She was the second of three children (Beverly was older and Lois younger), and she survives both her sisters today.  My mother’s father died before I was born, but I knew my maternal grandmother well. Afflicted with a brittle form of diabetes (oddly at a mature age), she lived with us, was known as “Bubbie,” and took care of me during my first few years of life. I remember her as a warm and kindly old woman with a strong Yiddish accent and extremely long hair, nearly touching the ground. Almost blind, she would spend much of her time in the garden, pulling weeds from the lawn, or otherwise trying to be useful. She was happy to talk to me, or walk with me or explore the yard. One of our routines was to “search for the Fountain of Youth” (which always turned out to be a drinking fountain in the back yard). She died within days of having a myocardial infarction at our California home in 1966.  My father’s parents, Alfred Beutler (1891–1962) and Kaethe Beutler née Italiener (1896–1999) were both physicians: he an internist with a particular interest in cardiology, and she a pediatrician. They emigrated from Berlin, Germany in 1935 to escape Nazi persecution. I knew my father’s father only slightly as he lived in Milwaukee, WI, visited only occasionally, and died when I was only four years old. My grandmother Kaethe, on the other hand, lived to be 102, residing near my parents’ house for many of the last 40 years of her life. I had innumerable interesting conversations with her, beginning at a young age and continuing into my 40s. She was, on the one hand, kind to all her grandchildren, generally patient, and attentive to us. But occasionally she would lose her temper and shout at us with a strong German accent, which could be quite intimidating. She had an extraordinary vocabulary in English, was highly informed of current events, especially national and local politics, and spent much of her time reading books and political magazines. She was a lover of classical music and a competent pianist, who in her 60s and 70s, gave lessons to children in her neighborhood. She remained intellectually sharp, trading on the stock market and even learning to program a computer in her late 80s and early 90s. She had high standards, was quite strict about punctuality (once excoriating my sister when she showed up to an appointment at 3:17 pm rather than the designated 3:15 pm), and was hard to impress. She was not one to “ooh” and “ahh” over a child’s drawing or any other minor accomplishment. On the other hand, she did encourage all of us, often through unstinting praise of great achievements in the world at large. It may well have been from her that I first heard the phrase “Nobel Prize” when I was still a small child, and on rare occasions, when I talked to her about science, I recall her saying “maybe someday you will win the Nobel Prize.”  My grandmother was never comfortable as a Jew in German society at any time she lived there, although she was the physician to children of prominent gentile families in Berlin. Among her patients was the son of Magda Goebbels (from her marriage to Günther Quandt), about whom she spoke to me a few times. She described Magda as an “elegant, beautiful woman” who was quite pleasant prior to her marriage to Josef Goebbels, whereafter she visited no more. My grandmother did not foresee the Holocaust, even two years after Hitler’s rise to power, but did foresee that her three children (my father, Ernst, his older brother Frederick, and his younger sister Ruth) would be denied an education and would have no future in Germany. She was the prime mover in the family’s decision to leave. For a time, it was undecided whether they should emigrate to Palestine or to the United States. My grandfather actually visited Palestine, but found opportunities for physicians to be limited, and decided in favor of moving to America. This was reportedly contrary to my grandmother’s wishes. “He asked me where I thought we should go. I said ‘Palestine,’ so of course we moved to America,” she sometimes recounted. In the years that followed, she regretted that she could not take part in building the modern state of Israel. At the same time, she was relieved that her children did not need to fight in the wars that beset Israel from its founding.  Both of my parents were born in 1928, my father in Berlin, Germany, and my mother in Chicago, IL, USA. My father was said to have been a somewhat difficult child, often in conflict with his mother. However, he performed extraordinarily well at school, and at the age of 15 was enrolled in a special program developed by Robert Maynard Hutchins, then President of the University of Chicago, which permitted him to finish high school and college within two years and then go on to medical school. This he did, graduating as the valedictorian of his class, with a doctorate in medicine at the age of 21. He specialized in hematology, and in time became the pre-eminent academic hematologist of the 20th century. His scientific contributions extended to many areas of biomedical science, and he received numerous awards and distinctions in recognition of his work, including the Gairdner Prize in 1975, and election to the National Academy of Sciences and the Institute of Medicine in 1976. His most celebrated achievement was the 1962 discovery of random X chromosome inactivation in humans, made independently of Mary Lyon, who discovered it in mice. He made many other advances as well, in diverse fields of study, and he was to influence my own career dramatically.  My parents met at the University of Chicago, when my father was in his junior year of medical school. My mother was an undergraduate there, majoring in mathematics. They married June 15, 1950, and remained together until my father’s death in October of 2008. In addition to me, they had three other children: Steven in 1952; Earl in 1954; and Deborah in 1962 (Figure 1). Like me, Steve and Debbie became physicians; Earl became a successful businessman. Our early years were mostly spent in southern California, because my father moved there in 1959 to accept a position as Chairman of the Department of Medicine at the City of Hope Medical Center in Duarte. My mother worked as a homemaker for about 18 years, spanning most of my childhood. She then began a late career as a technical writer, retiring in her mid-60s.  CA childhood and friends  I was born in Chicago, IL, on December 29, 1957. But I have only fleeting memories of my first years there. My earliest memory is of newly fallen snow in the autumn of 1959. Seeing that the world outside had changed overnight, I asked “Who did that?” I also remember crying when movers came to take everything out of my room, as the family was relocating to California, where, from the age of two, I grew up in Arcadia, a northeastern suburb of Los Angeles. I have warm recollections of my childhood in California, and often have dreams in the setting of the adobe brick house where I grew up, with its orange terra cotta tile roof, one-acre yard, orchard crammed with fruit trees, guest house (which served as my room from the ages of 12–16), large front lawn (which we called “the field,”) and swimming pool (Figure 2). Generally speaking, I recall sunshine year round; heavy smog and hot weather during summer months; snow on the surrounding peaks and frost on the lawn in the mornings during winter; family vacations to national parks; and the fact that I had a strong interest in nature (particularly in animals). Over the years, I raised many animals (dogs, ducks, rabbits, mice, chameleons, tropical fish, turtles, and zebra finches), watching them and generally marveling at their behavior. As I grew up, I did lots of hiking (chiefly in the San Gabriel Mountains), birding, and bicycling. There were stresses to be sure: quarrels with my sibs and worries about deadlines in school, but nothing serious. On the whole I was very happy, even if I didn’t always realize it.  I began first grade early (at age 5), attending public school until I was 13 years old. I was then admitted to Polytechnic School, a college preparatory school in Pasadena, CA. The content of the curriculum at Polytechnic, and the pace at which we were taught, was quite different from what I had experienced in public school. It was something of a renaissance for me, and I regretted having wasted so much time beforehand. Not only was I taught more, and taught better at Polytechnic than at public school, but I also had exceptionally smart friends, and have remained close to some of them to this day. David Brittan, Paul Spiegel, Bob Kleinberg, John Taylor, and David Horowitz were among those friends, and with them, I could discuss almost any topic of the day, as they had a wide range of interests, spanning music, politics, literature, and science.  During three years at Polytechnic, I learned a lot about many things, and certainly changed a great deal, with some mental transformations literally occurring from one day to the next. For example, when I was 15 years old, I attended a performance of Bach’s St. Matthew Passion. My father had intended to go, but could not, as he needed to rescue my brother Earl, who had been bicycling from San Francisco to Arcadia, and had become exhausted on the way; hence I went in his place. I had been exposed to classical music in my home as a child, but it didn’t make any special impression on me. Yet I was completely electrified by this live performance of Bach’s great choral masterpiece, the first I had heard, and at once began listening to other choral music and collecting it on vinyl records, especially pieces by Bach, Handel, Vivaldi, Mozart, and Haydn. I remember arranging my curriculum in such a way that I could bicycle to school early in the morning (a distance of eight miles), complete my classes by late morning, and then bicycle home to listen to a radio concert of Renaissance music in my father’s study. Later I would do my homework (generally until quite late at night, and usually accompanied by Bach). I have remained a music lover ever since, ultimately settling on Bach as the center of my musical world. But although music became a deep and enduring interest of mine, I never learned to play any musical instrument proficiently.  Early interest in science From childhood, living things appealed to me aesthetically. I could relate to them, and I was amazed by their similarity to humans. I was aware that life forms had changed continuously on earth over many millions of years, and concepts of genetic variation, natural selection, and inheritance were second nature to me, even from the time I was in elementary school.  In hiking and birding, and in looking at microbes through a microscope (one of my favorite diversions at some point), I enjoyed the observational side of science, which is where scientific inquiry normally begins. It was during high school, in the rich intellectual environment I have briefly described, that I first began to wonder about unanswered questions in science. The ability of inanimate molecules to assemble themselves into living matter was something that I found immeasurably interesting. My oldest brother, Steve, once introduced me to a quotation he attributed to [Camus](https://www.nobelprize.org/prizes/literature/1957/camus/facts/): “Life is the disease of matter.” Probably it was actually from Goethe, who as I later learned, wrote “Viewed from the summit of reason, all life looks like a malignant disease.” The idea resonated with me, not in a morbid sense, but because life was a process that compelled matter to do its bidding, co-opting it more or less automatically, and endowing it with special properties not seen in the inanimate world. In the early 1970s, I read the second edition of [James Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/)‘s “Molecular Biology of the Gene” (also a gift from my brother Steve, then in college at the University of California at San Diego) from cover to cover, and understood for the first time how DNA specifies the synthesis of proteins with specific functions, which in turn permit DNA replication, the development of a complex organism, meiosis, and the propagation of species. I became even more eager to participate in the study of living things, and to be an experimentalist rather than merely an admiring witness.  In high school and in college, I began to work in my father’s laboratory, and it was at this stage that I began to do authentic research. I was guided by my father and his interests, and learned to assay erythrocyte enzymes, and to characterize their electrophoretic mobility. One of the enzymes I studied most was glutathione peroxidase, unusual because it was a seleno-enzyme. At one point, striking out on my own a bit, I decided to see whether bacteria might have glutathione peroxidase, and whether it might be subject to biosynthetic control based on the availability of selenium, like the genes of operons, which had been described not too long before by [Jacob](https://www.nobelprize.org/prizes/medicine/1965/jacob/facts/) and [Monod](https://www.nobelprize.org/prizes/medicine/1965/monod/facts/). Lysing E. coli, I first found that there was no glutathione peroxidase activity. My father suggested I should add sodium selenite to the culture. I did so, and found considerable activity, which I interpreted as a success: I believed the selenite had induced synthesis of the enzyme. “Boil it,” said my father. The activity remained and was even slightly increased. Moreover, inorganic sodium selenite (and even more so, seleno-cysteine) exhibited catalytic activity. When seleno-cysteine was incorporated into the protein, this activity was enhanced many thousand fold. We proposed a reaction mechanism based on the catalytic properties of selenium in distinct oxidation states. We also found a polymorphism of erythrocyte glutathione peroxidase activity in members of my own family, and an electrophoretic polymorphism in others. I began to think as a biochemist, and to some extent, also as a geneticist, but only in a rather elementary way at that stage.  My father as a role model The foregoing vignette tells something of how my father influenced me. I was thrilled when he received the Gairdner Award, and when he was elected to the National Academy of Sciences, both of which occurred during my teenage years. Indeed, I sought to emulate him and took his advice seriously. When he suggested I read “Arrowsmith” by [Sinclair Lewis](https://www.nobelprize.org/prizes/literature/1930/lewis/facts/), and “The Microbe Hunters” by Paul de Kruif, I did so, and just as they had earlier affected him, they also affected me. Among the most important pieces of advice he gave me was to go to medical school. The explanation he gave was that disease often reveals new and important biological principles; also, as a physician in training, one acquires broad knowledge of anatomy, physiology, histology, pathology, and pharmacology: sciences that come into play in understanding many biological phenomena. Throughout his life, my father was an advocate of working on “something important,” rather than what he saw as esoteric topics. Generally speaking, he preferred authentic clinical research (with patients) to research with mice, and research with mice to research with flies or other distant model organisms. Notwithstanding his strong genetic and evolutionary orientation (which we shared), he tended more toward applied research than I myself did. And his judgment as to what was important rested chiefly on his medical experience, which was quite extensive.  With a strong focus and a sense of mission, I completed high school early (at the age of 16) and enrolled at the University of California at San Diego (UCSD), in Revelle College. I had taken certain examinations that gave me “advanced placement” credit, and I pursued an ambitious schedule in college. I worked through two summers, and graduated at the age of 18. I was a good student, but not an outstanding one. As a teenager and even for some years beyond, I was a bit emotionally volatile, often distracted by love interests, and generally speaking, in too much of a hurry. I took on an enormous course load, wishing to get through college quickly, go on to medical school, and become a scientist. It was an exciting time in biology, after all, with extraordinary advances in molecular cloning beginning to dawn. I was aware of what was going on, and impatient to be part of it. To my friend high school friend David Brittan (also my roommate for a time in college), I remember saying with frustration “The train of science is leaving without me.”  But despite the hurry, I did learn a lot, and only realized how much later on. I had a truly stellar introduction to genetics in the laboratory of Dan Lindsley (Figure 3a), a distinguished Drosophila geneticist interested in spermatogenesis and spermiogenesis in the fly, among other topics. In his lab, I attempted to map the gene for hexosaminidase (a project inspired by my father, who had studied this enzyme in humans, where hexosaminidase deficiency causes Tay-Sachs disease). When I was 18, I spent the summer working in the lab of Abraham Braude, most immediately with his postdoctoral fellow Arthur Friedlander (who later became well known for his studies of anthrax lethal factor). In Braude’s lab, I first heard the word “endotoxin,” also known as lipopolysaccharide, or LPS. I understood it was pyrogenic, capable of activating leukocytes, and also heat stable (which made it a particular problem in our studies of chemotaxis). All glassware had to be heated to 180°C to destroy contaminating LPS. I also knew that Braude had tried to passively immunize humans against LPS to protect them against Gram-negative septic shock. But my interest in LPS was casual and tangential at that stage, probably because its biomedical importance was still an abstraction to me. I had never seen a patient with sepsis, and didn’t grasp what a serious clinical problem it might be. The question of an LPS receptor did not occur to me at that time. I did not remotely imagine that searching for it would form the core of my Nobel Prize-winning work two decades later.  After completing college, I had still more exposure to genetics in the lab of Susumu Ohno (Figure 3b), a friend and colleague of my father at City of Hope Medical Center. I worked with Ohno for about nine months, and spent still another summer with him during medical school. A famous mammalian geneticist, Ohno had demonstrated that the Barr body observed in cells of female mammals was a condensed X chromosome. He had also developed the thesis that evolution depends upon gene duplication. He had written extensively on the phylogeny and origin of sex chromosomes. And he had observed that the genetic content of the X chromosome tends to be strongly conserved in all mammalian species. In short, he was a remarkable theoretical biologist at a time when experimental tools were not nearly what they are today.  Ohno inclined toward immunology after spending a sabbatical at the Basel Institute for Immunology. He hypothesized that major histocompatibility antigens act to anchor organogenesis-directing proteins. He adduced considerable experimental evidence supporting this hypothesis … which we know today was entirely incorrect! The time I spent in Ohno’s lab, working on this very subject, was quite enlightening for me from many points of view. In hindsight, perhaps the most important – if brutal – lesson was that even extremely intelligent scientists can deceive themselves if they embrace hypotheses too passionately. But I also learned much about immunology as it was understood in the mid-1970s.  I applied to several medical schools, confident that I would be admitted to most of them. I had good grades, extensive experience in laboratory research, several publications (including one first-author paper in Cell), and MCAT scores in the top percentile. But in the end, I was admitted to only one medical school: the University of Chicago. All others declined my application, perhaps because I was so young, and perhaps because I was unreservedly interested in science rather than clinical medicine. So I must be grateful to the University of Chicago for the chance it gave me. Luckily, it was (and remains) an outstanding institution. In the fall of 1977, I moved to Chicago and began my studies there at the age of 19, the youngest member of a class with more than 100 students.  Medical school My first impression of Chicago was that it was a “real” city compared to the southern California suburbs I had known. But it was also somewhat dangerous (where I lived, at least), and comparatively unwelcoming. The Chicago winter was something for which I was not prepared. I arrived dressed as a Californian, and nearly froze when I tried to walk the mile from the University to my apartment during the first winter storm, in high winds and sub-zero temperatures. As I remember, my ears were insensate for about an hour, and I initially feared they would become gangrenous and fall off! I recall the first years as quite challenging. Anatomy and neuroanatomy were especially tough, requiring spatial memorization of a type that was unfamiliar to me, but in the end, both classes were rewarding. My classmates were for the most part smart and competitive, and I had to struggle to do well. I particularly enjoyed histology, physiology, and microbiology classes.  When it came to my introduction to clinical medicine, the work was more demanding than any I had ever known. Ultimately this was beneficial, because I came to expect equivalent discipline of myself and others when I worked in the laboratory. But I did not get the same joy out of clinical work that I did from laboratory work. I was often uncertain as to whether particular therapies and practices had a sound rational basis, and when patients got better, I did not always feel I could claim credit for it. After all, there was no control group. And very rightly, there was no leeway for experimentation on the wards. I did manage to work for some months in the laboratories of Patricia Spear, an outstanding young herpes virologist, and Barry Arnason, a neurologist with a strong interest in multiple sclerosis. But overall, there was little time for research, and I began to miss the lab.  In 1980, when I was 22, I married Barbara (Barbie) Lanzl, then a dental student at nearby University of Illinois. She was three years older than I, and had previously been married to my friend and medical school classmate Jiri Sonek. The marriage lasted 8 years, with phases in Chicago, Dallas, New York, and Dallas again, before ending in divorce. We had three bright, healthy sons, two born in Dallas and one in New York.  Internship and residency I graduated from the University of Chicago in 1981, and again acting according to my father’s advice, decided to spend at least a year or two in residency, learning more about clinical medicine. I was matched with the internal medicine internship program and the neurology residency program at UT Southwestern Medical Center in Dallas. Dallas was my top choice, and arguably offered the finest clinical training in the country. It was known for giving interns and residents considerable responsibility and autonomy. During the year of my internship, for example, two interns and one resident would run the internal medicine emergency room alone through the night, with no attending physician present. And when necessary, medicine interns were expected to perform fairly invasive procedures, including intubation, placement of subclavian lines, cardiocentesis, insertion of chest tubes: in short, whatever was required, particularly during emergencies (which were not uncommon).  My father’s twofold rationale in suggesting an internship and residency rather than a laboratory fellowship had been that I would become “a finished doctor;” also that I would have something to fall back on in the event that research did not pan out for me.  As to the first point, I believe he was correct. At least the year I spent in internal medicine internship taught me many things I hadn’t known as a senior medical student. By the time I had finished, I feared no medical emergency; I felt secure in doing whatever needed to be done. But I also knew that medicine was not for me. I badly missed research and longed to return to it. I felt obligated to finish at least one year of neurology residency and did so. I learned quite a bit about neurology, which sometimes helps me to the present day in assessing mutations in mice. But perhaps the residency year gave me a bit more clinical training than I ever wanted.  As to the second point, my father was certainly being prudent. But to my recollection, I was supremely confident of success in science. I felt that no matter which lab I joined, and no matter what project I undertook, I would prevail, given the interconnectedness of biological processes, and my overall knowledge about how they worked. I was dead certain of my skills. I had a “feeling” for proteins and how to isolate them. I had a solid grounding in genetics and in immunology. And, true to my father’s earlier advice, medicine had taught me much about how an organism functions: far more than I would have learned had I gone to graduate school. Perhaps I was brash, but in recalling my mental state at the time, I would say I was imbued with the enthusiasm of youth, and felt invincible  Rockefeller University and an early success I was 25 years old when, on the evening of July 4, 1983, Barbie and I arrived in New York City together with our infant son Danny, who had been born in Dallas. I remained in New York for three years, and during the second year, our second son Elliot was born. Most of the time, the four of us lived on the 11th floor of a high-rise apartment building across the street from the Rockefeller University campus, with a nice view of the East River.  I had joined the Cerami laboratory at Rockefeller. There I began to work on cachectin, an unidentified factor expressed by macrophages in response to activation by LPS, and defined by its ability to suppress lipoprotein lipase synthesis in adipocytes. The prevailing hypothesis in the laboratory at that time was that cachectin was responsible for wasting in chronic diseases such as tuberculosis, trypanosomiasis, and cancer. From the start, I was skeptical about the idea that a single factor could explain all cachexia, given the diversity of inciting causes. At least, there was no strong reason to think so. But I did see early on that a single factor responsible for suppression of lipoprotein lipase in fat cells was secreted by LPS-activated macrophages. Moreover, I saw that this factor was a protein, and I felt it could be purified.  At the time I started work in the lab, no progress at all had been made in isolating cachectin. Cachectin activity had been ascribed by my predecessors to a protein with a molecular weight of 70 kilodaltons (almost surely contaminating serum albumin). Moreover, they had purportedly excluded tumor necrosis factor (TNF ) as a candidate mediator by exchanging material with the laboratory of Lloyd Old, who had discovered TNF and was then still trying to isolate it. They had erred in reaching this conclusion.  Within a year, I purified cachectin to homogeneity, raised an antibody against it, and affinity purified the antibody. I hypothesized that whatever role cachectin might have in cachexia, it was likely involved in endotoxic shock, as it was produced in large amounts when macrophages were activated by LPS, constituting about 2% of their secretory product. Moreover, I found that purified cachectin was capable of killing mice when as little as 20 micrograms was administered by an intravenous route. One evening, I passively immunized 5 mice against cachectin, and gave pre-immune globulin to 5 control animals. I had formally randomized the mice to the two treatment groups, and I waited for several hours to give the antibody time to distribute through all extracellular fluid compartments. I then challenged the animals with a carefully chosen dose of LPS: a low LD100. To my delight, I found the next morning that passive immunization protected all 5 recipients against LPS-induced death, while all 5 control mice had succumbed! I repeated the experiment many times and with many permutations, using hundreds of mice, and found the result to be robust and reproducible. I was thrilled because I knew I had isolated one of the key endogenous factors mediating the lethal effect of LPS. The inflammatory properties of cachectin, rather than an ability to induce wasting, proved to be immensely important.  Several months passed before I could determine the N-terminal sequence of cachectin, as my initial purification strategy left the protein N-terminally blocked. I needed to repurify it using an entirely different procedure. Eventually, 17 residues were called by Edman degradation. Initially, I believed cachectin was a novel protein. Its sequence did not appear in the rudimentary protein databases that existed at that time. However, I was soon alerted by the Ulevitch group at Scripps that my purified cachectin, sent to them for separate purposes, had high tumor necrosis factor activity. I directly compared the sequence of human TNF, only recently isolated and cloned at Genentech, to the sequence of mouse cachectin. I saw strong homology. Cachectin was the mouse orthologue of human TNF.  This worked to my advantage, perhaps, in that there was already great interest in TNF as an anti-neoplastic protein. Yet I had then shown that the protein also had toxic, inflammatory properties. In time, TNF became one of the most studied proteins in biomedicine, and attempts to block its activity with antibodies (or with recombinant proteins such as my group later developed) bore more fruit than attempts to administer it.  During my three years at Rockefeller, I published many papers, including several in high-ranking journals, and made a substantial name for myself in the rapidly developing cytokine field. Soon, many thousands of other publications cited my work. I obtained my own funding and was promoted to the rank of Assistant Professor at Rockefeller in 1985, but this post did not carry true autonomy. I wanted a lab of my own. When I was invited by Joe Sambrook to join the Howard Hughes Medical Institute (HHMI) at UT Southwestern Medical Center, I eagerly left New York to forge my own future.  Dallas and the Lps locus Returning to Dallas in 1986, one of my first and best decisions was to hire Betsy Layton as my secretary. She was 19 years old at the time, and had just moved to Dallas from her native Pennsylvania, attracted by the image of Texas and by opportunities for work. When I interviewed her, she struck me first of all as nice, cheerful, smart, and friendly; also as someone who had a strong will to work and to do a good job. I was right on all of these calls. Meeting Betsy was one of the luckiest things that ever happened to me, because she was truly devoted to me over the many years that followed. She helped me to set up my lab, offered advice with appropriate tact and candor, and became a true partner in my professional life. In time, she became an administrative assistant; then an administrative manager. She accompanied me from Dallas to Scripps, and then back to Dallas, where she still works with me today. I hope this will always be the case. In the end, choosing outstanding people and guiding their work well becomes far more important than the work a biologist does with his own hands.  When I first settled in Dallas, I began to pursue several topics related to TNF. The most practical of these was to develop a means of blocking TNF activity in vivo. I engaged with this challenge partly because I knew that it would be useful to do so both in chronic inflammation and in septic shock, and partly because I wished, in the “pre-knockout” era, to see what a chronically TNF-deficient animal would be like. David Crawford, an MD/PhD student, and Karsten Peppel, a postdoc in my lab, developed a chimeric molecule in which the ectodomain of one of the TNF receptors was fused to part of an IgG heavy chain, including the hinge and Fc region. As we had hoped, this yielded a non-antigenic, stable, and extremely potent neutralizing reagent that could be administered to mice (or humans) to block TNF activity in vivo for long periods of time. We patented this protein, and eventually sold the patent to Immunex, which in turn was acquired by Amgen. Today, the molecule we invented is marketed as the drug Enbrel, and is used as an effective treatment for rheumatoid arthritis and several other inflammatory diseases.  On a more basic level, I focused my laboratory on the question of how TNF biosynthesis might be regulated. I viewed this as tantamount to the question of how the inflammatory response might be regulated as a whole, in that it was already apparent to me that TNF was an excellent marker of the inflammatory response. I had earlier shown, for example, that anti-inflammatory drugs such as glucocorticosteroids could entirely abolish TNF biosynthesis in response to LPS, and felt that this explained a large part of their inflammatory effect. I deduced that TNF biosynthesis was regulated both at transcriptional and translational levels. TNF gene transcription was dependent upon NF-ƙB, a factor soon seen to induce many cytokine genes. Translational repression depended upon a sequence my colleague Daniel Caput and I had discovered in the 3′-untranslated region of the TNF mRNA, consisting of overlapping and interleaved octamers with the sequence UUAUUUAU. A similar sequence, I had noted, was found in many cytokine encoding mRNAs. Activation of the macrophage by LPS overcame translational repression. Both Véronique Kruys and Jiahuai Han in my lab closely studied these phenomena, but we did not succeed in elucidating the biochemical details of translational regulation during those years.  The more central question as to how macrophages became activated by LPS remained elusive. At the core of the question was the issue of the LPS receptor. TNF was made in large amounts in response to LPS. Hence, I was inquiring into LPS signaling when I attempted to measure responses of the TNF gene and mRNA. Yet there was no understanding as to how LPS was perceived by cells in the first place. And long before most others in the innate immunity field, I regarded the question as one of the most fundamental and important in all of immunology.  After all, since microbes had been identified as the causative agents of infectious diseases in the mid-1800s by Pasteur and [Koch](https://www.nobelprize.org/prizes/medicine/1905/koch/facts/), nobody had determined which receptors recognize their presence during infection. This was the first level of self/non-self discrimination by the immune system. LPS mimicked infection in all its complexity quite closely, and potentially, the LPS receptor might be responsible for all events that transpired during a real infection. In finding the LPS receptor, we could hope to know at least one key sensor used by the innate immune system to recognize microbes. Perhaps it might be a member of a receptor family; perhaps we would gain insight into how all microbes were detected within the first minutes following inoculation.  I was aware of two strains of mice that were specifically refractory to LPS, because of mutations affecting the so-called Lps locus. These were the C3H/ HeJ and C57BL/10ScCr strains. For each, a closely related strain (C3H/ HeN and C57BL/10ScSn, respectively) served as a control with normal LPS responses. And mice of both strains were known to be susceptible to Gramnegative infections. In my mind, these mutations abrogating LPS responses grew constantly in stature. What protein did they affect? Was it indeed the LPS receptor?  Positionally cloning the LPS locus was beyond my capabilities during the 1980s. I had isolated TNF in a lab in which molecular cloning had never been practiced, and I had to teach myself almost everything in the way of basic molecular biology methods. I understood what needed to be done, but did not at that time feel secure in tackling such an immense problem. I tried instead to look for a difference between control mice and mutants at the protein level. And I attempted to raise an antibody against the proteins of a WT mouse in a resistant animal (or vice versa) to discover a “missing” or altered protein in mutants. I also tried to use expression cDNA cloning to find a gene product that could rescue the LPS-resistant phenotype. We tried, too, to use insertional mutagenesis (with a retrovirus) to inactivate the LPS locus in heterozygous mice made by crossing C3H/HeN animals to C3H/ HeJ animals. But as all of these approaches to finding the LPS receptor were unsuccessful, I began to think positional cloning might be the only way to go.  I began to pursue this strategy actively in 1993, when Christophe Van Huffel came to my laboratory from Belgium to work as a postdoctoral associate. He had a background in yeast genetics, which made me think he would be a good person to isolate the YA C clones we would need to build a contig across the critical region. We began mapping the mutation in C3H/ HeJ mice to high resolution, ultimately including a total of 2093 mice in our meiotic analyses. We became stronger in our molecular skills, and gradually, more people were incorporated into the effort, until the entire lab had a single focus. Among these were Alexander Poltorak and Irina Smirnova, who worked devotedly and tirelessly to find the mutation, year after year. They were exceptionally able colleagues. Betsy too joined the effort, and helped to read sequence, organize data, pick colonies for sequencing. Alexander, Irina, and Betsy were as zealous as I was; they simply refused to give up.  I have not directly mentioned it to this point, but I tend to be an obsessive person in many ways. I am even somewhat proud of this, although in some circumstances it has brought me considerable suffering without tangible rewards. Finding the mutations that abolished LPS responses became one of the most gripping obsessions of my life. For years, it occupied much of my waking consciousness and sometimes my dreams as well. Once, in 1997, while staying in a hotel in the San Bernardino Mountains, I awoke from a dream in which I was sure I had come to understand what gene was affected by the mutation. I hastily wrote the name of the affected protein on a scrap of paper and happily returned to sleep. In the morning, I saw that the protein was complete nonsense; it did not exist (though from the suffix “ase,” I could tell it must have been an enzyme)!  Positional cloning of the LPS locus was the toughest challenge I had ever faced for three reasons. First, the critical region was gigantic: by far the largest ever tackled in the mouse. 24 BAC clones and one YA C clone were needed to span it, and even then there was a small gap we never closed. We know today that the genomic interval was at least 5.6 million base pairs in size. To have such a region within which crossover was apparently forbidden was simply bad luck, and at that, we needed to explore about 90% of it before we found the mutation. Second, we had limited sequencing power. We began sequencing with radionuclides (mostly 35S), loading gels by hand, drying them, and reading sequence ladders on X-ray film. Later we used slab gels with semi-automated fluorescence-based reading of sequence. But we never had capillary sequencers at our disposal. This made it difficult for us to examine the region for genes. Third, the methods used at the time to find genes were primitive. We began with exon trapping and hybridization selection. Only by the mid-1990s were complex expressed sequence tag (EST) databases available. Matches between genomic DNA in our interval of interest were sought in the EST databases using an algorithm called BLAST. And BLAST searching became a major chore, because we had insufficient local computing power. I taught myself to program in Perl in order to manage the many thousands of sequence files, and the output BLAST data in a semi-automated way. For years, no meaningful hits emerged. There were only hits derived from pseudogenes, which nonetheless had to be cloned, sequenced in full, and run to ground, so that we might be sure we could find no mutation distinguishing C3H/HeJ from the control strain C3H/HeN.  Pressures, criticism, and anxiety Both personal and professional pressures weighed heavily on me during the years of the LPS cloning project. My youngest son, Jonathan, was born in 1987, and Barbara and I separated in 1988. The divorce proceedings were contentious, and went on for years, involving innumerable depositions, preliminary hearings, and a jury trial, ultimately leading to a joint custody order. Of course, life did not immediately normalize thereafter. Particularly during their teenage years, my sons were each difficult to manage. I am happy to say that all three are extremely close to me today. It was a special joy to bring Danny and Elliot to Stockholm for the Nobel Prize ceremony (unfortunately, Jonathan was unable to attend). But in the mid-1990s, there was a lot of stress, and tough times at home coincided with the toughest phase of the cloning work.  While the importance of finding the LPS mutations was obvious to me, it was less obvious to other people. Years elapsed with no publications to show, and some of my colleagues thought that we did not entirely know what we were doing; some believed that the gene might, in the end, not be particularly illuminating; all believed that we were taking a terrible risk. Among these was my father, who urged me to diversify my portfolio and not to “put all your eggs in one basket.” I ignored his advice on this occasion; I simply couldn’t abandon or in any way diminish the intense focus on the LPS locus, because I knew we wouldn’t find the mutations if I did. In hindsight, I am sure I was correct about this.  At least two other groups were attempting to find the same gene. One was the group of Danielle Malo, in Montreal; another was the group of David Schwartz in Iowa. I worried in particular about Malo’s effort, because she and her close colleagues had an impressive record in positional cloning. At one point, I offered to collaborate with her, but the offer was declined, which meant we were formally in a state of competition.  HHMI was increasingly impatient with me. Over the 14 years I worked as an HHMI investigator, my program was reviewed by the Medical Advisory Board five times. After our final review, in April of 1998, I was told I would be funded through August of 2000, but not beyond. This was disappointing, since we had indeed made progress, and I felt that success was imminent. But their indulgence was at an end.  I felt we must continue come what might, and we did so, though some of the postdoctoral fellows in my group, Christophe Van Huffel, Mu-Ya Liu, and Xiaolong He, left to find other laboratories, as did some of the technicians, who also sensed impending defeat. Hence, it was an anxious time. Most of the critical region had been explored in depth. Surely we would find the gene soon. Or else, perhaps, we had made a mapping error and were looking at the wrong part of the chromosome. Were we on the cusp of success? Or had I been a fool to reject wise counsel, and would our efforts end with nothing to show for them?  Success The gene we had struggled with for five years was discovered very suddenly one night: on the 5th of September, 1998. I was reviewing the day’s BLAST results as they returned from NCBI and from our own server where we had begun to run BLAST locally. I was shocked by what I saw, as there had been a long dry spell, and here was one … then two … matches with a real gene: Tlr4. Almost certainly it was not a pseudogene based on the quality of the hit. That in itself encouraged me to think that this was the “holy grail” we had been seeking: here was an authentic gene, and only a small amount of genetic material that remained unexplored. Moreover, a good story could immediately be made about the candidate. It appeared to be a cell surface receptor with a single membrane spanning domain. The ectodomain was rich in leucine, which might be expected to bind hydrophobic molecules like the acyl chains of LPS, and was similar in overall structure to CD14, earlier shown to be required for sensing LPS molecules. It was a member of a family of proteins related to Toll, which in Drosophila was known to have both an immune and a developmental function. And on the cytoplasmic side, it was similar to the IL-1 receptor, well known to deliver an inflammatory signal.  I related these facts breathlessly to my father (who was somewhat nonplussed, I must say), and to Alexander and Ira, who were very much more excited, sensing as I did that our battle might be nearing an end. But we would not be on firm ground until we were able to find a mutation distinguishing the C3H/HeJ strain Tlr4 from the C3H/HeN strain Tlr4, and the C57BL/10ScCr strain Tlr4 from the C57BL/10ScSn strain Tlr4.  The very next day, we attempted to amplify the cDNA in all these strains by long-range PCR. Alexander succeeded in so doing using cDNA from the C3H/HeJ, C3H/HeN, and C57BL/10ScSn strains, but failed to do so using cDNA from the C57BL/10ScCr strain. We therefore concentrated first on the C3H/HeJ and C3H/HeN sequences, which Alexander established by shotgun sequencing. Within days, we saw the mutation for the first time: it was a single base pair change predicting the substitution of a conserved proline for a histidine in the cytoplasmic domain of the molecule. We later established that the gene was deleted in the C57BL/10ScCr strain. And this eliminated any remaining doubt that TLR4 was essential for LPS signaling.  I called James Gavin, my HHMI liaison, to tell him what we had done. In reply, he made no comment on our findings, but emphasized that the decision of HHMI was irrevocable. For my own part, I was so elated that we had made a truly great discovery that the blow was much softened. We submitted our work to Science, where it was promptly accepted for publication, and meanwhile, presented it at four international meetings, where it was received with acclaim (Figure 4). By now it has been cited over 4,000 times: more than any other paper in the innate immunity field.  Most exciting of all, perhaps, was the fact that the LPS receptor was indeed part of a protein family, and it could easily be imagined that other TLRs detected other molecules of microbial origin. In time, this proved to be the case. And in due course, we were able to show that TLR4 did in fact engage LPS in order to detect it. That is, TLR4 did not act as a signaling intermediate as its Drosophila homologue did, but as the receptor per se. We had opened a window into how mammals perceive microbes, and a great many laboratories began to study the question of how TLRs signal to initiate the inflammatory response, and how they might be involved in the pathogenesis of sterile inflammatory diseases.  La Jolla (2000–2011) and ENU mutagenesis In 2000, I relocated my laboratory from UT Southwestern to The Scripps Research Institute (TSRI). Eager to dissect innate immunity in mammals, I invested heavily in ENU mutagenesis as a means of creating new and interesting phenotypes in the mouse. The plan was to create many exceptions to the norm using a random process, thus acquiring fresh paradigms of importance equal to the C3H/HeJ and C57BL/10ScCr mice (which bore spontaneous mutations, and taught us so much about microbe sensing). In this way, I felt, we could take innate immunity apart gene by gene, finding all the parts of an enormous puzzle, and do so without hypotheses and their attendant biases.  I chose the classical genetic route because I knew the mouse genome would soon be sequenced and annotated; hence positional cloning would become much easier. All candidates would be known within all critical regions, and only mapping would be required to exclude most genes from consideration. Never again would it be necessary to build a contig and explore it for genes: the two toughest parts of positional cloning. Moreover, sequencing candidate genes was becoming progressively easier. Capillary sequencing was replacing the slab gels, and there was great potential for automation. In time, I foresaw, entire genomes might be sequenced all at once. The main burden would be to generate phenotype for study: in our case, immunological phenotype.  But until sequencing technology had advanced further, the crucial point was to cover critical regions quickly and efficiently. Toward this goal, Yu Xia, an exceptionally skillful programmer in my group, wrote software that would analyze genes within a specific genomic interval, mask the sequence to hide common repeats, and design optimized primers for amplification and sequencing. He also wrote code that would permit mutation identification: a human observer no longer needed to search through trace files to find them. This was a system that no other laboratory possessed, and using it, we were able to positionally clone as many as 50 mutations per year (as compared to one mutation in five years only a decade earlier).  As “next generation” sequencing became a reality, we modified Yu’s system to validate mutations identified within the whole mouse genome. At last, only the most cursory mapping was required to define the location of a mutation, whereon it could then be found by machines that sequenced DNA a million times faster than we were able to sequence it in former times. This brings us to the present state of the art. My colleagues and I have found hundreds of mutations responsible for phenotype, many of them affecting immune function. Like all mechanists and reductionists, we regard the innate immune system as a highly complex machine. Surely we have far to go to understand its workings as we might understand those of a pocket watch. But just as surely, the innate immune system is a machine, and one day it will universally be seen as such.  Over the 13 years that elapsed between our discovery of the LPS receptor and the announcement of the Nobel Prize, I made a number of close friends in the innate immunity field. Shizuo Akira made enormous contributions, as he and his colleagues used reverse genetics to dissect the signaling pathways incorporating the receptors, adaptor proteins, kinases, and transcription factors that lead to activation of the inflammatory response. Jules Hoffmann, who with his colleagues had discovered the immunological role of Toll in the fruit fly, went forward to analyze the Drosophila imd pathway (evocative of the mammalian TNF signaling pathway, and used by the fly to detect Gramnegative bacteria) and the upstream proteins that activate Toll and imd signaling. Jules’ group, Shizuo’s group, and my own began to study antiviral defense in insects and mammals, collaborating in an open and congenial manner. I developed the highest respect for their scientific acumen and integrity. Jules and I, in particular, spent pleasant days together over the past decade hiking, discussing politics, and talking about history, science, and people.  I also developed strong friendships at Scripps, none stronger than with Argyrios (Ari) Theofilopoulos. Ari had worked for many years to understand autoimmunity, especially as represented in systemic lupus erythematosus (SLE). A part of the premise for searching for the LPS receptor was the likelihood that it might ultimately explain sterile inflammation. In fact, TLR7 (and conceivably other TLRs as well) turned out to have an essential facilitating role in SLE, at least as modeled in the mouse. Ari and I had numerous discussions about this, and collaborated quite extensively on studies of autoimmunity using TLR mutants and other mutants generated using ENU mutagenesis.  In time, our work in the innate immunity field was recognized by some major prizes: first the Robert Koch Prize (2004), then the Gran Prix Charles Leopold Mayer (2006), the William B. Coley Award (2006), the Balzan Prize (2007), the Albany Prize (2009), the Will Rogers Institute Prize (2009), the Shaw Prize (2011), and others in between. In 2008, I was elected both to the National Academy of Sciences and to the Institute of Medicine. Each of these distinctions was an occasion to celebrate, often with family, friends and colleagues in attendance (Figure 5). I was happy that my father was alive to mark most of these milestones with me. But to the sorrow of all my family, he passed away in October of 2008, after a year-long battle with mantle cell lymphoma.  The present, the future, and advice to others who may follow me By March of 2011, I had decided to return to Dallas, and I had a dual appointment at Scripps and at UT Southwestern on October 3 of that year. By the time the Prize was awarded in December, I had completed my relocation. I have begun to build a Center for the Genetics of Host Defense, in which faculty with a forward genetic orientation, working with diverse model organisms, can join together to study the protective mechanisms that have developed to combat infection. They may also study autoimmune and autoinflammatory diseases: the destructive legacies of immunity, which was itself imposed on us by the enormous selective pressure that infections represent.  I must admit that many questions in biology appeal to me, and at times, it is difficult to maintain an intense focus on the immune system, important though immunity is. The great epiphany for me in solving a single, critical question – the conundrum of LPS sensing – was the embrace of genetics. This is a golden age of genetics, in which one may find the cause of monogenic phenotype almost immediately. The destruction of all genes in the mouse by chemical and/or insertional mutagenesis and gene targeting will soon be a reality. At this writing, the ability to clone mice from somatic cells, and the availability of haploid embryonic stem cells for genetic experimentation, also promise to accelerate progress in biology. When I first began working in my father’s laboratory, none of these technologies were foreseen by anyone then alive. It is fair to say that mankind’s understanding of living things has advanced more during the past 50 years than it did during all of history before. I have been a direct witness to most of this progress. So have many others who are older than I, and have been practicing scientists for a longer time. This is to say that we live in an exciting era, and should feel lucky about it.  The Nobel Prize gives an opportunity for introspection, and to conclude this brief autobiography, I offer some thoughts that arose in my mind during the last few months, mostly prompted by specific questions from students, journalists, family and colleagues. “To what do you attribute your success?” they want to know. “How does one win a Nobel Prize?”  In my case, the path to the Nobel Prize began with a love of nature and an earnest curiosity about the phenomenon of life. I was lucky to have an understanding father, who was himself a distinguished scientist. He gave me excellent advice during my formative years. But this might have helped little had I not been industrious, enthusiastic, and optimistic in pursuing a career in biology. I did not worry or make contingency plans to be used in the event of failure; I ran blithely ahead with confidence that success would come to me.  I chose an undervalued question, viewing the mystery of the LPS response as the key to understanding inflammation and the recognition of microbes – and I based this assumption on a strong and well-studied phenotype. While the LPS receptor did not turn out to explain everything about how inflammation works, it did give major insights. The choice of a question is a matter of scientific taste; a matter of recognizing what is interesting and important. Such taste is partly innate and partly learned. To the extent that I learned scientific taste, I did so by studying medicine.  Much later than I might have, I embraced genetics, preferring its unbiased character to hypotheses, which often lead scientists astray, mainly because they don’t like to be wrong. I do not eschew hypotheses. But not all scientists have the integrity to test them as they should be tested. Only the very best scientists do. The others try to “prove” their hypotheses. And this unfortunate fact is the cause of much error, wasted time, and wasted resources.  I have also learned that it is important to choose outstanding colleagues. Not only those who will frankly criticize one’s work or provide fresh insight, but also those with whom one works directly, as a mentor or supervisor. Recognizing talent, acquiring it, nurturing it, and retaining it is among the hardest things a scientist must do. It is a skill quite separate from scientific ability per se. It will usually determine whether the scientist succeeds, because none of us can accomplish much in isolation.  Finally, and maybe most important of all, my principal achievements resulted from addressing a single problem with relentless obsession. Once convinced that something could be achieved, I was not deterred by discouraging advice from others. I would suggest the same course to anyone. In the event of failure, one may always select another problem and begin anew. That is what I would have done had I failed. As it happened, it was unnecessary. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0531=BB  [Bruce Beutler] This is Bruce Beutler.  [Adam Smith] Oh, hello. Professor Beutler, this is Adam Smith calling from Nobelprize.org, the official website of the Nobel Prize, in Stockholm.  [BB] Oh, hello. How are you?  [AS] Hello, I’m delighted to hear your voice. First of all, congratulations on the award of the Nobel Prize.  [BB] Thank you very much.  [AS] We have a tradition here at Nobelprize.org of recording very brief telephone interviews with new Laureates. Would you be able to speak for just a few minutes?  [BB] Yes, I can. You probably hear beeping in the background because someone else is trying to call me. That might be a problem. I’m all alone with my cell phone. But go ahead.  [AS] I’m sorry, you’re probably being bombarded by press from every side. I gather I’m catching you in California, although you’ve actually moved your affiliation to Texas now.  [BB] That’s right. I’m in the middle of moving to UT Southwestern, which is where I did the work, that I’m being feted for right now, back in the nineties.  [AS] Oh, well, I’m sorry to catch you on the hop. What were you actually doing when you received the news, and how did you receive the news?  [BB] I was in bed. I happened to wake up in the middle of the night. I looked over at my cell phone and I noticed that I had a new email message. And, I squinted at it and I saw that the title line was ‘Nobel Prize’, so I thought I should give close attention to that. And, I opened it and it was from Göran Hansson, and it said that I had won the Nobel Prize, and so I was thrilled. And, I was a little disbelieving and I went downstairs and looked at my laptop, and I couldn’t get into the Nobel site for quite a while because it was all packed. So, I went to google news and in a few minutes I saw my name there and so I knew it was real.  [Both laugh]  [AS] You’ve been the recipient of quite a few prizes in the recent past. You must be getting used to it. And you must have had, I guess, some suspicion that this was on the way?  [BB] Well, one always hopes. But, one never knows. And, that’s kind of a special attribute of the Nobel Prize, that it’s done with such secrecy and, of course, I was absolutely delighted.  [AS] I can well imagine. You’ve been awarded half the prize, together with Jules Hoffmann, for your discovery that in his case Toll, and your case the Toll-like receptors were the eyes of the immune system – the sensors of innate immunity. Was it a great surprise to you that the immune system in flies and in mammals is so similar?  [BB] At the time, yes. Of course, we know that some things go very far back and are preserved even to the Cambrian times. And, nonetheless, it still was a surprise to me at the time that everything was so similar in the fly as in the mammal. When we made our discovery, which was a couple years after Jules made his, I had only a very dim awareness of the situation in flies. I didn’t really know him at that time. And, my first contact with him, on reading the bit about the namesake of the family, was to telephone him and ask for the picture that he and his colleagues had used on the cover of *Cell*, when they showed a fly was overwhelmed with fungal infection if it had mutation in Toll. Because it made perfect sense that in the mouse the same sort of situation applied and there was overwhelming gram-negative sepsis if you had a mutation in Toll-like receptor 4 (TLR4). So, I saw right away the parallelism. But, yes, it was a surprise.  [AS] And, the press release cites just your 1998 paper in *Science*, in which you revealed that Toll-like receptors were behaving in this way. But that was really the culmination of research that had begun long before – perhaps back in 1985, when you had first identified tumour necrosis factor as an inflammatory protein.  [BB] Yes, that’s correct. Yes, certainly that started me on a pathway toward finding the Toll-like receptor and I realized quite early on, as you’ve alluded, that TNF was one of the major executors of endotoxic shock. And, it was strongly induced by LPS, and therefore we always took it as a marker of the LPS response. It was the endpoint that we followed, just as Professor Hoffmann followed the production of antimicrobial peptides. It took a very long time to find the Toll-like receptor for a molecule because we didn’t use a genetic approach for quite a while. We used conventional approaches: cross-immunizing mutant mice with wild type mice and looking proteomically as it stood in those days to try to find a difference between the two strains. And all of that was fruitless. It took a very long time before we were able to start positionally cloning.  [AS] Sometimes the fruits of one’s labours look as if it’s just been a straightforward and rather rapid discovery. But, actually, there’s a lot of work that lies before it.  [BB] Certainly true in this case.  [AS] And, this was basic research, increasing our understanding of how the immune system works. But, of course, there are now applications, hoped for at least, from the understanding that we gained of innate immunity. What do you think are the most hopeful?  [BB] I think that the most hopeful lie in the realm of inflammatory and auto-immune disease because I believe now, as I believed long ago, that inflammation is something that evolved to cope with infection. And when we speak of sterile inflammatory diseases, like rheumatoid arthritis, and autoimmune diseases like lupus, probably some of the same pathways are utilized. And, it may very well be that by blocking TLR signalling we’ll have very specific therapies for those kinds of diseases.  [AS] In some ways your discoveries and those of Jules Hoffmann reignited interest in the innate immune system. Is that true, that it had sort of lain a little bit dormant before you reinvigorated the field with these discoveries?  [BB] Yes. I’d be careful to say that we only reinvigorated it. It’s not as though we discovered it or initiated the field! Because, of course, clinicians had known for a very long time that if patients are neutropenic – if they don’t have neutrophils – they’re at grave risk for infection of all kinds. And that’s nothing but innate immunity, of course. So, it shouldn’t have come as a surprise to anyone that innate immunity was important. But there weren’t the tools for understanding how the innate immune system detects infection, and I think that’s where we contributed.  [AS] Thank you. When you come to Stockholm in December to receive your Nobel Prize we will happily have the chance to speak at greater length about all this. But, I just wanted to ask in closing whether you’ve had time to think about how you might celebrate this in the midst of your move?  [BB] I’ve hardly had time to think about it, but I’ve had so many letters from friends and from people in my past, some of whom really are in the distant past, that it’s given me a warm glow. And, that’s kind of celebration in itself. And, I think there will be much more of that.  [AS] I’m sure there will. And I’m sure you’ll be claimed by both institutes: the one you’re leaving and the one you’re going to.  [BB] Well, perhaps so. That will be nice too, I suppose.  [AS] Anyway, again congratulations! Thank you for talking to us and I wish you …  [BB] Thank you, Adam.  [AS] I wish you all the best. Thank you.  [BB] I’ll look forward to seeing you. Bye bye. |
| Interview |  |
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| ID | 0532 |
| Biographical |  |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0532=JH  [Jules Hoffmann] Hello?  [Adam Smith] Hello, this is Adam Smith, from Stockholm.  [JH] Hello, Adam.  [AS] Hello. So, again, welcome back to France. And, you must have stepped from one media storm in China to another media storm here?  [JH] Sort of, yes!  [AS] You were in Shanghai on the day of the announcement. And, I gather the Committee failed to reach you, so how did you actually hear the news that you had been awarded the Nobel Prize?  [JH] Well, I heard it with a few hours of delay. Frankly, I did not expect it – I was not waiting for something like that to happen. So, I was I was in Shanghai proper; we were at the museum and then we had dinner with a Chinese friend. And then, when we wanted to go back to the hotel, there was enormous fireworks. They were celebrating – it was the holiday, the Chinese national holiday – they were celebrating, and then we were in the crowd and my friend got phone calls from the hotel saying that we should come back, but we were not clear about what it was! And they said journalists were there and wanted to see me. So, finally, we took the metro to get back because, with our car, the driver could not advance. And, so, we came to the hotel and there were journalists there from Reuters and others, and then they said, “Well, you’ve got the Nobel Prize.” And, I was still uncertain about with whom because I wanted to know what field it was given for.  [AS] Yes, of course.  [JH] And then when they said Bruce Beutler and Ralph M. Steinman, of course I knew that it was for innate immunity and then I started believing it!  [AS] Well how wonderful! So the fireworks were in part for you!  [Both laugh]  [JH] I don’t think so! But the Chinese were very nice. They were really … they were organizing a party and they did all they could. They were very happy about it!  [AS] How lovely, yes. What a nice place to be to hear the news. It’s been quite a year of prizes. Because you were in fact in China to receive the Shaw Prize, were you not?  [JH] Yes. The Shaw, that was the week before, yes. We were actually with Bruce Beutler. We shared it with Bruce Beutler and Ruslan Medzhitov  [AS] So, you must be getting quite used to all this media attention?  [JH] Well, I hope it’s going to calm down soon! But, yes, okay, I mean I have to stand up to it!  [AS] Are you somebody who enjoys the attention?  [JH] I mean, I wouldn’t downplay it now. I wouldn’t say that I *hate* people saying, “Well, it’s interesting what you did,” and so on. But, I don’t like it to be overplayed. And I don’t think – because we did, with my colleagues, some nice work on immunity – that I’m a competent person now to speak about everything in science and society. So, I try to avoid getting involved in that aspect.  [AS] Well, let’s turn to immunity then. You were awarded the Nobel Prize for your discovery that Toll was the sensor of innate immunity in the fly. What started you studying immunity in flies anyway?  [JH] Well, actually we started – it’s a long story – we started looking at antimicrobial defences in insects, initially in grasshoppers, in the sixties. And, the reason we did that was that I did my PhD in the laboratory which was working on grasshoppers, and grasshoppers were, at that time, still a very big plague in countries which were administered by the British and the French. And, so, our laboratory was doing endocrine studies, that is to say transplant endocrine tissues or organs from one insect to the next. And, they noted that it was never infection coming up – never opportunistic infection coming up – without any special care being taken to avoid microbes in the environment; there was no aseptic conditions.  So, actually, in the lab my thesis supervisor suggested that I take up the question of what helps the insects fight infections. And so that’s what, then, I did. And initially it was experimental biology with X-ray treatments and so on. And then we got from there, we got into the biochemistry of the effector molecules and then we discovered the antimicrobial peptides and so on. Then, finally, at a given moment in ninety or so, we decided with my colleagues – particularly Jean-Marc Reichhart and Charles Hetru here – we decided that we would go over to *Drosophila*. Also, no peptides had been identified yet. No effector molecules had been identified yet in flies. But we thought that we might be able to find something – we hoped we would be able to find something because we had, by that time, found in larger flies induction of antimicrobial peptides. And, so, we went ahead and then we went over to *Drosophila*, we hired in a *Drosophila* geneticist, Bruno Lemaitre and later Dominique Ferrandon, and the team then became both biochemistry, cell biology, molecular biology and molecular genetics and so on. Finally, at a given moment … Well, the way we came to Toll was through the work of [Nüsslein-Volhard](https://www.nobelprize.org/prizes/medicine/1995/nusslein-volhard/facts/) …  [AS] Of course, because she had identified it as a gene important in embryonic development, yes.  [JH] … Yes. And what she had seen is that this activates Dorsal – and Dorsal is an NF-kappaB family member. And, we found that there were sites … we found that there were, in the promoter sequences of the antimicrobial peptide genes, there were NF-kappaB binding sites, and then we could, through transgenesis experiments, we could demonstrate that those sites were mandatory, conducibility, and so, step by step, we worked up to … But initially it was not something obvious that Toll – Nüsslein-Volhard had described Toll as being a maternally expressed gene – and now here we’re working on adult flies, we were working on males, which there was no material effect involved. And so we first had to show that, really, the system was inducible in adult flies – adult males – and so on. And then this is what got us to find that this was an immune function for this cell receptor.  [AS] It very nicely illustrates the tremendous amount of background that lies behind a seemingly sort of singular discovery such as Toll’s role in innate immunity.  [JH] Yes.  [AS] When Bruce Beutler, two years later, showed that Toll-like receptors performed a very similar job in mammals, was it a great surprise to you that the systems were so similar?  [JH] Actually, Bruce got at it in a different way. Bruce had been working on TNF, you know, this..,  [AS] Yes. Tumor necrosis factor.  [JH] … inflammatory cytokine. And, TNF is induced in an NF-kappaB dependent manner by *lipopolysaccharide (LPS)*. That was known. But, the receptor for *lipopolysaccharide* was not known. And so he started out in the nineties to identify – to clone the LPS receptor. And eventually he had narrowed it down to some relatively short interval. At that time 60 genes was still a tremendous long stretch of DNA. And, in that stretch there was a Toll homologue. And so eventually what he found was that the LPS receptor, yeah, the receptor for *lipopolysaccharide* – *lipopolysaccharide* is responsible for the endotoxic shock, which is in a large part due to hypersecretion of TNF – so, Bruce Beutler found that this receptor was a Toll-like receptor, and then this made everything coherent.  Now, there still was a problem: which cells do react in the first line to LPS and those cells are in particular dendritic cells, which were found by were found by Ralph Steinman.  [AS] Yes, indeed, indeed. They act as the bridge between the innate and adaptive systems.  [JH] Yes, exactly.  [AS] But was it a surprise to you that the systems were so similar in flies and in mammals?  [JH] Yes. That really was one of the big surprises, yes. I mean, we might have – in hindsight – we might have anticipated that. But, we were maybe not Darwinistic enough, or evolutionary-minded enough. But, now in hindsight we know, through the work of other laboratories, we know that the system exists already in sea anemones and in sponges. So it’s a very ancient system which probably appeared at the moment when multicellularity appeared, that is to say about one billion years ago.  [AS] Right, right. But …  [JH] The essence of the – I mean the molecular circuitry and the building blocks have been conserved.  [AS] And although, as you’ve pointed out, you weren’t actually studying flies as models of human disease but for their own sake – in fact I suppose this illustrates how important flies are as models of human disease.  [JH] Absolutely, yes, in many respects.  [AS] Do you think that there’s enough recognition of that? Is that …  [JH] Well, certainly, well that’s one of the positive aspects of the Nobel Prize because it … people start wondering, as you just did, and many journalists whom I’ve met those days say, ‘Why would you work on the fly? What is particular in flies?” and so on. And then you end up illustrating examples and then you try to convince them.  [AS] And, this was all done to answer basic research questions, but of course there is application of the knowledge. What do you think will be the most immediate effect of understanding the sensors of innate immunity?  [JH] Well, I mean, in human systems it certainly will have an influence – and it has already – on working out adjuvants. Because some of the adjuvants which are used regularly now work though Toll-like receptors. That is one respect. The other respect is that autoimmunity also involves Toll-like receptors. And then inflammation often, if not always, involves Toll-like receptors. So you have a whole sequence of events where you can imagine therapy.  [AS] But this is for humans. In the case of the fly, is there a direct application as well?  [JH] No, certainly not for the time being. But, in the fly we are extending now, with co-workers here, with some of my associates – we are extending work to antiviral defences, which is a really new frontier, a nice frontier. And also in mosquitoes – again with other colleagues – the mosquitoes against … the defence against plasmodium/malaria parasites.  [AS] Okay, thank you. So, just to close: you’ve described the Chinese celebration, but you arrived back in France today. So, what is the French celebration that’s planned?  [JH] Oh! [Laughs] That will come. We just … well, we had, my colleagues, when I was in China, had champagne, and now there will be quite some celebrations going on here but it’s not yet settled.  [AS] Okay!  [JH] Okay!  [AS] Good luck with your plans and we look forward to meeting you in Stockholm in December, thank you so much.  [JH] Yeah, it was nice talking to you. Bye bye, sir.  [AS] Bye bye. |
| Interview |  |
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| ID | 0533 |
| Biographical | Ralph M. Steinman was born in Montreal, Canada, on 14 January 1943, the second of four children. His father Irving, a Jewish immigrant from Eastern Europe, and his mother Nettie owned a department store in Sherbrooke near Montreal. His father wanted him to continue in the family business, but in high school Ralph became interested in science. He received a B.S. with honors from McGill University in 1963, and an M.D. magna cum laude from Harvard Medical School in 1968. While at Harvard, he spent a year as a research fellow in the laboratory of Elizabeth Hay, who introduced him to cell biology and the immune system. During his internship and residency at the Massachusetts General Hospital, Steinman met Claudia Hoeffel, who was a medical social worker in the hospital. They married in 1971.  After completing his medical training, he was drawn to biomedical research. He joined The Rockefeller University in 1970 as a postdoctoral fellow in the Laboratory of Cellular Physiology and Immunology headed by physician-scientists Zanvil A. Cohn and James G. Hirsch. This laboratory was founded by the premier microbiologist René Dubos, who recognized the need to study the host during infection. Dubos, Cohn, and Hirsch were Steinman’s ideal mentors whose approach was not limited to immunology but embraced cell biology and biochemistry. He spent his entire career at Rockefeller, where he was appointed assistant professor in 1972, associate professor in 1976, and professor in 1988. He was named Henry G. Kunkel Professor in 1995 and director of the Christopher Browne Center for Immunology and Immune Diseases in 1998.  Steinman’s early research in collaboration with Cohn was an attempt to understand the white cells of the immune system that operate in a variety of ways to spot, apprehend, and destroy infectious microorganisms and tumor cells. In 1973, Steinman and Cohn discovered dendritic cells, a previously unknown class of immune cells that constantly formed and retracted their processes. This discovery changed the field of immunology.  For the next four decades, until his death in 2011, Steinman’s laboratory was at the forefront of dendritic cell research. He and his colleagues established that dendritic cells are critical sentinels of the immune system that control both its innate and adaptive responses – from silencing to actively resisting its challenges. He also showed that dendritic cells are the 2 main initiators of T cell-mediated immune responses. Steinman’s deep insights into medicine led him to take his dendritic cell research into the treatment of human disease. His most recent studies were focused on the interface of several diseases with the immune system and included clinical studies using dendritic cell- and immune-based vaccines and therapies for such medical conditions as graft rejection, resistance to tumors, autoimmune diseases, and infections. In 2010, he initiated at The Rockefeller University Hospital a phase I clinical trial with the first dendritic cell-targeted vaccine against HIV.  Steinman’s dynamic personality, boundless energy, and persistent leadership during these four decades allowed him to build international collaborations with many immunologists and scientists in other fields and to create an entire new field of dendritic cell biology. As part of his efforts in establishing this science, he personally trained and mentored more than a hundred postdoctoral fellows and graduate students in his laboratory. He published some 450 scientific papers. Beginning in 1978, he became editor of the *Journal of Experimental Medicine* and was one of its guiding forces. He also served as advisory editor of Human Immunology, the *Journal of Clinical Immunology*, the *Journal of Immunologic Methods* and the *Proceedings of the National Academy of Sciences*.  For the first two decades of Steinman’s research, dendritic cells were underappreciated, but by the mid-1990s, the scientific community began to recognize his work on their critical role in the immune system. Steinman received numerous honors, including the Freidrich-Sasse (1996), Emil von Behring (1996), and Robert Koch (1999) Prizes, the Rudolf Virchow (1997) and Coley (1998) Medals. In 2004, he received the New York City Mayor’s Award for Science and Technology. He was honored with the Gairdner Foundation International Award in 2003, the Albert Lasker Award for Basic Medical Research in 2007, the Albany Medical Prize in 2009, and the A.H. Heineken Prize for Medicine in 2010. He was awarded honorary degrees from the University of Innsbruck, Free University of Brussels, Erlangen University, and the Mount Sinai School of Medicine. He was elected a member of the National Academy of Sciences in 2001 and the Institute of Medicine in 2002. He was also a corresponding fellow of the Royal Society of Edinburgh. In 2012, the Ralph M. Steinman Center for Cancer Vaccines was established in his honor at the Baylor Institute for Immunology Research in Dallas, Texas.  Steinman was a trustee of the Trudeau Institute in Saranac Lake, New York. He also served as a scientific advisor to several organizations including the Charles A. Dana Foundation, the Campbell Family Institute of Breast Cancer Research in Toronto, Canada, the M. D. Anderson Cancer Center for Immunology Research in Houston, Texas, Baylor Institute for Immunology Research, RIKEN Center for Allergy and Immunology Research in Yokohama, Japan, and CHAVI Center for HIV-AIDS Vaccine Immunology, Durham, North Carolina. Steinman was a member of the American Society of Clinical Investigation, the American Society of Cell Biology, the American Association of Immunologists, the Harvey, the Kunkel, and the Practitioners’ Societies, and the Society for Leukocyte Biology.  Diagnosed with pancreatic adenocarcinoma in March 2007, Steinman believed that dendritic cells had the potential to fight his aggressive tumor. With many collaborators and leading-edge technology, he designed dendritic cell-based immunotherapies for himself that he thought might also advance medical science. For four-and-a-half years after his diagnosis, he remained quite healthy and continued to travel, lecture, and pursue new laboratory studies. Steinman died on 30 September 2011, three days before his Nobel Prize was announced. Unaware of his death at the time of its announcement, the Nobel Committee made an unprecedented decision that his award would stand. In addition to his wife Claudia, Steinman was survived by his three children Adam, Alexis, and Lesley, three grandchildren Isadola, Syla, and Robert; his mother Nettie; his brothers Seymour and Mark; his sister Joni; his daughter-in-law Jenny and his son-in-law Joseph.  Claudia Steinman and her children have donated the entire proceeds of Dr. Steinman’s Nobel Prize to charity, $500,000 of which they are giving to the Cohn-Steinman Professorship at the Rockefeller University and $250,000 to The Steinman Family Foundation to support the careers of young scientists and science education. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview |  |
| Interview |  |
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| ID | 0534 |
| Biographical | For biographical information on Robert G. Edwards, see the lecture ‘Robert Edwards: Nobel Laureate in Physiology or Medicine’.  <https://www.nobelprize.org/prizes/medicine/2010/edwards/biographical/> |
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