Lifespan: The Revolutionary Science of Why We Age – and Why We Don't Have To: A Special Interview With Dr. David Sinclair

By Dr. Joseph Mercola

JM: Dr. Joseph Mercola
DS: Dr. David Sinclair

JM: Welcome, everyone. This is Dr. Mercola, helping you take control of your health. I am just absolutely delighted to connect with Dr. David Sinclair, who is a professor of genetics at Harvard Medical School and generally recognized as one of the major thought leaders in the science of how to improve not only our lifespan but our health span.

He started in Sydney. He got his Ph.D. there, and then he went over to Leonard Guarente's lab at Massachusetts Institute of Technology (MIT), and then got his own lab at Harvard Medical School in 1999. He's been working there ever since and really come up with astounding discoveries, which we're going to talk about today. But one of the primary focuses is his new book, which is called "Lifespan: The Revolutionary Science of Why We Age – and Why We Don't Have to Do That." It's going to be available September 10th. If you're watching this and it's not September 10th, you can preorder it on Amazon. Welcome and thank you for joining us today.

DS: Thank you. It's great to be here.

JM: Yeah, yeah. You talk about a lot of great things in there. I want to really highlight some of the concepts that you discussed, because I think there's so much potential to help us hit this, really, the king of all diseases, which is aging. You talk about calorie restriction as being the only proven non-pharmacological method of consistently extending lifespan and protecting it against many of the age-related diseases.

You also discussed intermittent fasting. I'm wondering that one of the benefits of not eating is suppressing mammalian target of rapamycin (mTOR) and activating autophagy. I'm wondering what type of conclusions you've reached with respect to the optimal timing of the periods of time-restricted eating and the frequency of that and how you think integrating fasting or partial fasting into that series might look like.

DS: Yeah. Well, we've known for probably more than 5,000 years that being a bit hungry is good for you. This is not revolutionary. What's been more revolutionary in the last few years is the discovery of the biochemical pathways that actually seem to underlie this actual protection against disease and aging itself. We're not so much guessing anymore what's going on. Science has gotten involved and we're getting more and more studies, certainly in humans, but also in animals, to see what best diet works.

The bottom line – I get questions every day. I wake up to probably a couple of dozen emails about this topic. Nobody actually knows what's best. But we can go through them. I can talk about which is my favorite as well, because it's not just a science aspect. It's also social. We love to eat. We

have traditions. We have typically three meals a day. Trying to deviate from that is really quite challenging. Calorie restriction in animals and in humans is about 20% to 30% less than what a doctor or a veterinarian would recommend. I also struggled with that one, so I certainly wouldn't recommend it. It really means you've got to be hungry for most of the time. I'm sure you'll get used to it, but I didn't get that far. After about a week, I got too hungry and I gave up.

And then I didn't restrict my diet for many years actually. I had kids. That's really hard to do. But more recently, what I've done, which I find very easy to do is basically miss a meal once a day. I'm not hungry in the morning. Some people are not hungry at night. If you can go for – Say it's 7 o'clock at night all the way through to lunchtime, based on the animal studies that I've seen published and some in my lab, that's very likely to do you a lot of good in the long run and in the short run. The science behind it's really interesting. I'll come back to that, but there are other diets that other people have found to be effective in terms of improving biology and biochemical markers. One is the 5:2 diet.

JM: Michael Mosley.

DS: Exactly. I'm sure many of your viewers are familiar with that one. That one is also quite doable, especially if you have sodas and things like that that can actually, or just a bottle of water. More extreme are those diets where you go for a whole week every couple of months or every few months. I haven't tried that. I'd like to.

My view on that is that that's probably going to work the best if you can do it. Because it doesn't just trigger the short-term pathways that we've been studying in my lab. But a week of fasting will really start the body to start consuming its own protein. This is, as you mentioned, autophagy. That's what autophagy is. It's the consuming biological material, which is typically protein. Actually talking with people who've done these fasting regimens, after about three days, something different starts to kick in. People who try this tell me that they have a feeling of euphoria. They definitely get an added boost.

But let me just quickly go back to why we think this works. We've been studying in my lab for the last 20 years genes that respond to diet, to fasting and calorie restriction. The upshot of it is that our bodies respond to adversity or perceived adversity. They turn on these defensive pathways. It changes a bunch of genes that switch on to defend our bodies. At least from many different animals, things as small as worms and flies all the way up to mice and rats, these defenses of the body are extremely good at protecting us against diseases – from diabetes to cancer, heart disease, even dementia and Alzheimer's. These are things that modern medicine has struggled to combat. This seems to be a very simple way to get the body to fight against those diseases.

Often I'm asked how early should you start. In the animal studies, in rat studies and mouse studies, the sooner you start, the better. The longer you do this, the better in your life. Clearly, you don't want to be recommending or seeing teenagers or even people who are in their early 20s do this, because there's still a lot going on in their bodies and their brains. But after 30, if you extrapolate from the animal studies, the longer you do this in your lifespan, the better. I'm just turning 50 now, and I wish I had started earlier.

JM: Yeah. Me too. You mentioned stopping eating at 7:00 p.m. There's a large number of people who advocate – not so much necessarily tying it to a specific time, but at least three to four hours before you got to bed. I've been – largely as a result of exposure to your videos – fascinated by the nicotinamide adenine dinucleotide (NAD) and its family, its cousins, like nicotinamide adenine dinucleotide phosphate (NADPH). When I started studying NADPH, I realized that the biggest consumer of NADPH, which is a molecule that essentially is the battery of your cell and recharges your antioxidants, is fatty acid synthesis. If you're eating shortly before you go to bed, that energy can't be consumed and it must be stored as fat. That's going to really lower your NADPH levels, which is not a good thing to do at night. I'm wondering if you have any thoughts on that timing of the last meal.

DS: Yeah. I do. I wish I could take some of my own advice in medicine. I think if you can have a light meal at dinner, a typical European dinner – my wife's German, she likes to eat small meals – that's great. I tend to snack at night, so it's my downfall. But yeah, to be able to have that fast overnight, that'll boost your NAD levels up, NADP as well. These are all good things. They turn on the enzymes that we study called the sirtuins. They need NAD to function. You can use the whole night to ostensibly repair your body and protect it from what happens during the day.

I also try to take a couple of metformin pills for two reasons. One is that my family has a history of diabetes and metformin is very effective with treating diabetes and even preventing it. I do that for disease reasons, but also because the work of many labs has pointed to not just animals, but tens of thousands of people in clinical trials benefitting from that drug, which seems to enhance and mimic the benefits of fasting.

JM: You talk in your book about this concept of antagonistic pleiotropy, which is essentially multiple actions, some of which may be counter to the intended consequence of the intervention. With metformin, you describe the benefits, which is why you're taking it, but there are some studies published that show that it's a pretty potent mitochondrial poison and that it really targets mitochondrial Complex I and shuts it. It radically inhibits it, so that the end result is that you produce a lot less adenosine triphosphate (ATP). Yes, it upregulates AMP-activated protein kinase (AMPK), but in your evaluation of the literature, how do you reconcile those two?

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DS: Yes. Here's how I take the literature. There are hundreds – or probably even more – thousands of papers that I've read on this topic. Here's my summary. I'm a Ph.D. This is one man's opinion. But what I take away from it is that short-term exposure to metformin in high doses – Yes, it will inhibit Complex I and lower ATP. That's also true for resveratrol, by the way.

JM: And berberine too.

DS: Yeah. Right. But I regard it as hormesis. A little bit of what doesn't kill you actually makes you stronger. So the body recognizing that there are lower ATP levels and higher adenosine monophosphate (AMP) levels will stimulate AMPK, which is known to be beneficial and will actually compensate by revving up the mitochondria and building more mitochondria in various organs, particularly the muscle of your body.

A little bit of inhibition leads to a kickback and a conversation. That's why I think that actually metformin is beneficial, even if it starts out as a – as long as you don't overdose it – relatively mild mitochondrial inhibitor. In the history of humanity and in animal studies, there's a long literature of molecules that if you give a lot of high dose acutely, it can actually kill you. But as long as they don't do harm, can have a positive effect in the long run. The same is true for fasting. If you don't eat, we know what happens. You'll starve to death. You trick the body into thinking times are tough without leaving a long-lasting gap or any damage, and the body actually does better in the long run.

JM: Okay. Let's get into a really important part of your book, which is the balance between anabolism or the building of muscle tissue and catabolism, which is the tearing down and repair of it. Interestingly, when you fast, growth hormone levels increase. Maybe you can go into that, because it's somewhat counterintuitive because there are no nutrients available, so why would you think growth hormone would increase? Maybe you can discuss that a little bit and the influence on insulin-like growth factor 1 (IGF-1).

DS: Right. So IGF-1, insulin-like growth hormone, and growth hormone itself, also in the short run don't seem to be healthy, at least in animal studies. And also Nir Barzilai of Albert Einstein College of Medicine has studied long-lived families, centenarian families. What he's found, in particular to IGF-1, is that some families actually can have high levels of IGF-1 but still live a long time. The reason for that is that they don't have the IGF-1 receptor as active.

JM: Is that Laron Syndrome?

DS: I understand that's a growth hormone as well. No. These are Ashkenazi Jewish families who exceed 100 years old, but it's a similar concept. It's that if you're not responding to these hormones, it doesn't matter really how much the body produces. It'll still have an effect that mimics essentially the benefits you want. It's interesting actually that the growth hormone is stimulated by fasting. There must be something. I'm unaware of exactly why. But we know that fasting doesn't lead to bigger animals. It's actually the opposite.

It could be – now I'm just speculating, but I think it's worth discussing and thinking about – that the short-term bursts of hormones may help the body recover from injury. But those little spikes don't last long so that you're not having any downsides. The other thing about growth hormone – I know a lot of people, including viewers of this show, will be wondering, "What about growth hormone? Is it dangerous in the long run? Should I be taking it? Should I not?" Now, I haven't seen any evidence that growth hormone is going to make you live longer. Typically, it's the other way around, that people who have a lack of growth hormone activity live longer. Laron dwarves tend to have less disease.

But in the short run, if you need to repair your body and build up your muscle, which of course prevents falls and accidents in the elderly. I'm perfectly willing to entertain the possibility that they're building up body bulk. Testosterone's the same. It will prevent these accidents that are actually, largely a problem for longevity. There's a saying actually that "The best way to longevity is to hang onto the handrail." It's a real tradeoff. It's a tradeoff.

If I was to summarize everything that I've learned over the last 30 years, "Everything in moderation, and don't do anything too consistently," because it's like a frog in a hot water bath or in a frying pan. Your body needs to be primed and then allowed to relax, challenged and then allowed to relax. These diets and these growth hormone spikes – I think they're good, you just don't want them on all the time, because then your body doesn't have a chance to recover and you don't get the long-term benefits.

JM: Okay. Tangenting off the elevation of growth hormone during a time-restricted eating fast, 16 to 18 hours or even a longer fast. Many people believe that the optimal time to engage in resistance or strength training might be right before you have your first meal, so that you're still fasting. Your growth hormone levels are activated and you'll get maximum benefit from the anabolic stress of the exercise, which, of course, is increasing peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial biogenesis and a lot of other benefits that occur during exercise. Do you have any –

DS: Yeah. This is really good. You're talking about the cutting edge of thinking. People who are discussing that idea I think are similar to the way I'm thinking about biology. Again, in the full disclaimer, this is now – We're discussing the cutting edge of science, so we don't know fully the answers to this. But what makes sense to me is that we don't want too much protein in our lives. We don't want to eat a steak every meal. Because what we've learned through the work of David Sabatini and many others in the field that, at least in animals and it looks like in people as well, that inhibiting the mTOR pathway by having a lack of certain amino acids is healthy and does actually lengthen lifespan in animals. But does that mean that you shouldn't eat protein? Absolutely not. There are times when eating proteins is important. Same for probably testosterone. Same for growth hormone.

Now we're getting into the nitty-gritty. If you are pulsing these things, when do you do them together and when do you do them apart? To me – Let me talk about what I do personally, because that's actually a better way to approach the discussion. If I'm going to have a steak – I try to be a vegetarian – but let's say I'm going to have a protein shake, I'm going to do that just before or just after I've exercised.

But then I'm also going to have a period in the week where I don't have a lot of protein or I might just have some solids. That's how I get my protein. My body is going like this, but it's not out of sync at times when my body needs protein or, for instance, needs growth hormones. I think what you're saying is really going to be the future, that we can't just say doing one thing constantly is the right thing to do. You have to time these beautifully. Otherwise we're causing stress and damage. But then preventing the healing process by doing something else.

JM: Yeah. Thanks. I do agree with you. I think this is the cutting-edge. Really, an important question that many of us are challenged with, especially in the fact that you so well bring out in your book, is that when we age or we get beyond 65, our protein requirements actually increase for a variety of reasons, from about 1 to 1.2 grams per kilogram. The key is to cycle the suppression of autophagy by not activating mTOR and not giving these calories in protein. Because protein, especially amyloid protein and branched-chain amino acids, will activate mTOR, almost universally.

But I can just share my example. I'm wondering what your thoughts are on it. Because I have an 18-hour, time-restricted eating window that I don't eat. Once a week, I'll extend that to 42 hours. I'll take a day off. Do you think that that regular daily eating window of six hours, combined with a weekly, one-day full fast is enough to activate autophagy, suppress mTOR and not get the downsides of continuous mTOR activation?

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DS: Yeah. It does make sense to me. People haven't even done this in animal studies yet. People need to do that. But scientifically, it makes sense that being hungry a little part in the day will activate and turn on NAD and get an mTOR inhibition. AMPK will come on. But probably the way I'm doing it, which is not as diligent as you, Joe, I'm only doing this kind of a level of reset. I think it's good, but it's not perfect. All you really want to do is this and then, bam, really get a big reset and start chewing up the misfolded proteins, get the autophagy going, get the sirtuins to go and repair everything and sell what they possibly could. I think that's right, that a little bit of stress every day and a lot of stress once in a while is a great combo. But I think that that would be something to actually study in. I'm unaware of anyone who could've done that.

JM: Yeah. I haven't seen the studies on it either. I'm hoping someone is in the process of doing those, because we'd really like the answers. I guess the technology's advancing where we'll soon be able to measure metabolites more easily than in a research lab. By doing so, get an indication of what might be the best strategy.

Now, in your book, I was so happy when you started discussing glycine, which is the shortest amino acid that we have. It's a very important one. It actually – I think it may be the most common. I think it's about 11% to 12% of the total amino acid content in the body. I mean glycine ingestion didn't use to be an issue because we ate connective tissue and glycine is loaded in collagen, so one-third of the proteins in collagen in connective tissue is glycine. It didn't use to be an issue, but we're not eating connective tissue much anymore. Unless you're consuming bone broth or collagen supplements, you're not getting it. Why don't you talk about the importance of glycine, especially with fructose consumption that's so rampant in the United States and the advantage of doing it, especially with the glycine-methionine ratio.

DS: The reason that I take glycine, actually, specifically trimethylglycine, is actually to counter what I think might be dying on with an NAD booster. I'm certainly not an expert in glycine other than that. But I can talk about the trimethylglycine component if you'd like.

JM: Sure, sure.

DS: This is a big question in my field. Just to take a step back, my field and a lot of what my book is about is beyond to trick the body into being hungry and having exercise. One of the molecules that does that is NAD. NAD stands for nicotinamide adenine dinucleotide and we have it in our body. As we exercise and we get hungry, it goes up. As we get older, it goes down. It's needed for life. It's also needed for turning on these defensive enzymes that we work on, called sirtuins. Now, to raise NAD levels what we've done in my lab to mice for the last decade is we give them precursors to NAD. We give them molecules like nicotinamide riboside, or NR, or nicotinamide

mononucleotide, also known as NMN, not to be confused with M&M's. They have the opposite effect.

NMN is what I take each day. I take a gram of it. But the thing with nicotinamide mononucleotide, NMN, is that it has this nicotinamide group on it. It hangs off the main part of the chemical and it's the first bond to break. We see in animals and even in humans that the levels of nicotinamide go up quite rapidly after taking NMN or NR. Two high levels of nicotinamide are not good. In part because the nicotinamide gets excreted through the kidneys. That happens because it becomes methylated into methyl nicotinamide. Methyl nicotinamide had been used for years as a marker of all sorts of things, including at least experimentally to Parkinson's disease.

But the concern that's been talked about in social media, especially, is, "Is this drain of methyl nicotinamide a problem?" The methyl groups are needed for the body. We need methyl for a whole range of things, including antioxidants. As a precaution, I take trimethylglycine so that I continue to give my body a source of methyl groups.

Now I don't know if that's true, but people ask me all the time. I take it as a precaution because I know that trimethylglycine is not going to hurt me. Glycine's good as you mentioned, Joe. The other thing is trimethylglycine, also known as betaine, which on human cells is very good for them, including protecting them against stress. I don't see any downside. It's not an expensive molecule. The upside is that I'm preventing my body from being drained of methyl groups. But the reason that I can't say for sure that it's necessary actually is that our bodies can make methyl groups. There's a whole pathway. In fact I did a Ph.D. on it when I was in Australia 30 years ago. I take it as a precaution, knowing that it's probably not doing anything, except goodness in my body.

JM: Great. Have you looked at methyl cobalamin or methyl folate as a – ?

DS: I have actually. I think those are interesting too. I couldn't say which is better, in fact, because nobody has studied it. But those are options too. I'm seeing now companies selling bottles of vitamins with methyls on them. Those are vitamins that I think are worth taking as well. Those are options, I think. I think, like all professors, we like to say we need more studies before we know for sure. But in the absence of studies, I think those options are the best right now.

JM: Thank you for bringing up the topic of NAD. One of my favorites, for sure, and I want to express my deepest gratitude for you for helping inspire me to understand the importance of this molecule. I first recognized the importance of it – because, of course, we're taught it in any biochemistry class – when I watched one of your videos four years ago. But as I understand, NAD was discovered almost a century ago by Dr. Otto Warburg. But it only recently became to be deeply appreciated as a fundamental strategy for all of health and longevity. I mean it's a coenzyme in over 500 metabolic reactions in the body. I'm wondering, from your perspective, what do you believe was the catalyst for the reemergence of the prominence of NAD and longevity.

DS: Well, I'd like to think it was work that I was doing with Dr. Leonard Guarente at MIT.

JM: That's what I thought. I'm setting you up for it, but that's what I actually put on one of my new books. It's acknowledging you as really the catalyst for that.

DS: Well, it was a team. I'm not just being cool about that. We learned it at the right place and at the right time. We discovered genes that control aging yeast cells. Ironically, that's where NAD was first discovered. I would argue that if yeast weren't making alcohol, we probably wouldn't have discovered NAD for a long while. But, yeah, the Germans did discover NAD. We learned in high school that NAD is essential for all these reactions. We knew that.

But what we didn't realize until the late 1990s was that the levels of NAD in organisms, such as yeast and in our bodies as well, they're really dynamic. It's not just that it's a housekeeping molecule keeping us alive. During the day it's going like this, and then the yeast cell is going like this. That was a shock because, first of all, anything that's that important, you'd think, "How can it go up 50% or 100% during the day without killing us?" Turns out it does and it's actually very helpful.

The reason that we think it goes up and down is NAD isn't just making chemical reactions happen. But there are proteins that sense the amount of NAD in the cell. When times are tough, we're hungry or we've exercised, NAD levels will actually go up and turn on these defenses. That's why when you take a molecule like NMN or give NMN to a mouse, what we think is happening is that you're tricking the body into thinking that it's exercise or that it's hungry, because the NAD levels will go up. So you get the benefit, the protective benefits of these without actually having to necessarily exercise or diet.

But if you're wondering is it fine just to take the pill and sit on the couch and eat potato chips? The answer is probably not. I mean in full disclosure, we have published that resveratrol and NMN work through similar mechanisms that do make mice healthier even if they're fatter and don't exercise. But here's the important thing for those who want to maximize their body's potential, maximize their life, we find that the combination of low-calorie diets and these NAD boosters, or in the case of resveratrol we showed, has a doubling effect. They're actually added in. It's no excuse to just sit around and just pop a pill.

JM: Okay. I think you're right on. I think that the optimizing. In most people, increasing NAD levels, because it goes down pretty radically as you age to the point where once you reach 80, I mean it's almost not there and radically decrease at a minimum. You had mentioned NMN and NR as precursors as one strategy to increase it, but I'd like to discuss some other options. First is actually the NAD molecule itself, so NAD+, which is a charged molecule. If you swallow it, it will not work at all. It's accepted being metabolites to its precursors and to reconstitute it. But it can be given parenterally, either IV, subcutaneously, or transdermally.

There's been a lot of dispute in the literature. I'd like to get your view on it. But a good friend of mine, who actually was just here last weekend, James Clement, who speaks very highly of you, by the way, has done a lot of research in NAD also and uses Nady Braidy's lab out in New South Wales to actually measure it. From his analysis, he finds that –

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First of all, the NAD does seem to enter the cells. There's a transporter, which I didn't know about until he told me it's connexin-43, that substantiates the strategy of using NAD+ itself rather than

an intermediary or a precursor. We'll talk about some of the other precursors, because there's more than just what we're mentioning. But it's James' assessment that the transdermal battery patch applied maybe once or twice a week might be an optimal strategy to improve it. He's documented by NAD's Mass Spec measurements at Braidy's lab. I'm wondering what your thoughts are on that.

DS: Right. There are a variety of ways to raise NAD. This list is not exhausted, but I'll talk about ones we know of that have been really tested extensively. You can raise NAD levels just by taking nicotinic acid or niacin. Niacin has been used for decades to lower cholesterol. The only side effect is flushing. You feel a little bit warm. There's lower list versions. That will raise NAD. Actually there are some of us, myself included that are entertaining the possibility that the benefits you get are, in part, can cause – It also raises NAD.

But in head-to-head studies that I've read, niacin won't raise NAD levels the way some of these other molecules do. I think the reason is that niacin is just a tiny part of the NAD molecule. Let me think of an analogy. It would be like saying, "I can build a house out of bricks, but if you don't bring the mortar and the windows and the doors and the roof, it's going to be a lot harder." The windows and the roof come in with molecules like NR, which is nicotinamide riboside, and NMN, which is NR but with a phosphate group added.

Now you've got more of the house built and you're almost at NAD. So we're getting closer. There's a debate. It's a bit of a silly debate, "Which is better, NR or NMN?" In mice, I can tell you that both work well to improve the health and the lifespan of mice. We've done lifespan of NMN. We're repeating it. It looks good. NR is published that it extends the lifespan of old mice. They're both great. It's really – I think it's semantics to say that one is 10 times better than the other. It's just not the case. They both get into cells. They're transporters for NR. There's a newly discovered transporter for NMN.

JM: That must have been the last few months. I have not seen that.

DS: Right. It came out of Dr. Shin Imai's lab in Washington University Medical School. I wrote a News & Views article on it. It looked really convincing. What we don't know though is, "Is this transporter in all cells or just in the gut?" That remains to be seen. But it really doesn't matter. It's irrelevant. We can talk about transporters all day. What really matters is do you see health benefits and do you see NAD levels going up? I guess the third important thing is are there any side effects or negative side effects? I haven't seen any negative side effects. I've certainly seen niacin, NR and NMN raise NAD levels and provide health benefits. As I mentioned, NR and NMN seem to be better than niacin.

JM: Niacin does have problems. There's no question. Niacinamide even more, as you well know. You've done the research. Actually, I think your lab showed this. It's that the niacinamide actually inhibits sirtuins through a negative feedback loop.

DS: I'm impressed. You've done your reading.

JM: Yeah. I've studied this. I told you. You really inspired me. I mean I've read hundreds of studies about this. That was one of them. But the niacin in high doses is not without side effects, aside from the flushing that you mentioned, which is actually liberation of histamine from mast cells. It radically consumes methyl groups. Not a good idea to take high dose niacin.

But I've concluded – and I might be wrong here, I'd be interested in your thoughts, then we'd go into the details and dive deeper into the NR and NMN – that taking a very small dose of niacin, 25 to 50 milligrams, which shouldn't suck up too many methyl groups, but yet still can contribute to the – at least a normal human studies I've read about the 90 milligram loss of NAD+ per day, because we've got 9 grams in our body, but we recycle 99% of it. The niacin's really only ever good for the salvage pathway. What are your thoughts on 25 to 50 milligrams maybe twice a day – because the half-life of NAD is about 12 hours – to use that as an augmentation strategy to the other precursors or even NAD+ itself?

DS: There are two ways to think about it. One is, "Can you stimulate the body to make more NAD?" Because it is recycled. The other is – which is where I focused my thoughts on more – Which is if we give the cells so much precursor, they have no alternative but to put it into NAD. I think those two ways of thinking are, your way and my way, are guiding what we do. I think it's possible that low doses of nicotinic acid could stimulate the body and force the cell to make more than it otherwise would. But it would have to make more than it otherwise would, because the amount of NAD in your body is in the gram amounts, so milligram amounts are probably not going to, by mass action, push it up.

JM: That was one of the things that discouraged me from even considering NAD as a practical strategy, because there are grams in it. It didn't make sense to me why taking milligrams of something would be of benefit. But there appears to be a benefit.

DS: That's good news. I'd be curious how that works. My guess would be that –

JM: I'm going to attest it, because James Clement has developed this elegant blotter strategy where you can essentially pipette a drop or two of blood on a blotter, freeze it and these get into Mass Spec and his lab and he's going to be able to measure it. I want to do the test this fall and see if it makes a difference. I mean I just don't know. It's just theoretical at this point.

DS: Yeah. Well when it comes to NMN, which we've studied a lot. There were studies on NR on humans. I've seen insights into NMN in humans as well. That work isn't yet published. What can I reveal? I can reveal that taking doses, say, less than 250 milligrams don't have a big effect on NAD in the blood.

JM: That would make sense. Yeah.

DS: You do have to take high doses. But it's complicated by the observation that a single dose won't have a big long-lasting effect anyway. We see that in mice as well. You take one hit of NMN and it will go up, maybe go up about 50%. It'll quickly die or wane levels.

What's interesting in the mouse and the human studies is it's more like a positive stock market where over a period of – in the case of the NR study that I'm thinking of – after nine days, it was an accumulation up to a certain level. If a study has only done a one-time point in a human or in a mouse, be careful because that's probably misleading. You'd want to measure these things after at least nine days and hopefully after a few months. Maybe, Joe, that those low doses actually start to kick in.

JM: Yeah. What do you think is the optimal dosing strategy? Is it every 12 hours or three times a day?

DS: Well, that's also not known. I probably know more than most people on the planet and I don't know.

JM: That's why I'm asking you.

DS: What do I do? I take bolus in the morning. I take a gram in the morning. I know a gram is likely to be raising my NAD levels during the day. I also try to time it with my natural circadian rhythm, so NAD will go up during the morning, getting ready. But if I take it at night, what I find is that I'm actually starting to interfere with my sleep patterns.

JM: Interesting.

DS: Yeah. A lot of people have told me that that's the case as well, with resveratrol as well. It actually makes sense. There are a few science papers on this about sirtuin 1 (SIRT1), which is one of the NAD-requiring enzymes that we study. SIRT1, its activities are cycling through the day with NAD. Turning on genes that are required for morning activities and going to sleep at night, clearing the brain at night.

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If you get those out of kilter, it makes sense that you will not only affect your body's metabolism and find it hard to sleep, but you could even start to have the effects of jet lag inadvertently. I'd like to think that by taking the NAD boosters when I'm travelling, I'm actually resetting my body's clock. I do find, for me, in my experience, I do feel better if I reset my clock with an NAD booster when I arrive in a new time zone.

JM: How does that reconcile with the fact that NAD+ levels increase by about 30%, at least that's what I've read in the literature, once you're fasting? I'm just trying to reconcile that and the fact that you're having challenges with NAD+ at night because of the sleep interference.

DS: Yeah. Well, I don't think anyone's done a 24-hour time course of NAD in people. In mice, we do know that it's cycling through the day. Now, let's see. We're right on the cutting edge here. You have a choice. You can take it at night or in the morning. I think that probably what's happening is that if I take it just before I go to bed, my body's not in a fasting state yet. My dinner is still in there. It's mimicking-fasting. It's raising NAD levels just when it should be starting to tailor off. I think probably what's happening, Joe, is – I'm thinking out loud – is towards the early morning, your NAD levels are going to start coming up, because that's when your stomach's empty

and you've absorbed all of the nutrients overnight. As it's coming up towards waking up in the early morning, that's when I provide my boost.

JM: Okay.

DS: And catch it on the rise.

JM: That's certainly a rational approach.

DS: And then I try not to eat until lunch so I get that big spike.

JM: Okay. I want to dive in the weeds now on NMN and NR. I had the chance to attend a lecture by Charles Brenner earlier this month and talk to him afterwards. Because many people use NR, not as many NMN. But most of the studies done on, at least NR – I haven't really reviewed much of the NMN literature – but on NR, it's usually parenterally. It's intraperitoneal or IV. It's not orally. I mean there are some, but it's not a large amount of them that are done orally.

The problem with that is, as I understand, is that when you swallow NR – and this has some implications for NMN too – that the first bypass goes through the liver and the liver methylates it. The liver gets plenty of NAD+, but the amount that goes to other organs seems to be pretty diminished, which suggests to me that either a parenteral or a transmucosal approach might be a superior delivery method, which is one of the reasons – I asked Charles Brenner this after his presentation, what he thought about transmucosal delivery. He said he didn't know and he hadn't thought about it. I told him that I was using a rectal, NR, suppository that I make myself. He thought the compliance for the would be pretty horrible. But I suspect similar stories with going with NMN. I'm wondering what your thoughts are on it.

DS: We're doing experiments that are required to actually conclude and provide answers to those questions. We don't know the answer.

JM: Okay.

DS: But the experiments that are ongoing in my lab, also in Dr. Anthony Sauve's lab at Cornell, we have labelled molecules, labelled NMN, we were giving that initially to animals and mice. Eventually we could do humans as well. Those are the studies you need to be able to say, "Yeah. NMN's going straight into cells or is it getting modified?" It's early days. We think that a lot of it goes straight in, contrary to what people are gossiping about. But we have to do the hard science. I don't think it's good to just hang, wave and say conclusions that aren't yet justified without the hard science.

JM: Fair enough.

DS: On the NMN side, you probably noticed from the literature that we typically put NMN in the drinking water.

JM: Yeah. It's water-soluble. Right.

DS: It's very soluble. It's also more stable than NR in liquid, so we have the advantage that we can do that. NR in liquid is highly unstable. That's probably the reason that it's not done typically that way. But that's –

JM: Okay.

DS: We don't know what happens in the microbiome when it's ingested either. Otherwise bacteria utilizing it and converting it is different between people's microbiomes. We all have different microbiomes. That's the exciting part of the research now. It's to figure out once you put one of these molecules into the system, "Where does it go? Where are the best effects?" These are important because it'll guide not just the use the molecules in daily life as they are now, sold as supplements, but what I'm focused on is making molecules that will be drug-like and used as drugs that could treat different diseases.

If one molecule is better for liver, one molecule is better for muscle, one gets to the brain, if there are ways we can tweak the molecule and change one atom to make it last for two weeks instead of two hours, that's the exciting future that I see. That's what I spend most of my time on. In full disclosure, everyone should know, even if you see my name on a website, I have no affiliation to any supplement company. I probably do the science and stick with the clinical trials only at this point.

JM: So you have no financial interest in NMN?

DS: Well, yeah. I have biotech companies that I'm an adviser to and have licensed patents to. The chance that I'll save money out of that is pretty low. Most biotechs fail, so I'm not driven by that. But I've never received a cent from supplements. You know, one of my patents was licensed to a company once. As I said, I want that money to go to research and my lab instead. I just think it's better for me, Joe, because I want to be able to maintain the distance and be able to just talk about the science with some credibility.

JM: Absolutely. I heard your podcast with Peter Attia. You went into great detail. There were a lot of claims being made that you're recommending a specific DNA supplement. If you see it claimed like that, it's not true. It's false. You just spent a good portion of your resources to send seize-and-desist letters for those. I'm sorry you have to go through that.

But I want to get back, to just finish up NAD. We're going to go to sirtuins and then gene editing. You didn't mention any thoughts on the intravenous (IV) or subcutaneous transdermal NAD+ itself. The entire whole NAD molecule that you're using the precursors to create. With the transporter, connexin-43, being there, and lots of anecdotal evidence, especially in those with substance abuse and getting benefits from these strategies. I'm wondering what your thoughts are on the whole molecule being given.

DS: I'm the kind of scientist. I don't have an ego in this. If someone can show me data that's reproducible and reproduced in other labs, I'll take it on face value. I've heard the anecdotes on NAD. It seems like there are certainly stories out there – There's something there. What I'd like

to see is just like I'm doing with NMN, doing rodent studies – and like James is doing, James Clement, doing humans studies. Ultimately, putting these molecules head to head –

JM: Yeah.

DS: It can get a little annoying when, "Dr. X says this," "Dr. X says that."

JM: Right, right. Because you've got to have data to back it up.

DS: Yeah. I mean show me them head-to-head.

JM: Yeah.

DS: That's the only way. I don't care what your opinion is. Show me the data. That'll be the ultimate test. The problem is that these trials are really expensive. Typically doing one molecule is hard enough, but doing two in parallel is hard. Even in a mouse study, we don't typically do that. But that's where we need to go to be able to say which is the best. It really wouldn't surprise if NR, NMN and NAD IV are all beneficial in slightly subtle ways.

JM: Okay. Alright. Thanks for that. I hope to – with James – do some of this research this year. Maybe this fall, share some of that data with you, so that we can have some hard science to back it up. Now, I'd want to shift to sirtuins, which are essentially protein environmental stress sensors that are responsible for longevity. Longevity proteins, in simple terms. I guess they were discovered in the yeast and SIR, which are silent information regulators.

It suggests they work by suppressing DNA expression. This is typically done by deacetylating the DNA and other proteins. Now, you did not discover resveratrol, but you clearly, your lab, identified its effect on SIRT1, one of the seven important sirtuins in humans. Resveratrol happens to be one of the polyphenols that do it. But are you familiar with any other polyphenols, like quercetin or fisetin that have shown to have some impact? And then I want to discuss about some of the derivatives of resveratrol that you might be working on.

[-----50:00-----]

DS: Yeah. Well, yeah. You've come to the right person to talk about that. Resveratrol was already known as – It was called a phytoalexin. It seemed to have antioxidant properties. It was even thought at that time to be responsible at – I think some people still believe it's responsible for the French paradox, where the French apparently can eat fatty foods and have great cardiovascular health on average.

That was all there in the late '80s. I came – Well, mid-'90s probably was the real thing where – 60 Minutes did a story on it. I came along in the late 1990s or early 2000s. We weren't looking at resveratrol. In fact, I've never heard of resveratrol when we started working on it. The story goes like this – It's a pretty funny story. We had purified the SIRT1 enzyme from humans.

We were looking in collaboration with a company called Biomol. The lead scientist there was Konrad Howitz. He deserves a lot of credit for this. We were looking for molecules that would

inhibit the enzyme. It was a collaboration. We were sharing stories and results. Konrad called me one day and he says, "Are you sitting down?" I'm like, "I am sitting down. What's up?" He goes, "We've got these strange molecules that may activate the enzyme."

That was, of course, music to my ears, because we didn't know that NAD could be used at that point. We're just on the verge of discovering that. But what we did know was that we wanted to activate these enzymes, because they're beneficial. We knew in yeast and in worms that if we put extra copies of the sirtuin gene, they would live longer. We wanted more goodness. But finding activators of enzymes is extremely rare. I think there's only a few examples in the whole history of pharmaceutical development. When you find one, typically people call BS on you. But here was Konrad saying, "We've got something."

We tested it in the lab. We could repeat it as a result. Yes. It was an activator. But to really show that it was true, we had to put it on some yeast cells and on some human cells. We did that and we found that it extended their lifespan in the case of yeast, and in the case of human cells, protected them. You needed the SIRT1 gene for that to work. It wasn't just an antioxidant effect. It was actually through the same mechanism that we were hoping it was. You asked, Joe, about these other molecules. Well, we tested, Konrad – We screened about 18,000 of them.

JM: Wow.

DS: And published 21 activators in that first paper in the Nature journal, 2003. Now, resveratrol was the best one we had at the time. It got the most attention because the red wine story was pretty funny and interesting to the media. But there were others that were very close to resveratrol in structure and in potency. You mentioned quercetin and fisetin. These are plant molecules as well. They're all produced in response to stress when the plants are stressed, dehydration or ultraviolet (UV) light. They seem to have benefits on organisms when we consume them.

Interestingly, what has later been discovered, though rarely acknowledged, is that these same molecules work on killing senescent cells. The viewers will know of senescent cells, the zombie cells that accumulate in our body and cause havoc. Now, others have shown that quercetin, Dr. Jim Kirkland and others, have senolytic properties, same with fisetin. But what's not recognized typically or admitted is that these molecules were discovered 15 years ago to also be SIRT1 activators.

JM: I thought so.

DS: Yeah. It's really interesting. Now what I think is going on is evidence for the hypothesis that Dr. Konrad Howitz and I came up with, which we published in Cell – I think it was the year 2005. Anyway, the idea is called xenohormesis, X-E-N-O hormesis. It's the idea that we've evolved to sense our environment and molecules that are produced by plants and bacteria in our environment when they're stressed. If we consume those or put them on our skin, for example, our bodies will recognize those. We've evolved to sense our world around us. That's a very good way of getting a heads up if your plants are running out of nutrients or the water table is drying up.

Before we were conscious and we had brains, this was the best way for a worm or a fly to know that times were probably going to d eteriorate. What you want to do is get ready for those types of adversity before they actually happen. That can explain why so many molecules from the plant world have given rise to medicines and why some molecules, like resveratrol and quercetin, fisetin, even aspirin, have remarkable health benefits and target many different enzymes in the body that seems to be well beyond what coincidence could explain.

JM: Interesting. There is probably not a better person in the world to ask this question to, but you so eloquently described sirtuins as environmental stress sensors. When I heard that description, it immediately occurred to me that that's very similar to heat-shock proteins, almost identical. Heat-shock proteins, of course, for those who don't know, are really important to fold your proteins back to the right confirmation so they work properly. I'm wondering if there are any similarities or am I just making this thing up?

DS: Yeah. I want to quickly look at the literature. Because I recall that there were connections between sirtuins and heat-shock proteins. I can't remember which controls which, but they're connected. But in principle, you're right, Joe. This is all evidence of hormesis, that you can stimulate the body's ability to fight against problems.

It's thought that a little bit of heat, even a little bit of cold, a little bit of hunger, some exercise, some hypoxia, lack of oxygen in your body, these are all ways of activating these defense pathways, the same pathways that we've talked about before, such as sirtuins. There are seven of those, which, by the way, NAD and resveratrol will both activate. Just to recap, the mTOR, which lower amino acids, particularly leucine and arginine, and the AMPK pathway, so metformin and inhibition of Complex I; these are the main three defensive pathways. There are others.

But what's downstream of these pathways are things like heat-shock proteins and transcription factors that turn on DNA repair enzymes. There's a whole litany, actually. There are 1,000 papers per year on what are these sensors, as we call them, what do they do downstream?

Here's the good news, actually. We used to think that we had to understand what everything those sensors do to be able to understand aging and be able to live longer. But what I've been arguing, actually, for many years now, is that we don't need to fully know what they do. Heat-shock proteins are great, definitely a part of it. But we don't need to know everything, as long as we can find the right nodes in the cell, to turn them on in the right ratios at the right time. The body has evolved to take care of the rest.

We're getting to the point fortunately – it's been really remarkable to see – where we know what these nodes are. We have the tools to tweak them. We can also change them naturally by fasting and exercising. We can change them with molecules that we can ingest or inject. But now, the cutting-edge is, now, with this toolbox, when do you apply them and how much and in what combinations? That's really what people like myself and you and your listeners are onto right now.

JM: Okay. I want to go back to NAD for a moment because there's an important component that I neglected to discuss with you. That is another strategy for increasing NAD+ levels. It's to not use it as much. From my review of the literature, one of the primary – Well, there are two primary

ones, the inside the cell would be PARP, poly-ADP ribose polymerase, which is a DNA repair enzyme. It's really designed to repair DNA breaks, single- and double-stranded. Every time you have a break, it's my understanding that the PARP will suck out 100 ADP out of 100 to 150 NAD molecules, and basically deplete your level by that much for every break. And then you've got CD38 for extracellular consumptions, which has to do with immune system.

But I'm wondering what your thoughts are on lowering PARP activation. And a real common, not widely appreciated, but one I'm passionate about, it's really the topic of my next book, is EMF exposure. I mean it's pretty well-documented in the literature that I've reviewed that it does activate PARP and decrease NAD levels. In my view, if you could limit that exposure because you're not increasing consumption, you're going to, by default, increase NAD levels.

DS: Yeah. Right. This is a really interesting topic. I could talk all day about it. PARP enzymes, you're right. There are DNA-repair protein. The problem is when you hyperactivate this protein. There's PARP1. There's PARP2. There are actually more than 14 different PARPs. They do drain NAD quite effectively. In fact in my lab, we've discovered another PARP that when you have inflammation, it drains NAD as well. It does make sense to slow them down, as you mention, and in some cases inhibit them. But you have to be really careful because you do need them. We all need them.

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JM: But why would you want to inhibit them? Why would you want to inhibit DNA repair?

DS: You wouldn't, but you'd want to inhibit their overuse of NAD.

JM: Right. By decreasing the insults that would cause them to be activated.

DS: That's the best way. Right. Yeah. Because then you get the benefits of low DNA damage and the benefits of high NAD. We had a Science paper in 2013 that connected all of these together, that the sirtuin gene, the sirtuin enzyme, this SIRT1 we've talked about, actually controls PARP activity. PARP1 is not inhibited by a protein called "deleted in bladder cancer protein 1" (DBC1). SIRT1 controls that process.

Long story short, you'd want to activate PARP, but not too much. That's what we think is going on here, this fine-tuning. But actually, to get to what's actually more interesting, I think, is how do you keep your levels of DNA double-strand breaks to a minimum? I think that's the key, one of the main keys to longevity.

There are two reasons. One you mentioned, which is that double-strand breaks drain NAD. The second, which I think you're going to be familiar with because you've read my upcoming book, is the idea that DNA double-strand breaks also disrupt the cell's epigenome, the storage of the information that we get passed down from our mothers and fathers, mother and father, and the packaging of the DNA. We can get back to that in a minute, but basically what happens is if you have a broken DNA, proteins such as the sirtuins will leave their normal sites where they're regulating genes and they'll go help repair with PARP as well. But then they don't all find their way back to where they came from. Actually, some of them get lost and get distracted.

Over time, what we see is that these proteins that are essential for maintaining cellular identity and cellular function will be lost. We see that in yeast cells. Yeast cells get old because they're moving between breaks and back again to genes. It's two-fold. Before we get to the science – and I'd love to touch on that – The key way is to reduce double-strand breaks, I think – I don't know about irradiation, I have to trust you on that one – but CT scans –

JM: That's ionizing radiation. I'm talking about non-ionizing, but they both do it. Different mechanisms – Ionizing does it through hydroxyl free radicals and non-ionizing does it through carbonate free radicals, primarily through perioxynitrite.

DS: Yeah. Makes sense. I mean you can't avoid DNA breaks. In our body every day, we have about a trillion breaks. One per cell at least. And just living, DNA will break, especially when it's replicating itself and the cell divides, you'll have a break. So even if you live in a lead box at the bottom of the ocean, you'll still have breaks, which I don't recommend doing.

But you can minimize it. I go through the DNA scanners occasionally. I ask the people there – and I've researched this as well – "The amount of radiation is about the same as you get on the flight, but why double your exposure?" To me, it doesn't make sense. I try, if I can, avoid that exposure. X-rays, dental X-rays, you know they're important. I'm not going to deny that. I think that we should know what's in our mouth. But I would try not to overdo it. I think any physician who does X-rays should have a good reason for doing it. Usually they do, but be aware that there are consequences to exposing your body to radiation.

JM: Okay. Let's get to what you just alluded to, which was the resolution of some of these epigenetic damage that accumulates through aging. What I think is one of the most fascinating aspects of your book and which you are using technology, I believe developed by another researcher in your lab, Dr. George Church, who developed or co-invented, as I understand, the "clustered regularly interspaced short palindromic repeats" (CRISPR) technique, and were using those gene-editing techniques to insert three of the four Yamanaka transcription factors into aged mice that have either been experimentally or are blind in some way. You can actually restore their vision through this epigenetic resurrection.

DS: Yeah. We're running over three papers now. This is a sneak preview of what, hopefully, will be published later this year. What we've discovered over the last 10 years – This has been a 10-year project. I'm really grateful to the scientists in my lab who've had the endurance. We've discovered what we think is very strong evidence for what we call now epigenetic noise as a cause of aging. Not just in mammals, but throughout life, even in yeast cells.

What does that mean? Let's just quickly do a biology lesson for those who haven't been in high school for a while. The genome we know, DNA genome, epigenome is the organization of that DNA. The epigenome tells the cell that they should turn on this gene to be a nerve cell and in a liver cell, turn on that gene to be a liver cell. That's epigenetics. Cells inherit that information just as much as they inherit their DNA.

In my book, what I'm proposing is that those two types of information, genomic and epigenomic, they're quite different. The genomic, the DNA is digital, which is very well-preserved and can last a long time. We know that DVDs last longer than cassette tapes. But the problem for the epigenome is that it's analog information. Anyone who's had a cassette tape or a record knows that you can pretty easily scratch these or lose the information. In fact, you can scratch a DVD and lose the information.

We actually think that aging is similar to those scratches, that the information to be young again is still largely in our bodies. But we can access – Our cells can access that information just by metaphorically scrubbing the DVD or polishing it up so that the cell can read the right genes, or in the case of the DVD, the right song.

With that in mind, let me explain what we've discovered. We literally have – not literally but metaphorically – a way of scratching a mouse's epigenome. The way we do that is, actually, we cut the DNA. We create these double-strand breaks, let the cell heal them without making mutations, so there's no change to the digital information. But what we see is the process of proteins moving around and trying to repair that DNA. It eventually introduces this epigenomic noise and the genes that were once on, many of them get turned off. Those that were once off come on. Liver cells start to lose their identities. Skin cells start to lose their identity.

The consequence, we think, is aging. We actually will hopefully publish a paper that shows that if you create this noise in a mouse, it will go through accelerated aging. Not just looking old. It's actually literally old. If we measure the epigenetic clock – I think many of your listeners and viewers will know that there's a clock you can measure from blood in our bodies or in a mouse. It'll tell you how old an animal is or we are biologically. If we do that with our mice that we scratched up, they are literally, most likely 50% older, which is great. But you might say, "Well, David, that's all fun, but why do we care about making a mouse older?" Well, first of all, there's good evidence that we're right about the hypothesis, that every aspect of aging recapitulates.

Second of all, we have mice now that we can change the rate of aging and perhaps even accelerate aging so that they behave more like humans that we can potentially have a better mouse model for Alzheimer's, for example. But then the third thing is if you can give an animal something, then you can actually, with that knowledge, take it away. That's what we've done in collaboration with George. What we did actually was we wanted to reprogram cells. The genes that were once – Let's start with this. The ones on, now they go back off and vice versa. Genes that were once off come back on.

What we find is that by using these three Yamanaka factors, you can actually find the original information in the cell that tells it to be young again. Those genes actually switch, and the cell behaves like it's young again. In the case of the retina, we have preliminary results that we can actually restore eyesight by rejuvenating the nerves in the retina to be young again.

That's early days of what I hope is the future where we can reprogram cells in the body. It doesn't have to be the retina. It can be any cell type in the body you think to actually not just act young, but literally be molecularly young again. In my career, I've seen a lot of cool stuff. I haven't seen anything this cool before.

JM: I couldn't agree more. The potential is beyond extraordinary. I'm wondering if the cells that you're injecting, are they pluripotent stem cells that you're modifying with the Yamanaka transcription factors?

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DS: We're actually just giving the genes to the organism. We're turning on gene –

JM: With the virus. With the adenovirus?

DS: Right. We use the virus that's used by pharmaceutical companies to correct genetic diseases. It's an FDA-approved virus that is very easy to use in the eye, actually. One injection. There's no immune response in the eye, at least not a big one. That's why we chose the eye, actually. It's not just that we saw it as a challenge to reverse blindness, but we also knew that it could be the quickest part to testing this in people and helping them with this new technology.

JM: Is this mostly a local effect that you're achieving?

DS: In the eye, yes, and by design. We don't know the full safety profile yet, so we want to be careful. But we have injected mice intravenously with the virus. We've got mice that are healthy 10 months later. So far so good. It's early days. We've only been testing it on about 100 mice. We have a lot more to do. It's many years of work to make sure it's safe. But, yeah, I think the promise is there. It's just – Hopefully, evidence, if not proof in principle that aging is more reversible than we ever thought.

JM: Do you have plans on putting genes in to make additional sirtuins, like all the seven sirtuin genes in humans, to augment those? I mean that's going to be better than a sirtuin activator if you can have them beyond all the time, wouldn't it be?

DS: Yeah. It would. I only use viruses when absolutely necessary. I think the well-trodden path of small molecules means that there's a much greater chance of success and worse chance of side effects and toxicity with viruses. As great as they are and as exciting as they sound, it's still early days. We don't know.

JM: Yeah.

DS: I don't see a use for viruses and sirtuins in humans at this point, so I'll stick with small molecules. But I do see a future, you know, if you want to go crazy with predictions.

JM: Yeah, yeah.

DS: We could see a world where people do choose to be genetically modified. It's their choice, right? I don't think we can easily go in and modify children even though that's now being done, unless it's life-threatening, of course. But adults know that they should be able to have a choice if they're safe and it's approved then they should be able to do that.

Maybe there will be a day when we are able to carry these Yamanaka genes in our body. And when we get sick or we have an injury – Let's say we have a detached retina or we have a broken spine, then we get an IV that turns on those genes for a month. We recover and rejuvenate, then we turn them off again until we need them again. That would be a pretty wild sci-fi future, but both signs are pointing to at least the biology being possible.

JM: I believe in your book you mention that there's no rational, biological requirement for death. Not necessarily immortality, but you could live hundreds of years theoretically. I'm wondering in your mind what you perceive as the best bridge to pass the, clearly, 120-year limit that humans currently have. Would it be resetting the methylation clock, the Horvath Methylation Clock back to zero with, like, hematopoietic stem cells? What do you think is the biggest step to do that?

DS: Right. I couldn't write money on the DNA methylation reprogramming right now. I've seen old mice regain their eyesight. I haven't seen any technology able to do that previously. If you apply that technology in combination with some of the molecules we've talked about today, in combination with the healthy lifestyle that we're trying to optimize in real time here, I don't think anyone can say what our limit is. Anyone who says that there's a limit really doesn't know what they're talking about or is lying. We really don't know what's possible.

People who have lived to 110 or 115, they typically smoked. They've done no exercise. They had a lot of alcohol. Does anyone think that if they didn't have access to the kind of things that we're talking about today, they couldn't have lived longer? I think they definitely could have. We just don't know how because those people are so rare. Typically they didn't expect to live so long in the first place. Now, with what we know and what people in the future will know, why not? The longer we live, the more access we have to this technology.

JM: Yeah.

DS: I think anything should be on the table. It's hard to make predictions. It's very easy to poke holes in these things. More often, predictions are wrong rather than right. But I can tell you that I firmly believe that anyone who says that there is a biological limit is wrong, because there are plenty of species, and not just trees and not just jellyfish. There are warm-blooded, milk-giving animals in the ocean called whales that can live hundreds of years, three times longer than us. They're not that different from us genetically. They've figured out how to stabilize their epigenome and repair their DNA and do all the stuff you need.

If we can learn from them, I think we can live a life like that. I think historians will look back at the past 20 years as the turning point when we realize that this was possible and finally focused our energy on the topic.

JM: You are the world expert in the sirtuins and having made the association between resveratrol and other small molecules. I'm wondering – I think your lab is working on these small molecule derivatives of resveratrol and other ones that activate sirtuins far more effectively. Can you comment on any ones that are in testing or close to commercial production now that might be orders of magnitude better?

DS: Right. There are a couple of things we're doing in my lab still on this topic that's not widely known, but I'll share with everybody. One is that the question of what is resveratrol really doing. We came out with the bold hypothesis that resveratrol works through sirtuins in yeast cells and that's how that's working. That was very controversial. It was a shock that you could actually activate an enzyme. It was a shock that you could use one molecule, the "dirty molecule," to target very specifically one enzyme. I basically spent the last decade testing that hypothesis time and time again.

We have new research that builds upon our science paper that we had in 2013 that said, "Yes. Resveratrol's truly acting on this enzyme. We now have mice that we've engineered so that they are resistant to the effects of resveratrol on the enzyme." Those results are really promising. The question is, "Does resveratrol still work if you block its ability to activate the SIRT1 enzyme?"

The answer looks like, primarily, yes. That's good. The science is really solid. I wanted everybody to know that we're still working on the science. On the drugs side – Sirtris was a company that I co-founded in 2005. It was my first company. It was venture-backed company. It went public. It was eventually sold to GlaxoSmithKline for a lot of money. I was a child. It got, what's called, diluted down to almost nothing.

JM: 1%?

DS: Almost. Yeah. But the little money I made has been reinvested into new companies, which I'm excited about. But what did that teach me? It taught me that if you let go of your work early, it's very hard to champion. It went well, but it's still not in the clinic. I'll update you on that. The company made 14,000 different activators of SIRT1 but were up to 10,000 times more potent than resveratrol. Those molecules, two of them went into mice. Dr. Rafael de Cabo from the National Institutes of Health (NIH), he put those into mice. They lived longer. It's quite a poly-recognized finding. But it was very clear. They lived longer even on a normal diet, not just high-fat mice.

One of those molecules, called SRT2104, looked great. It went into a study in humans, actually. It was a pill given to patients with psoriasis, plaque-type psoriasis. In a small study, I believe it was somewhere between 20 and 40 patients, Phase 2A. It looked really promising. When the drug got into the body, there was this very significant effect on the disease.

Glaxo still has those molecules. I'm not sure what their plans are for those molecules, but you can bet that I'll do everything in my power to make sure that they make it to patients if humanly possible. We are working, actually, now, on derivatives of the NMN molecule and NAD precursors. Those are exciting as well, because they can boost the levels of all seven of the sirtuins, not just number one. That's where my efforts are currently focused.

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JM: Do they actually boost the sirtuin levels or do they just make them work better.

DS: Mostly it's making them more active because it's providing the co-substrate for their reaction.

JM: Right.

DS: Yup.

JM: Now, GSK, didn't they shut down that lab that they bought from you or your company in 2013? If they did, do you think it was related to the fact that they didn't understand the importance of NAD? If they were testing aging rats or mice, it's not going to work that well unless they do something to augment the NAD.

DS: Well, they had a little NAD program. But mostly they were working on those direct activators coming out of the resveratrol work. What I think they didn't appreciate was the wide scope of these molecules, that they were truly applicable. The other thing, Joe, that wasn't helpful to anybody in full defense of Glaxo, who were a very smart bunch of people, they bought the company right as the controversy around the mechanism blew up. It was Pfizer whose scientists published that this was wrong.

Now, all the trouble has died down now. We've, I think, proven without a doubt that we were right. But in those years of doubt, it was very hard for Glaxo to keep investing the tens of thousands of dollars that it was taking to go into larger studies. I think that was the biggest damage that they did. It was actually Pfizer that caused that controversy with one publication. In hindsight now, it's really remarkable what one study can do to a whole firm.

JM: Absolutely. Are your NMN derivatives getting close to commercialization?

DS: Yeah. They're pretty advanced. I don't talk about them a lot, mainly because we're not venture-backed so we don't need to loan it. We're privately funded for now. But I'll give everybody a bit of a sneak preview. I talk a lot more about it in the book. We are – In humans, we are doing human clinical trials. We finished two studies at Harvard Medical School. This is not my study even though it's at Harvard. It's at the hospital nearby. Of course, it's arm's length from me because I at least have the perception of the conflict of interest, so I'm not involved.

Those two studies have gone well. There are no indicators that there's any trouble. We're hoping to be able to have a Phase 2 study, at least one, possibly two studies beginning later this year and early next. Actually in rare diseases, not in aging itself. Not yet. Actually, you reminded me to say something that's often asked of me, which is, "Why not go treat aging?"

JM: Tell us why. I know why.

DS: It's not a very good business plan. You can imagine the amount of money that it would take to do a trial like that. Normally it would be expensive, but at the end of it, you couldn't sell a medicine if you tried because there is no disease called "aging" right now. I mean there is a disease called aging. You can look at it in the morning if you want. But in terms of regulation, it's not recognized yet.

JM: Yeah. The strategy, it seems to me, especially to obtain funding, is to figure out an anti-aging strategy that does marvelous things cosmetically, because the market for cosmetics is through the

roof. If you have something that's effective, you'll explode in revenues. You can use those revenues to support the real thing that's going to reverse aging.

DS: Well, that's true. That's partly what Lenny Guarente and his team are doing. They've gone to the market first. I'm taking probably a just as hard, if not more difficult route, which is to be able to raise enough money to get to pharmaceuticals, which is a lot of money. It's in the hundreds of millions, but I think that's the path that I think is a better one for me personally and for, ultimately, the product. But, yeah, you're right. It's a challenge. You've got to either get on the market early with something that's not well-proven, or raise the money and wait five to seven years with something that is eventually proven, but neither of those is an easy path.

JM: No, no. But most good things in life aren't.

DS: It's true. This is the big one. If you talk about what's going to play out in the planet and in our community, in our society, clearly global warming, energy crisis, these are obvious ones. But what most people don't realize is that the future prosperity of the planet is going to depend on our ability to keep our populations healthy for longer, in terms of productivity and cost in healthcare. Instead of doing whack-a-mole medicine where we treat one disease often too late to actually have a benefit, the approach really should be one where we're treating the cause of most diseases that will kill us, which is aging itself.

The idea of treating aging was fantasy even 20 years ago. But as I hope you and your viewers are actually appreciating now, the science is topnotch. Me and my colleagues, we publish on best journals. There have been Nobel Prizes on this. The time is now to be able to translate these discoveries into medicines that can have the best chance of giving our future generations, even our own, a chance of not being dragged down economically by the burden of dementia. Alzheimer's is a huge one. Just in general, frailty sucks trillion dollars out of our economies.

JM: Yeah. Frailty is a big one. Well, I want to extend my deepest appreciation and gratitude for all the work you've done and are going to do, because you're still a very young man. The motivations for your work and your book, "Lifespan: The Revolutionary Science of Why We Age – and Why We Don't Have to Do That," is genuine and pure, as far as I can determine. You described it in your book, your discussions with your grandmother and your understanding of death at a very early age, 4 years old.

You're doing a big thing to change the world at a level that is quite extraordinary. I deeply appreciate what you've done and would encourage people to get the book if this is a topic that interests them. I think it should interest most of us, because it's not just about living long. Who wants to live long if – you said it so eloquently – it's frailty? This is without frailty in obtaining all the capacities and capabilities, and certainly the mental ones that we have as a younger individual into older age.

DS: Right. Thanks, Joe. I appreciate it. I hope people who read the book come away with a new view of what's possible. Some people who have read it tell me that it's changed the way that they look at their own lives. That's what I wanted to do. I think we forget how important this topic is, that we can do things right now to alter the course of our lives. But also just the way you think

about aging itself. It's not something that we're used to think about, the way we used to think cancer and heart disease were diseases we couldn't treat. Aging is the frontier of medicine. I talk about what we can do now and what we can do in the future.

I also want to say, Joe, I want to commend you for doing what you do. I could rant on. I've been the victim of some really bad press. Mostly they're not so negative, but more it's hype and exaggeration, things taken out of context. That happens a lot in print media. I think that's just the nature of these reports, because that's what they're paid to do. But these podcasts and these venues – I mean, God bless them. They're a venue for a scientist to be able to be unfiltered and talk in depth about topics that people are really interested in. I think one thing that social media, YouTube and these podcasts have done, it's allowed people to have greater understanding in-depth and direct access to scientists like me, which have never been done before.

JM: Yeah. You cannot get this information on the conventional media. The best you could hope for at a big spot would be maybe five, maybe possibly 10 minutes. Although I guess some of the interviews – It's very rare. You're never going to get two or three hours like you did with the Joe Rogan podcast and others. I thank you for being so gracious. I know you're a busy man. For really taking the time to really dive deep. I think you've done a magnificent job in this interview. You've shared stuff that I really haven't heard you talk about previously. Thank you for doing that.

DS: Thanks, Joe. Thanks for having me on.

JM: Okay.

[END]