# Dr. Andrew's Perspective On The Current Theories Of Aging In The Context Of Telomere Biology? Transcript

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## Bill Andrews Background and Telomere Research

For many of you interested in telomere biology, doctor Bill Andrews needs no introduction. He is the founder and CEO of Sierra Sciences, a company focused on finding ways to extend human lifespan and healthspan through telomere maintenance.

As a scientist, athlete and executive, Bill continually pushes the envelope and challenges convention. He has been featured in Popular Science, The Today Show, and numerous documentaries on the topic of life extension, including most recently, the movie The Immortal lists.

Bill has been a medical researcher in biotech since 1981, focusing on cancer, heart disease, and inflammation. Research. Though his passion has always been aging, in the early to mid 1990s, while at Daron Corporation, Bill led the research to discover both the RNA and protein components of the human enzyme called telomerase.

Bill earned his PhD in Molecular and Population Genetics at the University of Georgia in 1981. He then served as senior Scientist at Almost Corporation and Codon Corporation, Director of Molecular Biology at Birla Sciences and at Geron Corporation, and director of Technology Development at EOS Biosciences before starting Sierra Sciences in 1999, where he now serves as president and CEO as well as Chief Scientific Officer.

Bill is also a named inventor on over 50 U. S. issued patents on telomerase, and author of numerous scientific research studies published in peer reviewed scientific journals.

Bill is also an avid ultramarathon runner. He regularly competes in 50 and 100 plus mile races, often finishing at the top of his age group. He considers endurance exercise, when done properly, to be a way to significantly slow down the aging process.

Bill's obsession is to cure aging, and that includes his own aging. His regimen to slow down his own aging and declining health is unique and based on years of his own research.

Well, Bill, it's great to have you back on the Telomere Summit. Last time we covered a lot of great material. Your whole history in telomere biology talked about mouse models.

Why do you think telomeres are sort of one of the keys to, to, reversing aging and preventing aging? At the very end of our discussion, though, I think I, you know, I asked you about whether you had any closing thoughts about things, and we got into a little bit about aging, and you made the statement that no one really knows, what causes aging.

And then I said, well, you know, I thought that there was some agreement on sort of the overall sort of understanding of aging, with the 2013 paper The Hallmarks of Aging.

And then I think Len Hayflick, published a paper in 2007 saying that aging is no longer an unsolved problem in biology. Of course, that was back in 2007.

And, you you basically said to me, I think you need a little schooling and just, you know, I want to talk about, you know, where we are with aging, and, you know, really to understand how to cure aging, you have to, I think, have a pretty good idea about what, are the mechanisms, you know, what, what to focus on.

And obviously, you've you've been focusing on telomere biology, but I think getting into, discussion about what are the causes of aging, you know, why aging occurs.

## What Aging Is and Why Itu2019s Hard to Measure

With your evolutionary background, and knowing that aging and cancer are two sides of the same coin. I think it would be great to sort of talk about where you what you think the current state of the art is of our understanding of aging.

Okay. Well, first, let me, let me, let me comment on some of the things you just said. The recent paper, Hallmarks of Aging. That's actually wasn't. I mean, it got a lot of press, but it actually didn't really provide anything new.

That, for instance, wasn't provided in Leonard Hayflick book. I forget what the title of that is. What is aging? And there's an other thing. Even back in the 19, 80s, late 70s, 80s and things like that, when I was attending aging conferences, all those things were discussed before.

So it was just kind of a review of where we we stand. So it's nothing new. But, the bottom line is aging is still just a guess. I mean, we know what aging is.

Everybody knows what aging is, but also, nobody knows what aging is. Okay. It's, I mean, we just all saw, William Shatner go up in his face. But when we look at a picture of him side by side from when he was in Star Trek Enterprise or the Star Trek series, it nobody's going to not know which photo of William Shatner was taken first.

Okay. So we do know what aging is. If we could turn William Shatner today into the William Shatner he was 30 years ago. Nobody's going to say prove to me that you actually reversed aging.

Okay. It's. So we do know what it is. We just don't have any way of defining it. Okay. And that's one of the reasons why we can't really do clinical studies just on aging, because I agree with the FDA.

And Donald said last night I was trying to remember who was at the FDA that I'm talking about. I said it was done, in fact, but I wasn't sure it was Donald Frank that I've had lots of discussions with.

And the bottom line is, you know, we don't have any way of measuring aging. We have these markers, okay, including our length and DNA methylation and and, glycosylation IG like constellation.

But, are those symptoms of aging? Are they causes of aging or what are what is what is really going on there? I mean, I think we come back to telomeres lately.

I think I can distinguish between telomeres and, and the other ones, if I didn't last time. But the fact is, is that if we let, let's say that many of these markers of these genes are symptoms of aging, not actually cause of the patient.

If we reverse those markers, have we reversed aging? And the bottom line is, no, I mean, well, we don't know. I mean, it's like in order to to actually prove that we have reverse aging, we need to show that William Shatner or oftentimes I use Betty White as an example.

People that have aged very well, if we have to show that and everybody looks at their picture and say, hey, they look like they did when they were young.

Okay. Are they they act like they're young or they behave like they were young, or feel like they were young? You know, it's all that kind of stuff. So.

So we don't have a good marker of aging, but we all know what aging is. So I always talk about to prove we've, curation, we have to have somebody pass the Betty White test for now.

And then we call it the William Shatner test. Awesome. Now, a lot of people are doing things where they're saying they're slowing down age, but there's no way to measure a slowing down of aging unless you unless you're going to do it in fruit flies where you have a thousand each different group.

And she'll show a statistically significant difference. In humans, you can't say you've slowed somebody's aging down unless you have a negative control to show that.

Like, let's say an identical twin. Okay. That has that didn't wasn't on the treatment and they, they, she didn't slow down like the, twin that was treated.

Okay, so but even one twin wouldn't be sufficient because of an effective environment. It's very difficult to control that. So you'd have to do thousands of identical twins, and you'd have to first take thousands of identical twins that were absolutely identical at the time the study started.

And that just happened. You know, I'm an identical twin, and my brother and I look extremely different right now. But it's it's, we do have 100% identical DNA, as shown by 23 to me.

So, so so what is aging is something that is very complex, but, I think we can still do clinical studies by measuring diseases of aging. Okay, so I say we we do a clinical study to cure Alzheimer's, or as we talked about last time, several other diseases to, and so we get an FDA clinical approved study to do this.

And then during the study, we have this surprising result that, people got younger. They passed the Betty White test or the William Shatner test, when that really wasn't something we were looking at.

Okay. So that's that's the only way I think we're actually going to get an, FDA approved clinical study to actually look at aging by looking at diseases of aging, because we don't really know what aging is.

Yes. But again, we all know what aging is. Well, I mean, it's like, Potter Stewart quote from about the famous Supreme Court case, talking about pornography.

And, you know, we all know what pornography is. We just can't define it. It's sort of one of those things where, Yeah, if you have. And I was think about this when you said it last time because as I mentioned to you, I'm, I guess very interested in and, invested because I spent a lot of time looking at biomarkers of aging.

But if you have a truly amazing age reversal technology or therapy, it'll be pretty obvious, right? I mean, it'll be obvious that the person is gone back to their previous self instead of, you know, you have people that run your you're a runner, you know, they're they're running nine minute miles.

Whereas when they were 25 they were running six minute miles. If they're back, they're running six minute miles again. And we know that they are you know, that they've had their aging reversal.

You don't even necessarily need to look at a lot of biomarkers of aging. But and we you know, we may have a therapy like that at some point. But I'm going to assume that it's probably gonna be a little bit more incremental progress.

And so perhaps if you look at many different biomarkers of aging, including the ones we've talked about, the molecular ones, epigenetic DNA methylation, telomeres, glycosylation, and you look at organ system ones as well, and you see arteries becoming less stiff, lungs becoming more capable of blowing out air faster, cognitive function being faster.

And those are all measurable, you know, with good low variability over the course of 3 or 4 years, I measured in my patients, you might be able to see, a signal at that point.

It's just what have you, I think a multi-point approach to it. So, you know, that's a that's my view.

## Evolutionary Theories of Aging

But what I kind of wanted to do today was also sort of look at aging from the standpoint of, sort of theories of is because there are when I after our conversation, I went and looked out there and, well, you know, I think you're

right.

The hallmarks of aging paper was, you know, widely cited, and got a lot of press. And I think there's a good laying out of sort of major factors that impact aging.

But, you know, it wasn't anything, you know, earth shattering new. There's there's two questions, really, that maybe the audience might be interested in, sort of, you know, what is aging?

But also why does aging occur, which has been something that I think, you know, George Williams talked about in his, you know, the antagonistic theory of aging.

And particularly with regard to telomeres, if there's such great things, you know, to keep long, why have we not had the select the pressures to keep them long?

And I think getting into that a little bit might be helpful. And then finally I read some other the people that are looking at this like me, like Escalante, who talks about, other things being more important, like this quasi programed hyper function of, of cells and mTOR.

There's a lot of talk about more rapid mice. And, you know, I'd like to get your thoughts about rapamycin, visually, you know, your approach from telomere biology standpoint, as well.

So I know that's a lot, but I think those are the kinds of things that I kind of like to get your thoughts on. And I really, you know, it's an open question for me.

Well, first let me say, just one thing on markers, I believe biomarkers of aging are extremely important to test. I think it's a really good measure of health and showing that you are actually have symptoms that are similar to a younger person.

And I think that's really important. But I all I'm saying there is from the scientists in me, that's the studying aging. That doesn't really mean we have reverse aging when we're reversals biomarkers, but it's still good to reverse those biomarkers.

And I think more biomarkers reverse that better. Okay. So and your antagonist antagonistic player Trump, that's becoming a really popular subject lately as to why curation.

And, you know, I kind of like wonder why it's become so popular, but I it is kind of fun to say, okay, antagonistic, neutral. You're like, I think it's gotten caught up in.

But if you ever studied poetry, which I was had to do extensively in my high school, you'd know that it's actually only one syllable short of iambic pentameter.

Okay. Which is kind of like a poem. Antagonistic heliotrope. I it's so it's it's gotten really popular. But I don't understand really. Why? Because, and I think there's, let me say a lot of theories about why we age, are based a lot on some possibly misunderstandings about evolution or biology, the biology of particular traits they're looking at.

But the, so, so my and again, nobody knows. It's all best guesses. But the question is we've been evolving for so many millions of years. Why why haven't we evolved to get rid of aging?

Okay. Why do we age when that seems like wouldn't that be an evolutionary great thing to have happen? Change to us that make humans better? But the fact is, it's the exact opposite of truth.

Okay. And so so that's why like understanding evolution is really important to really understanding the evolution of aging. And they evolve. And evolution is really comes down to the ability of a species to survive a rapidly changing environment.

And sometimes that environment is humans. Okay. So animals on the planet are disappearing and stuff like that because of humans. And really, let me go on a tangent here.

Just five days ago, science magazine published a great little study on tusks. Elephants. Okay. So elephants with no tusks. They've shown that the percentage of elephants that don't have tusks have gone from 2% to something like 40%.

Okay, in the last 30 years. That's great. That's why. Yeah, it's because of poachers. Poachers. So, so, so all of a sudden. But. So when you talk about different gene combinations, variations, you have your alleles, different different types of genes that occur at the same locus in the chromosome.

So different alleles and some are called risk alleles. Okay. Doesn't mean that they're a mutation. It means they're probably the event. Maybe they were the original gene.

And we evolved a different mutation. That's not a that's not a risk. And that's the mutation okay. But but sorry, I got confused there. But the fact is, is that tusks, the genes to produce tusks in the last 30 years or 40 years or whatever has suddenly become a risk allele.

Okay, so an elephant that has a gene to produce tusk is more likely to survive. And that may, in fact, in that study, they say 1 in 5, they have a five times better chance of dying from a poacher and an elephant that doesn't have any test.

So now all of a sudden, elephants have evolved partially to where they don't have tusks. And if we keep it up, they're going to be you're never going to see any elephants with tusks.

Okay. So evolution. That's so the ability to survive in rapidly changing environments. The onset of humans was a rapidly changing environment for the elephants.

Okay. So how do you what's the best way to survive for a species in the mirror? Evolution is not something that's geared to make the individual better as to make the species better.

Okay, so what what is a way? What is the best way for a species to survive change? It's rapidly changing environments and that is shuffling its genes.

Okay. So by by creating as many variations of the species as possible increases the chances that at least one or more of those variants are going to survive a rapidly changing environment.

An example is that elephants with the tusks. Okay, so so, you know, beforehand there was no evolutionary advantage to having tests or not having tests, or maybe there was an evolutionary advantage to having to us, but suddenly it got changed.

Well, we in in aging, we we have we we we want to survive a rapidly changing environment by shuffling our genes. But if you do the math on the shuffling of genes, you actually get a lot more shuffling by letting the offspring interbreed with each other and by having the, by than by allowing the parents to re breed.

Okay. So if you just if you let's, let's say go go to the extremes, let's say you have a population where the parents keep reading and producing offspring, but the offspring are allowed to breed.

Okay. Well the shuffling doesn't, doesn't, get very expensive. It gets more expensive by allowing the offspring to have whole variations of genetic genes than the parents. So.

So by so if you have two species and one is encouraging the offspring to interbreed and the other one isn't, the species that is allowing the offspring to interbreed is going to be more likely to survive that rapidly changing environment.

And what's the best way to ensure that the offspring interbreed? And that's eliminate the old okay, there is no evolutionary advantage to living longer than it takes to raise your young.

After that, you're just in the way. And that's why we age, in my opinion. Okay. I mean, but that's based on a lot of understanding of evolution and biology and stuff.

So, so it's it's if you have two species, again, one that doesn't have an aging process and one that does have the same process, that that species that has the aging process is more likely to survive.

And the one that has the it has no aging process. So, I mean, that is, the set of facts that you put forth there can also be consistent with the idea that it's the hostility of the environment that, a species is in that is the major factor.

So you take, you know, an example is given of the field mouse, and why they have a life expectancy of, you know, under a year, because the how the hawk is going to come down and take them out.

And Thomas, you know, Tom Kirkwood's, I think he was the originator of it, but the popularizer of the idea of the disposable soma that aging comes in through the back door, not because it's programed, but because it's not programed for its, you know, the mouse is going to be as fit as it can be for the time that it's likely to make it to reproductive maturity, and then after that, to invest in keeping the soma, healthy and not aging is energetically doesn't make sense for, for for, for selection for for evolution.

And therefore you don't have to invoke necessarily do you want to get rid of the older generation? It just is gotten rid of because you reach that peak where you know, this environment is such that, that, that species that, you know, doesn't want to invest more in because they're going to be dead of unnatural causes before them.

So that's where antagonistic atrophy comes in. You know, if you take the mouse into the laboratory, then you keep breeding them like, like they had and they start getting longer.

Telomeres. We all know that, you know, mice in the laboratory, live longer than the mice in the field. Then you get a sort of a different thing. And I don't know, I mean, and I'm just asking, does your theory necessarily outcompete not to use a, you know, an analogy?

The one of two sort of the disposable thumb or somewhere where it's just not invested in those repair and maintenance, or the longer telomeres that maintain the soma after peak reproductive age.

That's the kind of thing, you know, classically, what I've read in a lot of books and and you what you're talking a little bit is about group selection, I guess.

On a species. What selection is group selection? I guess you're kind of talking about, and, you know, you and I have talked about this before whether, you know, I guess that that's back on the table.

I mean, I think it had been sort of not thought to be what's happening with aging, but you're saying you think that is to a certain extent. And if that is, how does that does that change, though, the the understanding of aging and the understanding of how to how to alter it?

Well, first of all, I start off by saying I think aging is actually a very recent evolutionary event. Okay. And I think that, a lot of especially when there's more and more, animals on the planet and more possible.

So predators are changing environments, in different, different species have evolved different mechanisms of aging. Okay. And then they also have evolved different mechanisms of getting rid of the old to increase the shuffling of the genes.

But mice, I personally don't believe that mice age in the same way humans do. And we haven't gotten into telomeres, but telomerase is a big key there.

And, you know, Richard Cutler, for instance, I want to say 30 years ago published a really great study on, antioxidants, natural antioxidants in the body.

And humans have, let's say, like 100 times better antioxidants and than mice do. So, so mice actually, I think suffer tremendously from oxidative stress.

And their conjugate is function, whereas humans really don't. I mean, we would if we could overcome our other, which I think is telomerase, we overcame our other aging processes.

I think we might become victims of oxidative stress and that a cognitive function at a much higher rate than we already are. I see, and you said something that I wanted to come back to.

Yeah. Okay. So, in terms of, different species, I mean, you know, there's our strategists and strategists, for some reason, I think we discussed that at our last.

No, we didn't get any into you, and I have to, but I just listen to it. And we didn't talk about our species in K species, which we should. Yeah, I, I get the r and the K mixed up one sometime, but the, I can't humans are either.

I think we're partners for rapid. Maybe so I think that might be okay, but I'm not 100% sure. So workers. But but the point is, is that some species, breed young, produced lots of offspring, some breed some species breed old and produce few offspring.

Okay. And so they have to have to get to evolve different mechanisms to survive. Whereas the species that breed young and produce lots of offspring, they can afford to lose 99% of their offspring and the species will still survive.

Whereas organs like humans, we can't do that. We have to. We have to evolve mechanisms to keep us alive long enough to raise our young. Right? Okay. Now.

And that's all.

## Telomeres, Cancer, and Aging Mechanisms

After we've raised our young, as I said before, there's no evolutionary advantage to staying around. We're only in the way. So the, and what I want to say was, so the key strategies are synergies.

We want to, see, there's again something else I want to just come back for for longer. Life of the Soma, because they need to be around to be around longer.

So, I mean, I think that that is, you know, that's that's a that's a key distinction when you're looking at animal models in a lot of people. And you include I think mice are not a great, model for studying aging just because they're, they're, you know, they have that they are in our, in our species and a lot of things that might work in mice, you know, never mind see elegans or some of these other ones that are around for, you know, nine weeks, you know, that's, that's a different aging model.

So, you know, and I hear about growth hormone and, you know, people talk about how growth hormone is is pro aging and IGF one is pro aging. Because knockout models, you know, the mice live a little bit longer, but those mice are going to survive very well.

So you know, we're talking about optimum function as well as we get older. And I think there's a little bit of a trade off there. And to use a mouse model for that is I think it's not a great I mean, you Stephen asked stats talked about that.

We need to as we studying naked mole rats or bats, long lived mammals that that, that are, you know, that are more akin to humans. The other thing I wanted to bring up just briefly, was also, you know, you talked about getting out of the way.

There are some species, like whales, and particularly any species that doesn't reach a fixed body size. It just keeps on getting larger that don't have sort of any kind of major aging going on.

And what's in play there in your evolutionary theory? I mean, evolution is just probabilities and statistics. Okay. So even though there's a selection, it is you use the word selection when I talk about evolution because I don't like to use it.

Evolution is not a force. It's a result okay. And the result is that, some of us, some of the species have evolved aging, but that doesn't mean all of them have, okay.

It's just a probability kind of thing. So let's say whales and other animals like that haven't been through a, environmental, a rapidly changing environmental phenomena that had caused them to, need to have an aging process.

But we don't we of course, we still don't know if they have aging process. We just don't. We just know that so far, aging is undetectable or at least, it's very negligible relative to other things.

I, before I, I was saying I there's something else I want to say is, I do want to say I do strongly believe in antagonistic trouble. Okay. I do believe that there's a lot of roles that that has played in evolution.

But when we come back to the idea of telomeres and cancer, I'm, I'm going to give an argument that that really has nothing to do with it. But I do believe in all that.

I do believe that's a very strong factor in evolution. Just sounded like maybe I might have misrepresented myself there. No, I mean, I think go ahead.

Yeah, I wasn't I wasn't sure where there. So I'm glad you made that clear. And I think there are good examples of it. But I mean getting getting back to telomeres then if, if the idea is to, you know, aging is there to get rid of older, older members of the species that have already passed their genes along, is that to me?

I thought that the reason telomerase, and it's hypothesized that telomerase is suppressed, at birth is to prevent early cancers, you know, retinoblastoma and things like that that occur before peak reproductive age.

And that because it's continued, then it causes aging later, not necessarily the cause, aging to get rid of older, older adults. Let me ask you a question.

How does how does turning off telomerase prevent a young person who was younger than have been able to raise their young? How does that prevent them from dying from a cancer?

Well, I mean, for retinoblastoma, I guess. I mean, maybe they just lose their eyesight and they can't look around and take care of themselves. But, you know, anything that, if a cancer doesn't actually kill you, if it makes you dysfunctional, or like a Wilms tumor or something like that, then you know, you're not going to make it into the next generation.

If you can prevent that, then your life, you then pass your genes on to the next generation. But I again, I I've always been I'm agnostic. I still don't quite know that I understand, you know, whether because if it has just a I mean, how did it evolve?

That's really my question. If you have you're the me I'm asking, how do you think it evolved that it was turned off? If it would be such a great idea to keep our telomeres long?

Yeah, but here's here's the thing. So maybe you misunderstand. My question is because how does turning off telomerase prevent the I Chris I said dying from cancer, but how does it prevent the symptoms of cancer and the problem is I mean, the problem is, is that when you're young, let's say under 30 years old, or under 25 years old, your tumors are so long that if you got cancer, that cancer is going to get so enormous before tumors can shut it

off, you're going to die from it regardless.

Okay? So it's it's the only the only time shutting off telomerase or preventing the allowing telomerase to shorten is going to prevent cancer is in older people.

And as I was saying before, there's no evolutionary advantage to keeping older people around. So so that's why I don't believe antagonistic to me when it comes to telomeres in cancer.

I don't believe we shut off telomerase to keep us from getting cancer. So the widely discussed and I'm sure our listeners will have read papers or heard in or read in lay press books that, you know, the reason telomerase is repressed is as a tumor suppressor mechanism.

You don't believe that's true. And I think you're you're probably right. But, you know, these things get said and they just keep getting said. And, and I think it's good to sort of challenge that.

Yeah. Well I or my, my way is instead of debating all that kind of stuff, of course I'm doing an interview with you. I, I didn't get down here to date them, but I'm just telling you my personal views.

But to really, to really address that question, we just got to do the science. We got to. So, so I was saying so early on, I meant to say, we will never, ever be able to show that we have control of aging by slowing that, showing that it could slow down aging because slowing down aging.

So our the measures reversing aging is easy to measure okay. So what we so my research is geared towards finding a way to reverse aging. Partially. I don't want to say totally partially to answer that question or be able to ask the question so that we can answer, does telomere shortening have anything to do with aging?

And the only way to show it is to show that lanthanum actually reverses aging, not just in engineered mice, but in humans too. So we want to do that. But at the same time, when we lengthen telomeres, we want to find out does it increase the risk of cancer? Okay.

So in in all of our clinical studies and ones that you have been actively involved in to now not we haven't done any clinical studies. The ones that have been involved or you've been involved in.

So helping us with some of our clinical protocols, we're asking all those questions. We we're we're, we're we're going to when we start to study, we're going to be looking, for cancer in patients like doing Pet scans and stuff like that before they get treated and then again after they get treated.

But we're also going to be looking at every biomarker of aging, including DNA methylation and glycosylation and telomere length. But we're going to be doing all that kind of stuff just to answer the question.

So we don't all the answers. But, and nobody knows the answers. But there's so just theories. But instead of debating what's true and what's not, when everything is really just best guesses right now, I would rather just do the study and get the answer.

Okay, so that's my focus. So that's why you don't find me getting up on stage debating a lot of these things or writing books. The debate them, I just I call them my best guesses.

And usually when I get on stage, you know, I think, you know, look that's that that makes perfect sense. If, if you can show that and it's obvious through the biomarkers and through just the Betty White or the William Shatner tests, now that you have reversed aging, then you know, you don't have to know the call of aging that we do.

You've already fixed it. And in some ways. And then you can reverse engineer what you actually did to sort of come up with more credible theories of aging, that, you know, that have been because, I mean, that that is, I think, I think the, the, the proof is in the pudding, as they say, but that kind of thing.

But but to know what to spend your time on, like, so there are people that talk about telomere as being passé in terms of aging, which is kind of I think it's been a bit of a trope lately.

You know, in that, you know, they don't have that much to do with aging. I point to them, you know, the examples of telomere biology disorders. I mean, those people don't make it in in the first generation past 50, in the second generation past 30.

And then after that they don't make it out of the womb. So clearly telomeres are important for the aging process. And I don't know why, you know, it's it's not thought that the telomeres still are, you know, the one of the major aspects of it.

But, yeah, I mentioned earlier that there is a lot of interest in rapamycin and turning down mTOR. And this theory that aging and senescence is all about, a program that makes you go from a single cell to a fully grown adult, a growth program that then doesn't get turned off completely.

And then causes these, which is would be a classic example of an antagonistic peer dropping. In some ways, turns on these hyper functioning programs with increase in lip agenesis and an increase in cytokine production and senescence.

You know, what are your thoughts about that and what role mTOR might have in aging? And whether there's any mechanistic links to telomere biology? Because I know a lot of people are talking about there's I'm sure hundreds if not thousands of people that are taking intermittent, rapid rapamycin.

Now, and I was thinking that perhaps we're going to do that. You might want to do that. You know, after taking something to help your telomeres, the telomerase activator, too. But maybe you could address that or enters like a, central station for us.

I can't think of like a central station where everything comes in and everything can go a different directions. The mTOR plays a tremendous multiple roles in health and aging.

And I do believe rapamycin is an extreme, important thing to take. I, I, I, I'm only concerned. The only reason I'm not taking rapamycin myself is because of the side effects of rapamycin.

But there are there are some, rapamycin kind of analogs, but it's not really an analog. I mean, you tell me what this is. There's there's now rapamycin packaged inside of nanoparticles that would target specific cells that would make rapid myosin an analog.

But it does make it the drug kind of an analog of rapamycin. And, it delivers it delivers rapamycin to the correct cells, not the incorrect cells. Because rapamycin targets, it goes to a lot of different cell.

What's the company name? Selecta Biosciences, I think it is. They have this, and you and I, I've talked about this a lot. SVP Rapa, which is, right as he stands for, small something particle I can't remember was it's not viral particles, small vaccine part, and it packages rapamycin in it.

And the results that they had is that it? There's no side effects, okay? It just does all the good things and none of the bad things. They're still in clinical studies, but boy, when that comes out, I think that's going to be a blockbuster.

And I think personally I would start taking, I think everybody start taking it, but it's, it's biggest claim to fame is going to be to actually prevent, graft versus tissue versus graft disorder or when, when you do a transplant, scratch versus, tissue.

Yeah. Graft principles and tissue transplant. You that person often develops an immune response against it. But if you if you treat with SVT rap a they've changed the name to Inter IMT for some still in clinical studies.

But when they apply that to the patient at the same time, putting the tissue on the patient never gets any immune

responses to the tissue. So it's the all the good things about rapamycin and not the bad things.

But yeah, I'm, I'm, I'm a big, big fan of the whole inter mechanisms of, of controlling, health and aging. But they talk about mTOR, inhibition being, a pulsatile thing as the best.

You don't want to do it all the time because you do need to, you know, repair wounds and, you know, have healing take place. And I think, you know, the low dose protocols, at least, that I hear about the lot or something says, yeah, well, low dose would be better than five milligrams once a week.

Six milligrams, seven milligrams, whatever. Once a week. There really are very low to, to, quite minimal side effects with it. And, you know, the question is how effective is it at that dose.

And that's being studied, you know, actively right now. And it's also being looked at and, I have a few patients that are starting it on their own. And we're looking at their biomarkers and with a lot of curiosity about what's, what's going to happen with them.

Do you think that there is a tie in with telomeres of some sort and how telomerase activation might work with that? I think I think there's a chance and that, but I can't prove it.

I think there's a chance that if we prevent telomere shortening, there won't be any need to take rapamycin. But I don't think that, all the pathways involved in mTOR have anything to do with telomeres, shorter telomere.

So like I said, I'll come back to this later. Methylation, DNA methylation, glycosylation, those those might be symptoms of aging but also causes of aging okay.

But they are more symptoms of aging. Telomere shortening is not a symptom. It's not it's not a symptom of aging okay. There's nothing that aging does.

It causes telomere shortening except at a lower level of increasing inflammation and increasing oxidative stress. That will have some effect on telomere shortening.

But if you did away with all that, you still have the telomere shortening, because the main cause of telomere shortening is just the basic process of cell division, one cell divides.

The new chromosome is made shorter because the cell lacks the ability to replicate all the way to the end. Okay, so so that kind of thing mature is not going to have anything to do with the basic basal level rate of telomere shortening, which is just from cell division at the accelerated rate of tumor shortening caused by, oxidative stress and inflammation.

It's really cell division. Just increasing cell division is also going to cost you, a shorter. So in that way, yeah, I take that back more. So solving the entire problem would, would decrease inflammation okay.

And therefore decrease rate of tumor shortening. So thinking out loud I'm glad I just put that together. Yes. So I definitely believe that that that should have some benefits.

## Rapamycin, mTOR, and Senescent Cells

Whether or not it's going to be as significant as the basal level I'm not sure. And just from cell division, I mean, we have cells that divide all the time.

That's our skin cells, our immune cells, our gut cells lining the gut. They're called interesting system. I forget what they're there's there's intermittent replicators.

Non replicators. Can in terms of types of cells. And there's the other one which are cells that constant, the type of cells. That if those are one type. Yes.

In the guts lining the guts, they're the, the actual stem cells that actually produce all the other cells and the same as the bottom over your ridges in your skin are the stem cells that produce all the other cells.

So the, yeah. So, so not fitting where I was going, but it's it's, homozygous. Yeah. People are involved in that, obviously, because if they can't continue to, until they get to certain they can't do so if rapamycin helps, helps stuff by reducing inflammation, then perhaps, you know, that there would be a synergistic action, which I, I think that makes a lot of sense as well.

We've been I going was that. And so cells divide all the time. They're still going to divide okay. Even in the even when working with rapamycin. Oh right. That's true. Right.

That's the problem I and doesn't do anything about, you know, telomerase activity or anything like that. And and the cells continue to divide the. So you have this sort of mTOR inhibitor rapamycin side of things.

You have the telomere side of things. A lot of people are looking at, the role of so-called analytics, in, in, in aging and how to treat aging, because, you know, accumulation of senescent cells and tissues not only reduces the ability of those tissues to regenerate, but also secretes a lot of inflammatory cytokines that can cause, tissue dysfunction, and, and potentially cancer.

Judith Campisi has done a lot of work in that area. And so there's quite a few biotechs now looking at analytic therapy. But you know, Michael Fossil, has written a paper, you know, kind of criticizing that approach, saying that if you get rid of these cells, then they're just going to have to be replaced by other cells, which would then cause the remaining cells to have shortened telomeres, which will then further accelerate the process.

And so he thought that, particularly, you know, in probably in your camp, but I'm curious to hear, that the better way would be to increase telomere length by turning out telomerase so that those cells, would potentially get reverted back from senescent cells back into normal, healthy cells. Do you think that's a possibility?

And what do you think of Michael's, potential criticism of satellite therapy? I agree 100% with Mike fossa. He knows that he and I talked a lot about that.

I've been I've been talking about the idea that, getting rid of, near senility, senescent or senescent cells. You are going to have to have other cells divide to replace those.

And that's just going to accelerate telomerase, okay. Because of the induced cell division. So so analytics I mean is a temporary solution works really well in mice.

But again mice I don't believe age by telomere shortening. They're they're killing it fairly much. But the bottom line that really worries me about Celebrex is that I haven't really seen any studies yet that show in a 95 year old person what percent of their skin cells are senescent.

Okay. And if you were to kill all the senescent cells in a 95 year old, is that going to kill the person? Okay. And it's it's so I think we've got to we've got to come up with a better solution, I think.

Yeah. Senescent cells are bad, but I believe that what the later thing is that turning a senescent cell into a nonsense and so would be the better thing to do.

And what do you write? And Jerry Shay did do that, in vitro. Okay. They were able to, to put a inducible telomerase gene into, cells, let the cells get to senescence and induced attrition to turn on.

And when consumers and the cells came back again, they published that, I want to say 15 years ago. So it's it's and you know, why nobody's gone and reproduced that?

I think it's because those experiments are expensive and things like that. But it was a it was a pretty good study. Yeah. I mean, so so go ahead. Yeah, I think that's I think that's the better solution.

But here's the thing is that it is true that cells do accumulate damage. Okay. And so senescent cells, especially when telomeres get short. The damage increases a lot because short telomeres accelerate mutation rates.

But the bottom line is that it's 99.9% of the time a cell gets mutated into an unhealthy state. It can be replaced if you if you take, like, let's pretend our skin and other organs are like cells in a petri dish.

If you mix healthy cells with unhealthy cells 5050 and let them grow. After a few passages, the healthy cells are going to far outnumber the unhealthy cells because they're going over growing.

And so by by allowing senescence only allows for us to collect these damaged cells, by preventing senescence, it's going to allow us to replace those damaged cells.

The only exception is cancer. Of course, cancer is going to be a case of when cells mutate to become cancer. They're going to probably outgrow the non cancer cells.

So if if we were simply looking at cancer cells in a petri dish, yes, cancer is going to win. But when we look at cells in a human, we also have our immune cells.

And our immune cells are one of our best defenses and best ways of fighting cancer. And by keeping the tumors long in our immune cells increases our ability to fight cancer.

But still, they could lose to I mean, that cancer's evolved to, let's say evolve, mutate to, to find ways to actually overcome the immune system. So you we're we're in a situation where there's no win win, perfect win situation.

Turning, keeping keeping telomeres long does have ways that you can imagine to allow the cancer to kill you better, but also keeping telomeres so keeping to because keeping telomerase longest at that, keeping telomere short actually has a better chance of allowing that cancer to kill you.

Because of the fact that your immune system gets weak in other, defensive mechanisms decrease. So so it's a kind of a balance. Is are more people going to die from turning telomerase on?

Are more people going to die from cancer by turns to on? Or more people can die from tolerance by turning polymers off. And that's still an as a testable thing that we have to test.

But I my best guess is that the, the idea of keeping telomeres long is going to traumatically decrease, the death rates and or side effects rates of having cancer.

So we can it's just a guess and we have to test it. And I think it's a really good guess. Based on everything I know about cancer, you know, I have a strong, very strong cancer background.

Understand cancer very well. And I also understand aging very well. So when I, when I look at this, I actually see this at, there's still always going to be people getting cancer, but people are going to be getting a lot less cancer if we keep telling as long.

Yeah. I mean, I think that, right now, the prominence of evidence that we're not have enough of it, but is certainly in agreement with that, as a I mean, we went from theoretical thought, you know, the theories of aging and talking about curing aging as a practical matter.

Right now, people are doing things like taking analytics, potentially taking small molecule, you know, activators like to use 65, what would you say to them in terms of what is, something you think would be a good idea, a bad idea?

I was thinking, you know, you're going to take a step analytic like a less potent one, like, you know, physician or quercetin, that you would probably, given what you and Michael have talked about.

And, you know, this idea that you want to be able to replace those cells is going to be more of a need to replace

those cells that you want to take telomerase activator.

At the same time. Is there anything you would avoid, like the Sassanid or some of these other ones that maybe a little bit more potent? So lytic therapies and I know you're not a clinician, but just theoretically I'm wondering how you think, oh, I know a lot about the seven, 5 to 10.

And the third one is you just said, of course, the, you know, quercetin. And, you know, I take quercetin every day. But the, that's funny. That's that's one I couldn't remember just now.

But I do strongly encourage it right now. Okay. I, I, I just think that we medical research has to come up with better ways, but in the meantime, those are the best things that we're doing.

Okay. As, as I said, I just worry about the 95 year old, but but again, that's something that, you know, we have to just test or the doctors just have to test, and maybe low doses might be, better than no doses, you know?

Zero doses. So it's right now, I, I'm very, very in favor of analytics. All kinds of the natural ones. And the new synthetic ones that are being developed.

## Practical Biomarkers and Closing Thoughts

But I and I, I don't think we need to do it in combination with its long race inducer. When we get a tolerance inducer, I believe that that will replace the need for, analytics.

Okay. But we don't have a really potent one. A milder one could get around the problem that, too. Oh, yeah. Okay. So good. And combination of to 65 and and analytic is a really good.

Thank you. Yeah. That's that's what I'm thinking about. And then as a last thing I know, we just have a little bit more time. Reversing aging would be fantastic.

I'm 62. I'd like to get back to my 25 year old self. But, if telomeres are sort of the, the most upstream thing, would it make sense? And would you expect that aging could be slowed?

You know, if, say, a 25 year old started taking something like a small molecule polymerase activator, could you expect that if they got enough telomerase activity into enough tissues that their aging process would just stop?

Well, so there's nothing yet except for gene therapy that could potentially stop it. But there's a lot of them that can slow it down. And I strongly believe it's they can't, but there's no way to measure it as the problem is like it's like, yeah, I would I just I'm faith just an unscientific studies and stuff like that.

I'd be taking every telomerase inducer I could get my hands on right now just to slow down the aging process. But there's there's nothing to compare to.

There's nothing to measure. And, you can't say you can. I mean, you could say you measure telomere lengths every year for ten years and then go on to, telomerase inducer and then measure to and relax for another ten years every year.

And you can say, well, well, there was a difference, but you still have to have a negative control to show that, that difference when that happened anyway.

Well, to make it scientifically completely credible. Yes. But in and of one medicine, if the patient sees that, you know, their multiple markers are staying flat and not declining of organ system function like lung function, arterial stiffness, brain function, and their telomeres and their DNA methylation age and their glycogen.

The glycan age has stayed steady for the last five years. I mean, I think that's probably pretty good for where we are right now. Excellent. That's exactly what everybody wants to do right now.

That's the best thing they can be doing, is looking at all their markers and stuff. And, you know, which the question is, which is the best marker we talked about that last time, right?

I mean, I think I probably the answer is it's a whole panel. All of them. Yeah. As many as you can afford at this point. All of all the markers. Yes. Right.

Well, Bill, I mean, I think we you know, we did cover that question that came up at the end of the last interview in terms of, you know, the theory of aging, where we stand right now.

It's been very educational for me, as always, talking with you. And I really appreciate your, you're taking the time to, to talk to me and the listeners about this fascinating subject and look forward to seeing you again soon at one of the conferences.

We're out in Reno. All right, well, thank thank you, thank you. All right. Talk to you later. All right. Take care. Bill.