At the leading edge of cancer research: an interview with Joan Brugge

Joan Brugge has been an innovator in cancer research since the beginning of her career, when she isolated the viral and cellular forms of the Src protein as a postdoctoral fellow at the University of Colorado. In this interview, she describes the exciting sequence of events that opened up the field during this time, and discusses why a career in cancer research is still such an inspiring path to follow today.

When Joan Brugge started college in the 1960s, scientists could only speculate about what caused cancer. Evidence was accumulating to suggest that viruses caused the disease, but the lack of molecular techniques at the time limited scientists from probing the underlying pathological mechanisms. A penchant for problem solving and a fascination with experimentation led Joan Brugge to pursue research questions in cancer during graduate school, when she joined others on the quest to find out how viruses might cause cancer. The isolation of the Src protein – the first retroviral oncogene product ever identified – during her postdoc represented a major advance, as it paved the way to characterise the functional activities of oncogenes and their cellular homologues.

Since then, Joan Brugge has continued to shape ideas and new techniques in the field of cancer biology. Among these are key findings related to the mechanisms by which the extracellular matrix controls the survival of normal cells, how loss of adhesion leads to the death of normal cells and how tumour cells adapt to escape from these death mechanisms. Currently, a main focus in her lab is understanding how the extracellular matrix controls responses to cancer therapies and how tumours convert from being non-invasive to invasive – all using three-dimensional models that aim to recapitulate the organisation of cells in tissues and in tumours.

You're currently Chair of the Department of Cell Biology at Harvard Medical School. How did your interest in science develop: did you start off as a cell biologist or a cancer biologist?

I was really a cancer biologist first. I started out as a math major in college, and then my sister developed cancer. As a college student who was very interested in problem solving, my first response was to try to find out what caused cancer, and to study cancer. I read a lot of papers on it, and I became fascinated – not just by the aetiology of cancer but, throughout this process of reading, I was exposed to the concept of experimentation. This fascination, coupled with my emotional draw to understand cancer because it had affected someone very close to me, caused me to switch majors and become a biology major. I then spent a summer working at The Jackson Laboratories after my junior year, which was a very formative time in my life. I basically got hooked on research, and have been ever since.

At that time, when I entered the field as a student, there were predominantly two lines of investigation in cancer research: first, there was chemical carcinogenesis and, second, there were viruses. There were hints that viruses could cause cancer, and viruses had genomes that you could work with – the cellular genome wasn't accessible at that time. So, I decided to study tumour viruses, and applied to graduate programmes that had this emphasis. Because Baylor had, I think, the only Department of Virology in the country at the time, I ended up going down to Texas for graduate school.

Our understanding of cancer and the current approaches for studying it are completely different now than at that time. What has it been like to be a part of this conceptual evolution?

There's never been a lull in excitement in this area. First of all came the identification of the genes associated with viruses that caused cancer, and the first studies that tried to understand this connection. An especially exciting finding occurred when I was just starting my postdoc: it was found that the *Src* gene encoded by *Rous sarcoma virus* was actually captured from the cellular *Src* gene. That was the first hint that the genes that contribute to cancer are normal cellular genes that are altered in some way.

The next really exciting step was the finding that there was a mutation in the *Ras* gene in human tumours that was identical to

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a mutation found in experimental tumour viruses. That really validated all of the work that had been done on tumour viruses, because it served as evidence that the same genes that the virus captured were involved in the aetiology of human cancer. Studies of the functions of the cellular genes that were captured by viruses provided the first hints about the cellular pathways that are key to regulating normal cell proliferation, survival, migration and invasion. So, it was really through virology that many of the most important processes were initially understood.

The next exciting realisation was that these genes that were associated with viruses and found to regulate the proliferative capacity of cells were not only regulating proliferative capacity but also many other cellular functions. For example, it was found that Src was activated by almost every family of cellular receptors, and in each context it was activated, it regulated a different set of functions. We found that Src was dramatically activated during platelet activation and, because platelets don't have a nucleus, we knew that it couldn't be regulating proliferation. These findings provided the first clues that nature has been very conservative in its use of cellular genes, and that genes can regulate very distinct functions in different contexts. Even though these findings actually complicated the picture of cancer tremendously, it was also a very important realisation. Now, we have the whole genome available to us, so there's just tremendous excitement and challenges associated with findings from more global analyses that look at the integration of multiple processes simultaneously. It's been really fun to watch the whole evolution of the field.

But what's missing from a technical perspective that will help move the field forward?

I think what we need to do is something that no-one has really done yet – and that is to do a very systematic analysis of which assays provide the most meaningful information with respect to drug sensitivity in humans. It's not straightforward, because the results from that experiment would require that a drug had gone all the way through to at least phase II in the clinic in order to really know whether an in vitro assay was meaningful. We can't use the efficacy of a drug in a xenograft model in mice as evidence to measure whether a cell-culture model has worked because, in some contexts, a cell-culture model might allow the architecture of the tumour to be recapitulated better than a subcutaneous xenograft model. So, there may be some contexts where you get a better assessment of drug activity in vitro.

The bottom line is that we now know there are many factors in the microenvironment that can affect the outcome of a tumour, and it's difficult to recapitulate them in cell culture. Also, we don't know to what extent the tumour epithelial cell response to a targeted drug will be influenced by the tumour microenvironment. So, I think we need to have a 'think tank' to figure out what will be the best way to address that question. With respect to drug sensitivity, we and others have some very interesting results that strongly suggest that interactions between the tumour and the extracellular matrix can provide drug resistance in an in vitro 3D system. We have some hints that this might be true in vivo as well.

I think we should continue to work towards developing better in vitro models because it's just too hard to screen drugs in vivo in mice. There are just too many lead compounds to screen. Genetic screens, such as those involving short interfering RNAs, can be very useful for identifying candidate targets; however, the relevance of the information that comes from in vitro assays would be enhanced by using models that replicate in vivo conditions more accurately. Also, most of the tumour cell lines that we are working with now are clonal variants that evolved from the whole population of a tumour, and are not entirely representative of the original tumour. So, identifying conditions that would allow the whole population of tumour cells to survive will be very valuable as well.

You previously spent some time in industry during your career. What motivated you to make that move?

Yes, I spent some time working with a start-up company called ARIAD, which was founded with the aim of using structure-based drug design to develop inhibitors of protein-protein interactions involved in disease processes. At the time I made the move I felt I was being pulled in a hundred different directions in academic research. I was capable of juggling a lot of different things at once, but it was frustrating that 1% of me was in 70 different parcels, in addition to carrying out my main activities in research. I got so excited about the overall objectives and approaches that this start-up company was aiming for, and I felt that it would be very satisfying to use my different talents to work towards what I thought was a very meaningful goal – to do discovery research in an environment where it could be translated into something meaningful for patients. I felt that I was going to be able to continue to be very involved in discovery research. We were going to discover pathways that were crucial for disease processes, and contribute to the translation of those findings to benefit patients, and it would all happen under one roof. So, I got very hooked on that concept and felt that the opportunity would be a good fit for my temperament.

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Many students and postdocs struggle with the decision to choose a career path in either industry or academia. Do you think there are certain characteristics that make a person well suited for a position in one environment versus the other?

If you know that you are an independent spirit and prefer to pursue things on your own, then you will likely be more suited to academia. However, I think that science is now at the point where it's almost impossible to have a completely independent lab, as technology has advanced to the extent that no one lab has the expertise required for all of the technologies that are needed for a successful project at all different levels. Also, if you love working at the bench, you have a better chance of being able to do so for a longer period of time in industry. Although this can be accommodated in academia, I see more and more junior investigators leaving the bench even within the first year, because running a lab today demands so much more of your time and is much more complicated

than it was when I started. I stayed in the lab for 7 years. I know specifically when I made the shift from spending 70% of my time in the lab to 30%, and then less. These days, you need a lot more money to run a lab, you need a lot of grants and there are a lot more activities in science that make demands on investigators. You have to be a very good manager of operations and of people, as well as a superb scientist, innovator and communicator.

So, I think that you need a broader set of talents to be successful in academia compared with industry. There are also many different types of opportunities in industry – regardless of your particular set of talents, almost everyone can probably find a niche if they work hard, are collegial and have talents in a specific area.

I also think that the distinctions between the work environment in industry versus academia have changed significantly over the last 20 years. For example, there are now a lot of industry scientists that are very well integrated into the academic research community in terms of being able to give talks and have very fruitful collaborations.

You obviously enjoyed science right from the beginning, but you must have met challenges along the way. Do you have any advice for junior scientists facing challenges?

I think that I was extremely lucky during the time I was a postdoctoral fellow. We made a finding that opened the door to so many different questions that, when I ran into experimental challenges in addressing any one question, we would always have multiple other questions on the go, at least one of which led to something interesting. So, I would advise postdocs to pursue a couple of different questions at once: you can work on a challenging problem that might lead to a really important answer, but at the same time be working on less-challenging questions where any answer you get will keep your engine running and give you some positive reinforcement. You have to weigh your options in terms of how important each question is versus how much time you can afford to spend working on it. If you can't figure something out in a reasonable period of time, then switch gears and move on.

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It's also important not to blame yourself if you're running into experimental challenges. Your first response should not be that you have done something wrong, but that you need to find a new way to approach the problem. Some trainees take failure personally and become very discouraged. These are often the most talented people! Science is difficult, and trainees should maintain the confidence that they *will* be able to overcome challenges.

As an advisor, I see so many different types of productive scientists, and it's important to be very careful not to put a square peg into a round hole. Part of our job as advisors is to figure out the scientific temperament of the trainees in the lab, and to help them find the right type of science for them. Someone who is very detail-oriented might thrive on biochemical approaches, whereas someone who is not detail-oriented might be better suited to asking developmental or biological questions. The same thing applies for helping guide trainees towards the type of career that will give them great satisfaction in their future. It's not always straightforward, but as an advisor it's a very rewarding process.

And what about the next generation of scientists?

I'm concerned that young Americans are not being attracted to science as a career for a variety of reasons. First of all, there's media marketing. There seems to be a culture developing in the United States whereby other types of professions are being hyped as being more attractive to young people, but it's very important for our youth to really appreciate what a fulfilling and interesting career one can have in science. The types of benefits afforded from this type of career can be more important than some of the more material benefits that other types of professions bring. I don't know if we are really getting that message across to our youth.

How do you think we can reach out to the younger generation and encourage more young, bright minds into science?

It's not straightforward – educators have been trying to figure this out for a long time. It's possible that exposing people to 'exercises' in discovery might help: fashioning some of the curriculum to include not just rote learning but the process of discovery. Of course students have to learn the basics, but if education could frame the basics around how this information is needed to solve problems, I think we could potentially get kids hooked early on. And you don't need to be famous to get enormous satisfaction from science.

Excerpts from this interview can be heard in the podcast associated with DMM Vol. 4, Issue 1 at http://www.biologists.com/DMM/podcasts/index.html. DMM greatly appreciates Joan Brugge's willingness to share her unique thoughts and experiences. Joan Brugge was interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewee.