Kicking Off Episode Five: Interventions on the Cutting Edge

0:00
- Welcome to the Lifespan podcast where we discuss the science of aging and how to be healthier at any stage of life.
0:09
I'm David Sinclair, I'm a professor of genetics at Harvard Medical School and I'm co-director of the Paul F. Glenn Center
0:17
for Biology of Aging Research. This podcast series is about why we age and why we may not have to.
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Things you can do today and going forward to increase your wellness and to potentially live a much longer healthier life.
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We've talked about the biology of aging, we've talked about things that you can do at home, preferably under the supervision of your doctor,
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and today, we're going to talk about things that you definitely will be talking to and requiring a doctor's supervision to do,
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and even things that your doctor is unable to do, but potentially in the future may be able to.
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I'm joined today by my co-host and my co-author, the lovely Matthew LaPlante. Hey Matt. - Hey.
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We're back. We're doing it again. - We are definitely doing it. Today, we're doing a deep dive into some, you know, somewhat controversial stuff.
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- This is a scary episode. - Well, I don't know if it's scary, but we have to do a disclaimer, I think.
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We have to say that what we're going to talk about today, a lot of it isn't approved by the FDA, but maybe in the future,
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and some things that were available until recently, and were banned by the FDA, and currently available only off shore.
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- And just as was the case when we had the conversation about drugs and supplements, and maybe even more so in this case,
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there's a lot of misinformation out there about a lot of things that we're going to be talking about today,
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these potential avenues for addressing longevity. We're going to try to cut through that,
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but we are not doctors of the physician type. - That's right.
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I'm a PhD in genetics, I'm not a physician. And so the things we've talked about in this series should always be done with the supervision
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and advice from your physician. - Yeah, a podcast is no substitute for a physician. - That's right.

2:00
But I'm a scientist, I can read the scientific literature, can distill that down, you're a science communicator, and we're here to be able to distill
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the wealth of information that's out there and distinguish what's fact from fiction and give people a starting point as to really, how do they figure out
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what's best for their wellness and what's actual complete bull out there. - And so today we're going to be talking about
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stem cell therapy, peptides, exosomes, testosterone, growth hormone, and then we're going to spend
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a little time talking about one of your favorite subjects, epigenetic reprogramming, but we can't do that
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until we do something else first. - Well, we need to thank the sponsors who make this podcast freely available.

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2:51
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Again, go to athleticgreens.com/sinclair to claim this special offer.
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Today's podcast is also brought to us by Inside Tracker. Inside Tracker is a personalized nutrition platform
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that analyzes data from your blood and DNA to help you better understand your body and reach your health goals.
3:54
I like Inside Tracker because they present the data in a really clear form, and the nutritional advice
4:00
is really actionable and has been shown scientifically to improve many blood biomarkers.
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And if you're not looking at what's going on in your body, you have no idea whether what you're doing is actually working or not working.
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Another feature that Inside Tracker has is their inner age test. This test shows you what your biological age is,
4:18
and you can optimize that. They also make the tests really easy to take. You can have people come to your house
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4:39
Today's podcast is also brought to us by Levels. Levels is an app that syncs with a continuous glucose monitor that they provide
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and interprets your glucose data for you. I've been so impressed by Levels that I recently joined them as an advisor.
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By monitoring your blood glucose, Levels allows you to see how different foods impact you. I've been really successful at impacting
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my blood glucose levels positively. I found that foods like grapes spike my glucose
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and potatoes don't do so much, so that's really important, because I don't get those highs anymore followed by a crash
5:13
which leads to a brain fog and lethargy. So if you'd like to try Levels, you can skip the 150,000 person wait list
5:20
and joined today by going to levels.link/sinclair.
5:25
That's levels.link/sinclair. - All right, let's dive in by starting today

Testosterone Replacement Therapy

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with testosterone. Super popular subject. Lots and lots of growth in testosterone replacement
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right now, because of the fact that testosterone decreases as we age,
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and that's disconcerting to a lot of people. - Oh, for sure. After the age of 30 to 40, we lose about
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1% of our testosterone levels, men and women, it's important for both sexes. But the market has grown.
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So TRT or testosterone replacement therapy has grown from a few hundred million 10 years ago to multi-billion dollars now.
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And it's widely used not just to supplement for sexual dysfunction,
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which is a common side effect of low testosterone, but for other things that include mental health, building muscle, overall fitness, vitality.
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- And people swear by this. I mean, a lot of people did, they do this, they say they feel younger, they say they feel more vigorous.
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They want to have sex again. They want to have sex all the time. There's an important distinction to make here though,
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which is just because you feel younger, does not necessarily mean you are reversing your biological aging.
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- Right. Let's make a clear distinction. We've talked about adversity mimetics and the last episode, we talked about the supplements
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and the kind of things that you can do in your life to mimic that. We want our bodies to be in a state of fear.
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That times are tough, and they need to hunker down and survive. There are other types of things that we're going to talk about,
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which are abundance mimetics. Testosterone is one, we're going to get to growth hormone as well.
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These tell the body that times a good, to build your muscle, to reproduce, go forth, multiply.
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- And that's what testosterone is doing. We get testosterone replacement therapy, we are putting a substance back into our body
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that has been reduced, but which signals our body that times are good enough, it's okay to build muscle,
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it's okay to run around chasing wooly mammoths, chasing the cave women around.
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- Yes. That for sure. And that benefited our ancestors very well, but it didn't help them long-term.
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What we now are appreciate is the body has cycles of want and need and adversity, which is good for the long-term health of the body,
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and times where things are abundant, times to grow, reproduce, which are great short-term,
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but probably not great for long-term health and longevity either. - Okay, so let's talk about what actually happens
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when our testosterone lowers and what happens importantly when we put it back.
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Because this is helping a lot of people with a lot of problems that are coincidal with aging.
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- Oh, for sure. There've been a lot of studies, millions of dollars, and many thousands of people treated with TRT
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as it's called. Shelly Basin, who's a colleague of mine at Harvard has done a lot of these studies,
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and he's found some improvements, short term improvements, so of course improvements in libido, but also he shows a dose dependent increase
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in skeletal muscle mass, so you get bigger muscles, you got more power, you can climb stairs,
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you can walk further in six minutes, improves aerobic capacity. These are all good things that he sees,
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but actually it's not all good news. There were some side effects and may actually impact longevity.
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So some of the risks of TRT, there's worst sleep apnea, you can actually get larger breasts.
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A little lower fact is your testosterone can be turned into estrogen, which is a risk for men particularly.
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You can have what's called benign prostatic hyperplasia. So bigger prostate, need to go to the bathroom at night,
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shrinking testicles, not something I think many of us would want, and increasing red blood cell protection,
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which could lead to blood clots. - And if you're already predisposed to prostate cancer, you have cancerous growth already.
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This could actually aggravate the tumors. - Yes. And actually the opposite is true for you. If you look at the history of eunuchs, they live longer.
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And so it may actually be that supplementing with testosterone is not conducive to longer life.
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- So this is an important principle here, and we're going to come back to this a couple of times on this episode, which is just because
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something makes you feel good today, and just because it might even be medically beneficial
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to you today, that does not necessarily mean it is addressing the causes of biological aging.
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It maybe fixing something that you have a problem with, it may be improving even your quality of life right now long-term, that's not the same thing
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as reducing or eliminating biological age. - Yeah, let's go back to the main concept here today,
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which is that adversity mimetics are great, things that mimic lack of food and a lot of exercise,
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but these abundance mimetics are probably a problem long-term even though they make you feel great short term.

Human Growth Hormone

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- Okay. And that's sort of giving away the punchline for HGH, but we need to talk about HGH as well. Human growth hormone, also something
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that is really popular right now, people supplementing with human growth hormone
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to address things like decreased exercise capacity, decreased bone density, decreased muscle mass,
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and increased body fat. This works, right, for those things. HGH is helpful.
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- Well, no question. Short-term, you'll feel better, you'll grow muscle, you'll have less fat on growth hormone therapy.
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The science says that this may not be good for long-term health and wellness. Going back to the original studies of Cynthia Kenyon,
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which we talked about in episode one, those mutant worms had low levels of growth hormone and insulin like growth hormone signaling.
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- And they live longer. - Twice as long. And this has been reproduced also in mice. And even in humans, there are the Loren dwarfs,
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we were talking about earlier. These are smaller people that have low levels of growth hormone, or actually IGF-1,
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one of the versions of this pathway, they are relatively resistant against cancer and heart disease, and may even live longer.
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Conversely, if you're supplementing with growth hormone long-term, the chances that you're having the opposite.
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That you feel great, but long-term, you might have even greater risk of cancer and heart disease. - And you know people who are on HGH for various reasons.
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One of the immediate side effects, even before we get to the sort of like the longevity implications is sore joints,
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carpal tunnel syndrome. - Right. This is the kind of thing that that does happen. Now, I just want to be clear.
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There are some benefits to bringing the levels back up to normal, okay? But going to high, which a lot of people do
11:51
if they want additional benefits, that's where I think that the main risk comes from. - Another risk immediate is increased insulin resistance.
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- That's true. We get high levels of blood sugar or we get high cholesterol, carpal tunnel, edema, so buildup of fluid, joint pain.
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- Okay, so soreness in your joints, insulin resistance, another one is an increase in the likelihood
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of type two diabetes because of that insulin resistance. All of this actually kind of sounds like symptoms of aging.
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- Right. And that's the risk, that the animal studies are telling us that growth hormone will tell your body that times are good,
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abundance mimetic, and that's not good for long-term effects of health, and probably what's going on is some acceleration of aging.
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- Okay, this isn't to say again, I think this really, we don't want to say human growth hormone is bad.
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Testosterone is bad. People need to have a naturally healthy level
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of these hormones in their bodies. - There are ways to do that naturally. So with testosterone, you can work out the bigger muscles
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in your body and that also help with growth hormone. So I work out my thighs and my back particularly,
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keep those nice and strong, and I've found my natural testosterone levels go up to normal levels with that.
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So that's the way to do it. With growth hormone, it's all about eating at the right time and sleeping. So if you eat not too close to sleep time,
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and then you rest through the night, and have a good night's sleep, that's the best way to improve your growth hormone levels.
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- And if you're doing all of that and you're still struggling to keep these levels up, that's the time to talk to your doctor
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about supplementation, but that supplementation needs to be aimed not at a hyper increasing the levels of these
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in your bodies, but just keeping them at that sort of like that natural healthy level.
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- Well, exactly. But I would encourage everyone to try it naturally first - So so far, this sort of feels like bad news,

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'cause these are the things that a lot of people have gotten into their heads that might be beneficial to anti-aging,
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and what you're saying and what the evidence suggests is that there is no anti-aging benefit,
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there might be a short term gain, not a long-term anti-aging benefit, but these aren't the only things

Peptide Supplementation and Regenerative Signaling

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that are sort of like hot on the market right now. Another thing that's really popular to talk about,
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really popular to try, where it is legal, is peptide supplementation.
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- Yeah. So peptides, just like hormones, are made of strings of amino acids, but typically smaller. About a hundred amino acids.
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You can synthesize them on a machine or extract them from tissues, and they're used by cells to communicate between each other.
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So your brain will put out peptides to signal the body, your liver, and your muscle, and some of these are really good.
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Some are really bad. We don't know what they all do. There are probably a thousand made by the body.
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We've probably only know about what 20 of them do in great detail. - What we do know is, as a class,
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they help cells communicate to one another. - Right. - And so just sort of like holistically speaking,
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it's like, oh, that's really good, because in part aging is a loss of cellular communication,
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and so peptides help increase that cellular communication. Voila, they must be great for aging.
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- Well, again, it's whether you're in adversity mimetic, or an abundance mimetic.
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That's the difference. And really you have to make a distinction between those two things. One of the best studied peptides of all time is insulin,
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and clearly that's important if you're deficient in it. We've known this since the 1920s. - We actually have a hundred years now, it was in 1921,
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which was when insulin was first discovered. - Right. Banting and Best was 1921, found they could extract
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this insulin extract from the pancreas of a dog and injected into a dog that had diabetes
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and cure it within hours. - And within months, they were trying this on human beings,
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because that's how things worked back then. - Yeah, and they even won Nobel Prizes quicker. It was only one or two years afterwards
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that they won the Nobel prize for that. - So they went from this works in dogs to let's try this out in a 14 year old boy
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to Nobel prize in the span of like two years. - Well, it was worth it, because in those days,
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particularly type one diabetics, which is the childhood version of this, the lack of insulin meant that they would have to go,
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the kids would have to go on a starvation diet and even then, they would die within a year or so. It was horrific.
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And suddenly people were living for decades. That first patient lived for another 13 years. - And so this set us down the road of studying peptides
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and their health benefits, and then a really big thing happened in the sixties,
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which is we figured out how to synthesize peptides. - Right. That was a big deal. And then in 1978, they started to be made
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using recombinant DNA technology. And that's where we find ourselves today is that most of these hormones and peptides
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that are available on the market are made using recombinant DNA technology. Though these very small peptides are unique
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because you can synthesize them on machine, which makes them very cheap. - Didn't you say like some people
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have these machines at their homes? - Yeah, I'm aware of some people that have them and they're making them at home and injecting themselves.
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I don't recommend that. That's currently, that's off label use of drugs
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and you don't want to do that, but that gives you an idea how it possible it is to make a drug these days, especially these peptides.
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- Because there are at this point, so easy to synthesize, and because they're relatively cheap,
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and because they are relatively non-toxic, there's been lots and lots of clinical studies
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on the use of peptides. - Right. Thousands of human studies. And it's interesting.
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Why are they so safe? Well, they're not foreign. They're typically already found in the body, and they're small, so they don't typically have
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an immune reaction, though the risk is not zero. - They're metabolized quickly. - They're also metabolized quickly.
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And so that the risk is relatively low, and for that reason, there are a number of doctors who have been okay giving these peptides to patients.
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- And what we're looking for when we give peptides to people, specifically for the cause of anti-aging,
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is a boost of regenerative signaling. - Right. So what you're looking for is the ability
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to recover from damage, increased wound healing, lower blood sugar levels, increased mitochondrial activity.
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Those are examples or signatures of an adversity mimetic, not an abundance mimetic.

MOTS-c, Humanin, and Other Peptides

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- Okay, let's talk about some of these we have discussed in the past, MOTS-C. - Right.
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- MOTS-C. - MOTS-C. So M-O-T-S dash C. That's a really interesting peptide, an unusual class that actually doesn't come
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from the nucleus, that normal chromosomes that we talk about, but from the mitochondrial DNA in mitochondria,
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and up until about 10 years ago, we thought that there were only 13 genes encoded in the mitochondrial genome,
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and there are now about a hundred known and MOTS-C is probably the best characterized of those.
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There's another one called humanin as well. MOTS-C, when injected into mice, lowers blood sugar levels, increases mitochondrial activity,
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gives you the signatures of long life, probably promotes life, there's some evidence of that,
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and has been in humans. In fact, there's a clinical trial that was just released, the results of which showed that it reduces fat in the body
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and improves fatty liver, which are again, signatures of potential longevity. - And so your belief at this point is that
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there are likely peptides that are valuable when it comes to addressing the causes of biological aging,
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unlike these other things we've talked about today. - Well, almost certainly, but we don't know enough yet to say for sure
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that these are perfectly safe or we'll increase lifespan, they lot less is known about these peptides
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than testosterone or growth hormone. - And to that end, the FDA agrees.
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They're nervous. - Well yeah, because they became so popular, typically on the west coast, LA,
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there was a real megatrend and still is to try these out. And they have variety of properties
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that seem to be beneficial anecdotally. Improving memory, muscle mass, lowering inflammation.
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The FDA looked at this and said, "whoa, hold on. We don't know enough." And they sent a letter to a company saying,
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"stop making this." And then that sent shock waves. This was March of 2020. And so since then, it's been impossible
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to get some of these peptides in the United States. - Because they've stopped compounding them. - Right.
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So even though there have been some promising results with peptides, the FDA has said some of these need to be regulated, and many of them now
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you cannot get in the United States. - So they're still in clinical studies, researchers are still examining them, but the avenues for getting these in the United States
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have become more limited, there are still people getting them overseas,
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compounding them in their own machines at home. - Right. But still we have to be careful,
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because they're not all perfectly safe. And one of the reasons the FDA was nervous about this and banned many of them is that there are some side effects.
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It's not just that they can be redness where they're injected, but actually it seems like you can induce arthritis type effects
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when the immune system recognizes these peptides as foreign. And that would be something you definitely wouldn't want to have
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is an immunological reaction. - A lot of these have names, they're like star wars droids. And so people have heard these, heard of these,
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they might wonder what they're doing. One that's really popular in conversation right now is BP-157.
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- Yeah, BP-157 is one of the more popular ones. It's been used to increase blood flow, lower inflammation,
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and even regenerate neurons for cognitive ability. But there are lots of others. There's one called SS-31 which targets the mitochondria
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and improves mitochondrial function, could seem to be good for the heart, maybe for longevity. There's another popular one called GHK-Copper,

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it's part of a copper complex, was first identified in human plasma. later, is found in saliva and urine.
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And it's been used to help wound healing, attract immune cells, and it's an anti-oxidant,
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stimulates collagen, protects tissues against inflammation, can even be used apparently
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to reduce fine lines, wrinkles, and grow hair again. There's a whole bunch of- - Is this based on, I mean, is this anecdotal evidence?
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Is this research-based evidence? How do we know these things about these different peptides? - Yeah, most of these come from mouse studies
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and then they're anecdotal from studies that clinicians are currently doing. But yeah, again, I want to stress
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that most of these things that we're saying are anecdotal and not yet scientifically validated.
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- These are some people's experiences and this is all one of the reasons why there is a pretty significant movement right now,
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this sort of like save peptides movement of people who are contacting the FDA and saying, "please make these things more available to us again."
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- Well, yeah, there's one in particular, thymus and alpha one, which has been known since the 1970s to be beneficial, it seems to be great,
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particularly for helping against fighting bacteria and viral infections, but it was also listed on the banned substances in 2020,
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and there's a movement to bring it back, because with COVID-19, it's thought that it could help.
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Talking about other ones, some of these work with fat loss apparently. We've got to some Tesamorelin CJC-1295
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is taken with one called Ipamorelin, there's AOD-9604, and the BP-157 again,
23:05
can be good for weight loss apparently. One of the other ones I mentioned humanin is, again, one of those mitochondrial derived peptides
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like MOTS-C, and in mice at least, has been shown to help against type two diabetes, high blood sugar, cardiovascular disease,
23:18
and even help with neurodegenerative disease like Alzheimer's. But in humans, it's not clear if that's true.
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Pinealon is a really interesting one. It's actually an active peptide complex
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and has been thought to treat memory, attention deficits, brain injury, stroke, chronic fatigue, et cetera.

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But again, early days. We don't know for sure if this is actually true in humans. And then finally, oh, we should just mention,
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there are others that are used to combat fatigue and also boost the immune system. They go by names like Dixhexa, Cerebrolysin, Semax, Selank,
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or even BPC 157 is used with some Semax, and Cerebrolysin together. Again, these are all pretty much experimental.
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They've been shown to be effective in mice, but still we have a long way to go before we know if they're truly effective in humans.
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And there, we always need placebo controlled, double blind clinical studies. - Which are underway.
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I mean, there's lots and lots of clinical studies going on. It's just not moving as fast as I think a lot of people would really like it to move.
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But that's the reality of the space that we're in right now. - Well, it is, and often it is frustrating
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and I can speak from personal experience how long it takes to make a drug can be extremely slow, and we're all getting older, we're not getting,
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in the case of most of us, we're not getting any younger, and there is a desire to rush into things,
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but I think we need to exercise some caution here, because you can have these negative side effects, particularly in the case of peptides, an immune reaction
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they could be deleterious in the long run. - And in that long run though, you see these
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as a very promising avenue for a lot of therapies that are going to help a lot of people. Not just with individual conditions,
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but you think with aging. - Oh, for sure. Not all of these, of course, but those that mimic adversity.
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MOTS-C is a good example of one that I think has the right signature. I think they have a lot of promise. - Because there is an explosion of research

Exosome Therapy

25:08
going on sort of at the same time with peptides and this other thing that we're about to talk about, exosomes, I think these happened in the same breath.
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A lot of times people talk about peptides and exosomes. Both of these are cellular signalers,
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but exosomes work, well, they are different, and they work a little differently. - Well, very different. These are packages of information.
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They contain, well, they're membrane bound, so they're little vesicles, they're about the size of a virus, so they travel between cells and into cells very easily,
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and inside, it's not just one message. There's multiple messages. There's peptides inside, there's DNA, there's RNA,
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even what are called micro RNAs, which are similar to peptides, very small pieces, in this case of nucleic acid material,
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that can go from the brain to other tissues from tissues back up to the brain. And this is essentially the way the body can coordinate.
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So if there's an injury on your hand, your brain will know, or if your brain gets injured, the rest of your body knows,
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and you need to have these messengers to coordinate the system in the same way you could imagine the US post.
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And so these a little mail deliveries of cargoes that we can both intercept and read,
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perhaps we can use these to diagnose diseases, including cancer, but also we can make more of them
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and infuse them into people to give a false alarm, perhaps even, to simulate this adversity
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and make us live longer. - And before we get to those therapeutic processes, one of the really fast moving avenues
26:32
for using exosomes is basically collecting them from the blood, counting them up,
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and being able to diagnose different injuries. And even like, you can pull people's blood these exosomes,
26:46
and then you can say like, "oh, they have an injury here. They have a disease there." - Right.
26:51
Yeah, there are companies now that, there's one called Zar Therapeutics, there are others, that you can read the cargo,
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and you can say, "okay, that comes from the pancreas. That is a signature of a stage three pancreatic cancer."
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So we may be able to use these to diagnose cancer years in advance. - Without biopsying- - Right, just a blood test or even a finger prick at home,
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send it off, and diagnose cancer. - And that would be reason enough to be excited, I think, about the potential for exosomes
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to tell us what's going on in our bodies, but what else we're learning right now about exosomes is that if we supplement these into the bodies of mice,
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like by injecting them into their, back in to their bloodstreams, it can help with injury.
27:31
- Yeah. I mean, there's a really well-known paper now from August 2017, by my good colleague
27:37
down at Albert Einstein College of Medicine, Dong Shanghai, and his expertise is looking how the hypothalamus, the little organ
27:43
at the base of the brain communicates to the rest of the body, and he's found that inflammation in and damage to that part of the body affects the rest of the animal,
27:52
including aging. And in this case, he found, interestingly, that neuronal stem cells, these progenitors in the hypothalamus,
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they secrete exosomes that tell the body to hunker down and survive. And the mouse can actually live longer
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if you isolate these exosomes and give it to the mouse. They also did the opposite, they deleted these special cells
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that make the exosomes and the mice got diseases of aging and lived shorter. - Why is it happening?
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- Well, we don't know. In most cases, there's so many things within the exosomes that we, it's very hard to figure out
28:21
which of those particular cargoes is responsible for the biological effect, but ultimately if we can figure that out,
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we could make exorcisms with just that particular component, and that could be a drug in the future. - There was another fairly recent paper on exosomes,
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2019 paper from some Chinese researchers that used exosome replacement to address ulcer healing,
28:46
and what they concluded was that the exosomes are actually rejuvenating senescent cells.
28:52
Really fascinating here. - Well that, so senescent cells, if you miss the previous episode, our cells,
28:58
that as they get old and they have ex-differentiation, they lose their ability to read this their DNA correctly.
29:04
They become senescent. They stopped dividing. They sit there, and they start secreting inflammatory molecules, can even cause cancer to develop.
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We try to delete these cells. We know that in a mouse and probably in a human, if you get rid of these inflammatory senescent cells,
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it's good for health. But here we're saying, what the researchers are saying, is that these exosomes,
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a particular type of exosomes can reverse senescence. That's unheard of. If that turns out to be true,
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that would be quite a remarkable thing, meaning one day we don't have to kill off these cells, which in the brain,
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you wouldn't want to do that necessarily, we could actually rejuvenate them, and get them to grow again, healthily. - Right now, the way we understand how to do that
29:42
is through the Yamanaka factors, but this would be another avenue toward that same goal of taking exdifferentiated cells
29:52
and sending them back into a differentiated state. - Well, the Yamanaka factor,
29:58
rejuvenation of senescent cells is preliminary. This is some of the work we're doing in my lab,
30:04
and it's not even clear if the Yamanaka factors are pertinent enough to reverse senescence, but this finding that you referred to is the first instance at that that might be possible.
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- All of this is why there's a lot of excitement around this particular potential therapy.
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But again, just like peptides, this is sort of the wild west right now, but people are already taking exosomes
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and having them shot into their bodies. - They can be delivered by IV or intramuscularly,
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but again, we, we don't know what the longterm benefits or side effect are. So we have to be careful.
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It's still available in some parts of the US, but we don't know. - This is not one of those things you have to go to Costa Rica for, at least as of right now,
30:45
the FDA hasn't cracked down, they haven't said this is a step too far. - That's right. But while exosomes aren't completely banned
30:52
in the United States, you can bet that the FDA is looking at this for a potential safety concerns. And we'll see how things go over the next few years.
30:59
- That's not the same thing as saying, like, "go do it now!" - No, no, that's not what we're here for.
31:04
oWe want to educate and look at what might be available down the line once things are proven
31:09
to be safe and effective. - And this is another one of those things, like peptides, you're feeling positive that there is going to be
31:17
actual clinical research that will show us the actual benefits of these. We don't have to make super, super guesses,
31:24
we can actually see in the research how exosomes are going to be beneficial and then start to implement them into our longevity regimes
31:34
in a responsible way. - That's right. And just to be clear, exosomes are a highly validated scientific pursuit,

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and there are biotech companies, pharmaceutical companies, building giant factories, billions of dollars,
31:47
to make exosomes, to treat diseases. The question is, do they work for long-term health and longevity and how safe they are
31:53
to be used over decades. That we don't know yet. - Okay, let's move than into an area of research

A Primer on Stem Cells and Yamanaka Factors

32:00
that is even further along. Still, we're learning more about every single day,
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but also has potential anti-aging implications.
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Stem cells. Let's start with a little primer. Stem cells are? - Stem cells are cells that can divide asymmetrically
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to produce cells that go on to make tissues. So for skin, you need stem cells to make all the skin that grows over your lifetime,
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and they retain youth so that they can keep dividing over and over, and they don't become any particular certain cell type over time.
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- And stem cells can become more stem cells or they can become any kind of cell.
32:38
- And there's a few different types. - Right. - The two main classes are multipotent, which can make a few different types of tissues,
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these are cells that you typically get from an embryo. We can go all the way back to age zero,
32:51
and what are called pluripotent stem cells, which can make any type of cell in any type of tissues.
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- And you can think of this sort of like as one of those trees, right? Like you have the pluripotent cell that can do anything,
33:03
and then after a while, a little further down in the development, you have the multipotent cells, which are still able to transition
33:11
into several different kinds of cells, but not all the different kinds of cells.
33:17
- Exactly. And so if you want to build a mini human brain or rebuild a kidney out of a skin cell,
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you have to wind the clock all the way back to zero and start again, and that's called inducing a pluripotent stem cell state.
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- And that goes back to what we were talking about earlier, the Yamanaka factors, this is one of the ways that we've identified that we can turn a stem cell

33:37
or any kind of cell from being a stem cell back into a state of pluripotency. - Yeah, let's just talk about Shinya Yamanaka,
33:43
because it's really quite an amazing story. So Yamanaka in Japan, in the early well, 2010s
33:48
was, in his lab, was figuring out or trying to figure out how do you take an adult cell from an animal or a human
33:54
and make it pluripotent. 'Cause if you could do that, imagine you could build any tissue you wanted,
33:59
and he was trying lots of different gene combinations and hit upon five genes that when put together, worked to take, so I could take your skin cell now
34:07
using Yamanaka genes or Yamanaka factors and make a pluripotent stem cell line and rebuild you.
34:12
I could even turn you, by the way into a sperm and an egg, and clone you, but I won't do that. So Yamanaka found the following genes.
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So KLF4, SOX2, c-MYC, and LIN28. We use three of them particularly in my lab,
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we'll talk about that later, O, S, and K for short, but this was a major breakthrough, because finally you could take anybody's skin cell,
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which you could easily get from the cheek or a biopsy, grow that in a dish, reprogram them,
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which takes about a week once you put these genes in, and when they grow up into what we call a colony, which is an assemblage of about a hundred cells,
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you pick those, and now you could grow basically anything you want from plant cells.
34:51
- Well, and I've seen this in your lab where you've taken cells from a mouse,
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you've induced them into a state of pluripotency, and then you have trained them, for lack of a better word,
35:03
to grow into brain cells. And now you have these little clusters of brain cells
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that look like little brains. - Well, we've done that for mice, and we've done that for human. We have many human brains,
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and we take these from old individuals, old normal individuals, and also patients that have susceptibility to Alzheimer's disease.
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And again, I think we're going to talk about this later, but we have the ability in my lab to drive aging forwards
35:29
in those what are called cerebral organoids and even in reverse. And that's what's important really
35:35

for being able to study the human brain without having to touch patients. And we can go a lot quicker that way.
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- Before we sort of go down that rabbit hole, can I take us back just a couple of steps
35:47
to how this actually happens? Like how do you take these factors and put them into a cell?
35:56
- Well, it's actually really easy. Any high school student could do it. There are a number of ways. The old ways of doing it are you can pass electricity
36:04
through the cells in the dish and they take up DNA that encodes these Yamanaka genes.
36:10
You can put them in what are called liposomes or liposomes, which are fat membrane bound little balls,
36:16
but the way we do it in the lab, which is the most efficient, is we use viruses, domesticated viruses, that are typically used in patients
36:24
for gene therapy, we use them in the lab, they called adeno-associated viruses, or AAVs,
36:29
we package inside those the Yamanaka genes, and just throw them into the dish, and they infect all the cells in the dish,
36:35
and now those cells are transgenic, they carry these genes, and we can turn those genes on and off at will
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using drugs and see what happens. - And the implication here is that we can take these now pluripotent cells, and then we can use them
36:50
to treat areas of the body where the cells just aren't acting the way
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that they're supposed to act anymore. But there's still a problem with pluripotent cells, right?
37:01
Or sorry, induced pluripotent cells right now, and that is cancer.
37:06
- Yeah, if you take the age of a cell back to zero and allow it to just grow and if you put it into a mouse and probably a human, you'll get cancer.
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Teratoma's particularly pernicious type of cancer, which can be, you know, a hairy ball of mass,
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sometimes with teeth in it. You don't want that. So you have to be very careful not to put these pluripotent stem cells back into the body
37:28
and just let them grow. - Which is why right now, most stem cell therapies aren't using induced pluripotent stem cells,
37:36
they're using harvested stem cells, and we can get those from a variety of places. - Right. Mainly what we're using, or what scientists and doctors
37:44

are using are what are called autologous stem cells, so cells that you take out of your body from various parts of the body,
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typically fat cells on your back or your hips, and then purifying them out, freezing them down
37:56
and or putting them back into the body in different places or into the bloodstream. - So we can just suck stem cells out of fat,

Stem Cell Aging and Cord Blood Banking

38:02
out of adipose tissue. A lot of people think like, well, why would we even go through the process of trying to induce pluripotency
38:09
if we can just take stem cells out of fat? But one of the things that I think needs to be said, and you've done some research on this,
38:15
is that stem cells age also. - They do. They undergo epigenetic changes that make them
38:21
less able to regenerate new tissues. And that's also true. You see that with gray hair and hair loss.
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That's the loss of the stem cells in the hair follicle. One other thing that just happened recently, was discovered that you don't just have
38:35
stem cells getting old, they can even be kicked out of what's called the niche, where they belong, they like to reside, and that's true for the hair cell.
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There's a fascinating video that I threw up on Twitter and the stem cell, you could see,
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they captured it under the microscope, which got kicked out. Anyway, suffice to say, what is really going on
38:52
is that the stem cells need to be a slowed down in their aging process or even replaced,
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and we're only just learning how to do that. - The other thing that we can do is capture them at a much younger state.
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That's where cord blood comes in. - Right, and you can even do that for adults.
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The idea is that if you capture these cells when they're very young, or if you're in your twenties and thirties,
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you can bank them, put them in a freezer for later use either to replace the blood
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if you have leukemia, or even using new technologies to modify them and grow new tissues,
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perhaps even replacing old blood when we get very old. - A lot of people that are doing this now,
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it's becoming more and more common for people to say, "hey, look, I want to preserve my child's ability
39:38
to use those stem cells later on, even if we're not exactly sure how they're going to be used, and so they're banking them.
39:45
Your kids are, in their teens and early adult years, but if you could go back in time, would you do this?
39:53
- Yeah, we didn't do that because at the time it wasn't clear if they would be useful, but now it's very clear that there are uses for them,
39:58
especially if they get childhood cancer. And so I would do that. If I was a new parent, I would aim to bank those.
40:04
How about you? - Yeah. I mean, so as you know, I haven't followed you down every longevity rabbit hole
40:10
that you've gone down and the other people have gone down, but this is definitely 100% something that if my child had been born today, I would absolutely do.
40:18
I would be banking their cord blood. - Yeah. - If I did want to do that now, though, how would I go about doing that?
40:26
- Well, there are companies you can contact and often the hospital and the doctors you work with know how to do this, but you need to get ready,
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you at least need a few days, often a week to get ready for this, because you need to spin them down and put them in a freezer.
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But when you have a placenta, there are particular parts of the placenta you can take the cord blood, you can take a thing called Wharton's jelly,
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which is this gelatinous substance made of hyaluronic acid, where there's particular concentration of stem cells
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you can also isolate. - We can also isolate stem cells from adults. Again, these are stem cells that have, you know,
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gone down their trajectory from pluripotency often to multipotency, and so they're not,
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you know, they're more aged, but sort of the earlier we do this, the better, right? - Yeah, these stem cells in adults don't just age
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and become dysfunctional, they can out-compete each other. They can grow faster. If you have mutations in genes like Tet-1, Tet-2, DMTs,
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they grow faster and can actually out-compete the rest of the immune system. If you look at hundred year olds, often they only have one or two
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instead of thousands of types of immune cells, which is a real problem if they get pneumonia. It's often why these elderly people
41:32
don't survive in infection. So what you might want to do is to bank these HSEs,
41:37
hematopoietic stem cells when you're younger, so that you can replace your immune system as you get older. - However we obtain the stem cells,

The Therapeutic Potential of Stem Cells

41:45
researchers are using them for all kinds of diseases.
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They're being used to regenerate and repair disease in damaged tissues, in people with spinal cord injuries,
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type one diabetes, Parkinson's disease, ALS, Alzheimer's, heart disease,
42:03
stroke, burns, cancer, arthritis, and the reason why I'm like making this big list is because now thanks to what,
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I mean, like really you've done this to me, anytime I hear a big list of diseases, and one singular thing that can address all of those diseases,
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I don't think of those diseases separately anymore. I think of aging. And there's a lot of implications here
42:25
for the potential to use stem cells perhaps to treat aging and a lot of people like these other things
42:31
we were talking about, are really excited about this potential avenue for anti-aging.
42:37
- Well, they do have a lot of potential. First of all, we can make new organs using these induced pluripotent stem cells or IPCs.
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And even these autologous stem cells we're talking about that you can pull out from children and from adults,
42:49
they can be used to replace stem cells that get old. But there's a real fundamental drawback
42:54
to using stem cells to live longer. And that is that they often don't find their niche, their resting place.
43:00
Even if you inject them into the eye, often they don't find their home, and in fact, one of the problems was
43:05
when researchers did this to patients in Florida, there were three people who became blind when it wasn't done correctly.
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So- - That coincided with an FDA order that said, "hey, everybody, slow it down.
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Be careful." - You can get some stem cell therapies now, but the majority of them have been banned for now.
43:25
But what is really a problem is that if you can't get them to the right place, they're not going to rejuvenate the whole body.
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So what we're looking at now is, how do you rejuvenate the existing stem cells and stop them getting old, or even reverse the aging of the stem cells, in situ,

Cellular Reprogramming

43:40
where they exist, and we'll get to that, but this is the reprogramming technology that should work, not just on normal cells,
43:46
but even stem cells to make them young, truly young again. - All right, and there's been a lot of research showing
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that stem cells can have a therapeutic effect in like specific parts of the body, but when we talk about this like aging umbrella in general,
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there was one study, actually two studies, a phase one study to phase two study from researchers
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at the University of Miami in 2017 that gave stem cell therapy, harvested stem cells
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from younger donors, gave them to older frail patients
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and small scale, but it showed improvements
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in the distances that these people could walk, it lowered the levels of cytokines,
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it improved their mental state, and they had a reported quality of life improvement as well.
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- Yeah, I mean, that's remarkable. Couple of studies can be reproduced, but for now what most people are using
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the mesenchymal stem cells for is in joints when you wear out the joint and there's not a lot of collagen,
44:46
injections of stem cells into those joints seems to be at least therapeutic for a short amount of time,
44:51
whether or not it's because the stem cells stay in there or the secreting exosomes or other peptides, it's unclear.
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- So this is another area of research then that again, probably people don't want to
45:03
just walk into a clinic tomorrow and get a stem cell injection. Because like you said, the stem cells might not even know where to go,
45:09
but in the future, this is likely to be part of

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people's common anti-aging regimen. - Well, I'm sure. I think the future looks like this, that we can keep our bodies healthy by eating right,
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doing physical exercise, taking the right medicine slash supplements, and when that doesn't work and things fail,
45:28
you can then rebuild the body, replace cells, put in your organs. And that way, we'll live probably many decades
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longer than we can currently live. - And then there's one more thing that in the future we may be able to do,
45:41
and this leads us to this thing that you're doing in your lab right now, you've had quite a few published studies on
45:48
that are pretty darn exciting. We're talking about cellular reprogramming.
45:53
- Well, this is the big one. We've been working for many years on slowing aging, but we've wanted, how do you get that to be reversed?
46:02
Is there a reset switch in an old cell? And we think we found it. We're standing, of course, on the shoulders
46:09
of Shinya Yamanaka who showed you can reset the age of a cell back to zero, but that of course causes cancer,
46:14
and if you do that in a mouse, it'll die within days. So that's not going to be a therapy anytime soon. I don't recommend it. But what a wonderful student, Wan Chang Lu did
46:24
a few years ago in my lab was he found a set of genes that are Yamanaka factors that were able to reverse
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the age of cells and tissues in an animal and in human cells to a certain point, going back about 80% of age, but not to zero.
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So that this was a new, safe approach to reversing the age of the body without any negative side effects.
46:45
- And he did this is by instead of using all five Yamanaka factors, you use three of them. - Three, and the c-MYC, which is the M,
46:52
we definitely don't want that in there, or LIN28. These are what are called oncogenic genes,
46:57
cancer causing genes. So we left those out, and surprisingly those other three, O, S, and K for short, worked.
47:03
Not just in cells in the dish, but even in the whole animal. We focused on the eye because we thought reversing blindness
47:10

would be pretty cool and could be a drug, a very quick drug to develop relative to the whole body. And it worked.
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Wan Chang sent me a text of a picture of an eye where he also regenerated the optic nerve that was crushed,
47:22
and then he went on to restore vision in mice that were given glaucoma, which is pressure in the eye, and even restored eyesight to blind old mice.
47:30
- Let's slow this down a little bit and take people through the process, because if we've gone from like, you know,
47:35
Yamanaka factors to restoring eyesight in mice. Let's talk about first, the conditions that were trying to be fixed
47:45
were damaged optic nerve cells. And you used AAVs, these delivery viruses,
47:52
to send the three Yamanaka factors into the cell. Once they were there, what started happening?
47:58
- Well, to be clear, our genome has the Yamanaka genes in it, but they're normally only turned on when we're little embryos.
48:04
So we had to reintroduce those three genes with a system where we could turn them on at will,
48:09
and we were using an antibiotic to turn them on called doxycycline. We injected them with the virus into the eye.
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It's a very simple procedure. In fact, a lot of patients that are blind get this treatment already with other drugs.
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So it doesn't hurt. Only takes 10 minutes. We put into the eye of the mouse. We damage the eye and asked,
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could those reprogrammed eyes that we reprogrammed for a month, could they regrow? And the answer was yes.
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- And not only did they regrow, but these mice that were effectively blind, they were blind, you can do little tests
48:42
and you can see that their eyes actually work like young mice eyes again. - We put a pressure in the eye to mimic glaucoma,
48:49
which is a major cause of blindness in the world, or we just let the mice age out to one year of age and they were blind essentially.
48:55
And we could tell that they were blind because we show them little images that move, lines actually that moved from left to right.
49:01

And if a mouse can see that, young mice will move their heads, it's called the opto-motor response. - Literally, you can see videos of this.
49:06
It's really cute. They're like watching a tennis match. - Yeah, we do that too by the way. We also, of course, we measure the electrical activity
49:12
of those nerves. We also measure the age of those nerve cells, we look at which genes are switched on and off, and the conclusion was that the nerves went back in time,
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back to the reset, full reset to about 80%, their genes, the gene expression patterns as we call it,
49:26
which is which genes are on and off, was reset to being young again, and the mice got their vision back, as almost as good as they were when they were young.
49:34
- So a lot of people will hear this and say, "man, this is really cool. You can reset blindness in a mouse or reset vision in a mouse.
49:41
Can we do this with other cells?" - Yeah, it turns out that it's not just nerve cells
49:46
that can be rejuvenated and sent back in time. We've done this for skin cells, we're doing it for muscle cells,
49:51
we've done it for other parts of the eye, and in fact that the shape of the eye and the structure of the eye,
49:57
it doesn't just go back in time, it actually rebuilds itself like it's young again. So we're super optimistic that this may be
50:03
a universal mechanism of age resetting in the body that can not just be applied to different mouse tissues,
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but also in humans as well. And we're in the process, hopefully in a year, year and a half, of trying to restore vision
50:16
in human patients that have lost their vision due to either glaucoma or genetic diseases.
50:21
- So this is happening because it's accessing the backup copy of the original state of the genetic code
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that the cells are building themselves up by? - Well, the genetic code stays the same, the epigenetic code, which is the reader of the DNA,
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which we talked about in episode one, that gets reset. So those structures of DNA folds
50:42
that have gone awry during aging, this exdifferentiation process where cells lose their identity,
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that gets reset back to youthfulness. But how that happens, how do you get a loop of DNA
50:54
to go back into a bundle, and a bundle to go back into a loop? We have no idea how that works.
50:59

We know that there's a backup copy of not the genome, but the epigenome, the structures that read the DNA,
51:05
similar to polishing the scratches on a CD with the analogy we talked about in episode one, but how does the cell do that?
51:11
How does it reestablish that original software, and re-install the software in the cell?
51:17
We're only just trying to figure that out now. Eventually we will know how this works and maybe we'll even develop a pill
51:23
instead of a gene therapy that could reset the age, not just of the eye, but the whole body. And when that happens,
51:29
suddenly it can be a very different world. But until then we'll work on vision, and then we'll see where we go from there.

Resetting the Aging Clock

51:35
- Well, suffice it to say, there are several ways that we think that we can get the human body to do this,
51:43
to reset the epigenetic clock. We can do it through cellular reprogramming,
51:50
it looks like it's possible to do through exosomes, and you just mentioned pills.
51:57
And it does appear that it's possible that this is what Metformin is contributing to,
52:03
and some of the other drugs and supplements that we talked about in an earlier episode,
52:08
but I mention Metformin because a lot of people are going to say, "okay, all of this stuff is great.
52:14
You've told me a bunch of stuff that probably won't be accessible to me anytime soon."
52:19
There is a treatment regimen that is being tested out right now
52:26
that starts with Metformin, but a couple of other elements as well. Let's talk about that.
52:32
- Yeah, this is my colleague, Greg Fahy, Dr. Greg Fahy, and he's been working on anti-aging or longevity treatments for awhile,
52:39
and he hit upon a triple treatment. He uses growth hormone, which is known to raise blood sugar levels,
52:46
we talked about that as a downside, but then he realized if he could include DHEA, a hormone that is depleted during aging,
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as well as Metformin, he could mitigate the negative effects of growth hormone. And he gave that for 12 months to 10 healthy men

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that were aged 51 to 65, and lo and behold, when he looked at the biological clock of those men,
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they went back two and a half years. Which may not sound like a lot, but as I thought about it,
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if you could truly reverse your age every year by one year, that means you're not going to age.
53:18
- All right, something that confuses me about this combinatory therapy regimen
53:24
that Fahey used in this small-scale trial
53:29
is that it takes advantage of human growth hormone, which earlier in this episode we said
53:34
probably not a long-term anti-aging benefit. So what was the idea, do you think, behind using HGH?
53:42
- Well, HGH had been shown previously to reconstitute the thymus. This is a little organ gland
53:49
that's here in your chest that is important for the immune system. This is where your T cells, your immune cells come from,
53:55
and growth hormone can stimulate the regeneration of this as it degrades over time. I'm age 50, I probably have what's called
54:01
a lot of thymic degeneration and involution. It's a vestige of what it used to be.
54:07
And growth hormone can stimulate that, but it comes with side effects as we mentioned, not least of which is increase in insulin insensitivity
54:15
or glucose intolerance. In other words, the cell doesn't take up the glucose from the body when you have a lot of growth hormone around.
54:22
So he combined that with two diabetes therapies, one is Metformin, which everybody knows,
54:28
and Greg also showed actually in an experiment that he did on himself that DHEA, this hormone that some people take for longevity,
54:35
can also control blood glucose levels. So that combination of three gave the best effect. But I should say that measuring the clock in the blood
54:43
doesn't mean the whole body is being rejuvenated. That's just one indicator. So what I'd like to see Greg and his colleagues do
54:49
is to measure aging of other tissues and measure it using different clocks, not just the Horvath or epigenetic clock.
54:55
- We talked in an earlier episode about the proteomics clock. - There's a variety of clocks.
55:00
There's glycan age, which are sugars that are attached to proteins that change over time, and there's one called immuno age.

55:06
You measure various changes in the immune system. Altogether, these can be used to get a better picture of whether Greg's treatment is truly reversing aging
55:14
or just some aspects of it. - But the really frustrating thing is, even with these clocks right now, we don't know what we don't know, five years,
55:22
10 years, 20 years down the line. So it's a really good indicator if we can get these clocks to reset, if we can get these clocks to lower, like Greg did,
55:31
at least in the short term. In the long-term, do we have to wait for the longterm?
55:36
- Well, it depends. I know that Greg's research is ongoing and that I was with him a couple of months ago,
55:42
and he told me that repeated treatments over more than a year actually reduce age based on this blood clock, even more so,
55:49
and people are going back by a decade apparently, so super interesting time. I would say the jury is still out
55:55
whether this is truly reversing aging or just some aspects of blood aging, but it's a very interesting time that we live in
56:02
where people are ostensibly going back in time. - One of the commonalities, I think,
56:08
in almost all of these things that we've talked about today is there are these early indications
56:15
that something might have effects and people are jumping over one another to get to them,
56:21
and you know, I mean, some people are going overseas, if they can't get it here, they're finding doctors willing to do this,
56:27
they're finding suppliers from wherever on the internet they can, and it's understandable, right?
56:35
Because people are suddenly awakened to this idea that aging may not be something
56:41
that we have to tolerate in the long-term. So they're eager, but there's still work
56:48
that needs to be done. - There is. But what I think is really exciting is we wrote our book, "Lifespan" in 2018, '19,

The Future Looks Bright

56:55
and we envisage a future where people could turn their clock back and be rejuvenated. It's only been a couple of years since then,
57:03
and there's been a huge advance in the ability to reprogram the body, to measure it.

57:08
These tests are now available to the public to measure biological age from blood and from spit.
57:14
We're in an age where I would say it's hard to even predict where we'll be in five, especially in 10 years from now.
57:20
- But if you're frustrated, if you're really overeager, there are things I think this needs to be said.
57:27
Like you can take steps right now. You don't have to necessarily be taking peptides and exosomes and you don't have to hunt down Greg and say,
57:36
"you know, like give me this combinatory therapy!" Just slowing down the biological clock right now,
57:44
doing the things that we talked about in the first few episodes, is going to buy you that time for these therapies
57:51
to mature to the place where we know that they're safe, we know what they're going to do.
57:57
- Right. - So stay young, stay alive, because the future looks bright just with the current pace of medicine
58:03
and medical technologies, if you live an extra year, you get another three months of life. We could easily approach a time where every year you live,
58:12
you get another year of life. And that's when the world becomes super interesting. - What are we talking about next episode?

Next Week's Episode: External Aging

58:18
- We are talking about aging on the outside. So we've talked a lot about how to keep your insides young. Next episode, we can talk about your skin, your hair,
58:25
your nails, how to keep those looking good, and it's not just superficial. It's really important. It's actually been shown that if you look younger
58:32
on the outside, you probably young on the inside too. So stay tuned for that. If you're enjoying this podcast and would like to support us,

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59:03
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