TRANSCRIPT: Why We Age—And Why We Don't Have To—Dr. David Sinclair & Dr. Leroy Hood Institute for Systems Biology — Town Hall Science Series, April 21, 2021. *(Watch video here.)*
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Dr. Lee Hood:

I have to say, I'm incredibly excited about the conversation that's about to happen. I do want to thank Town Hall for its partnership with ISB in bringing good science and I think this is really terrific science.

Dr. Lee Hood:

And let me say a few words about Dr. David Sinclair. He was born in Australia and transported himself to MIT for a PhD and later to Harvard, where he is now a professor of Genetics. David is probably the face of aging in the U.S. and in the world today. The book you heard about Lifespan: Why We Age - and Why We Don't Have To, I think is really one of those transformational books that when you read it, it changes how you think about a topic. And I suspect you'll get that feeling tonight from our conversation.

Dr. Lee Hood:

David has many academic honors. Many beautifully published papers, but it's interesting to note that Time Magazine in 2014, declared him one of the most 100 influential people in the world. And then in 2018, declared him one of the 50 most influential people in healthcare. And I think in many ways, you'll see from the conversation tonight, that that certainly is true.

Dr. Lee Hood:

So, with that introduction, I'd like to begin our conversation and throw out the first question to David. And that is, you were born in Australia, David. How did you evolve from Australia to become one of the pioneers in aging and longevity?

Dr. David Sinclair:

Well, Lee, thank you for the introduction. I've been introduced by a lot of people, but I think the introduction that you just gave was probably the most important to me, because I've had such respect for you even before, before you even knew who I was. So, thank you for that and thanks for the opportunity everybody to be able to speak tonight.

Dr. David Sinclair:

So, yeah. I'm Australian, so I have to be humble. We in Australia, if we start to boast about ourselves, we'll have no friends. So, I will try my best to talk about myself tonight as much as you want. Yeah, I was born in Australia. I was a pretty normal kid growing up on the edge of the bush. My family had a place with all about 1000 acres of forest in the backyard. So, I spent a lot of time looking at biology, but I always had ambition.

Dr. David Sinclair:

I was the kind of kid that if I was born in ancient Greece, I would head to Athens and so, I wanted to go where the action was. And as nice as Sydney is, it's not the center of the world where I like being. I also was raised by my mother and my grandmother. And particularly my grandmother gave me a very special education. She was a survivor of World War II and realized that humanity can do terrible things. She was from Hungary and escaped to Australia with my dad.

Dr. David Sinclair:

And so, I was raised, being told that humanity can do a lot better. And that, "David, you should spend your life making humanity as best as it can be and as great as it can be because we know humanity can do much better. And so, I remember her telling me that. And so, I've spent my life really trying to leave the world a better place. Every day I wake up, it's another challenge.

Dr. David Sinclair:

To get to the U.S., really what happened was, I realized at the age of 17, 18, as I was entering college, that we're probably the last generation of humans, at least my generation, to be living a normal human lifespan and the technologies of the future, our kids, our grandkids will greatly benefit from these, the understanding of why we age. I was also told by my grandmother that everybody eventually gets sick and dies, which to a four-year-old is pretty shocking and we'll go through that, but I couldn't get it out of my mind.

Dr. David Sinclair:

So, combining all of that, Lee, I set my sights on the U.S., on Boston. On MIT, I met Lenny Guarente, who became my mentor at MIT. I coincidentally met him in Sydney in 1993. And I said, "I want to do that. I want to study aging in yeast cells." And to cut a long story short, a famous scientist, Doug Melton, interviewed me for a fellowship, for Helen Hay Whitney Fellowship. They'd never given it to a foreigner before and I just argued that they should give it to me anyway and they did. And the rest is, I guess, history.

Dr. Lee Hood:

Well, terrific, David. One of the most interesting aspects of your book was early in the book, the delineation of the information theory of aging and I say that because I think from that, conceptually comes absolutely fascinating hypotheses. So, can you explain simply and in layman's terms, just what that means? And I'll say it's also interesting, because you made the fascinating point that aging is easier to deal with than cancer risk. And this all comes out of the information theory of aging.

Dr. David Sinclair:

That's right. Yeah. So, I've been studying aging since I was at MIT, this is now in 1995. And the first set of genes that we were working on in Lenny's lab, came out of a random screen for any gene that would make a yeast cell more stress-resistant and longer lived. And out of that came the discovery that there are certain genes, which we now call sirtuins. They didn't have that name in the beginning. But the interesting thing about the name is that the S-I-R in the name stands for Silent Information Regulator. And at that time, we really have no idea why a Silent Information Regulator, in other words, something that controls the expression of other genes, turning other genes off. Why would that be controlling aging? At that time, the idea was that and still, for the most part, is that just things break down and there's not much you can do about it. You could try to slow it down, but we're basically all going to fade away and be corrupted, and degenerate.

Dr. David Sinclair:

But that information part of that acronym is very important. And so, I've been focusing on what is it about information that's relevant to aging. And we did a lot of work in yeast and then in mammals in my lab at Harvard. And so, I've always been trying to think about information. One of the breakthroughs

came when I realized, I was reading about Information Theory, Claude Shannon, I'm a big disciple of his. He's a professor from MIT in the 1940s. And he came up with the mathematics of information preservation and actually, his mathematics led to the internet, among other things. And his idea was that, that things degenerate over time, including signals, such as radio signals, because of introduced noise.

Dr. David Sinclair:

And that really clicked with me. I could see that we could be the biological equivalent of a radio signal that degenerates and has introduced noise. And it fit with most of the work that was being done in my lab, if not all of it. And so, I came up with the Information Theory of Aging, as I call it. And really, the idea is that we are born with relatively pristine set of information. Our DNA is a digital code, four bases, four letters, instead of digital zeros and ones, but nevertheless, it's digital.

Dr. David Sinclair:

But there's another type of information that's just as important for our survival and that's called the epigenome that controls how the DNA is expressed. In other words, which genes are on and off and you need that because the brain has a different set of genes required for a liver cell and a skin cell. And that's what the epigenome does. And the analogy is, excuse that the old fashionist, but a DVD or a compact disc has digital information, but the reader which is the head that moves and use the laser is analog. And the cells have two types, they have the DNA, and then they have the reader. And it seemed to me that everything we were learning was that the readers, the readers of the DNA and the control systems were going awry during aging.

Dr. David Sinclair:

And that led to the realization if that was true, then here's the really interesting corollary is that there might be a backup copy of the original information, the genetic information and even the epigenetic information. And we published a paper in December that we're pretty excited to even receive the cover of that issue, that said that we could actually tap into a backup copy of the original epigenetic information in a cell or in a tissue. In this case, we rejuvenated the eye of mice and made them able to see again after suffering from glaucoma or just being old. And so, what I think is this could be a turning point, dare I say it at risk of being wrong, but if I'm right, then there really is the ability of truly not just slowing aging, but resetting the body to an earlier age and aging out multiple times and resetting multiple times.

Dr. Lee Hood:

Yeah. Well, I think the really important conclusion from that experient was there are actually two aspects to aging. It seems to me. One is, can we slow it down and the second is, can we reverse it? And it's never been shown to be reversible before. I think the paper that you described was one of the very first. And I think a fascinating question is, "How far can we reverse it?" And another interrelated question I'll leave you with these two is, "When should we start thinking about aging? And actually doing things which will slow or even begin to reverse the process?"

Dr. David Sinclair:

Right. Well, like all science, I mean, seriously, I'm standing on the shoulders of giants. There are giants that figured out that you can reset the age of somatic adult cells to be zero. So, John Gurdon and Shinya

Yamanaka did those experiments in tadpoles and in skin cells, respectively, and won the Nobel Prize, deservedly in... was it 2012, I think? So, that was part of the initiative of reversing aging, but we needed to do that. We needed to reset the age of cells not to zero, but by 50 or 75%, without causing the cells to become tumors. And that was the challenge.

Dr. David Sinclair:

We spent all about three years trying different genetic combinations. Trying genes that come on in embryos. Trying genes that that are helpful to cancers, but not causing cancer. And finally hit upon a three-gene combination that resets the age of the cell by about 75%. And you might say, "Well, how do you know how old a cell is?" Well, we actually now have a very accurate way of measuring the age of a cell or the body. Some people call it the Horvath Clock. It's also known as the DNA methylation clock. We can read the chemicals that change over time that are on the DNA called methyls and that gives us a really accurate measure of age.

Dr. David Sinclair:

And so, we could now take those mice that have restored vision and truly ask, "Are those cells just acting young or are they literally young?" And the answer was they are literally young again. And that was, I think, the first discovery that in a living organism, you could safely reprogram and reset the age of the body. How soon is this available to humans? Well, we're working towards doing our first clinical trial in the next couple of years. We've already got two years of work under our belt there.

Dr. Lee Hood:

Wow.

Dr. David Sinclair:

Yeah. But what about other parts of the body? I think that it's going to be possible to reset most parts of the body. The question is the safety issue, of course. But my lab has now had some early results resetting other parts of the body. Muscle is looking promising. We've got other labs doing the brain. Actually, we got some early results with Alzheimer's disease and old age, dementia. And there's another lab at Stanford, I should shout out Sebastiano's lab at Salk Institute. I should credit Juan Carlos Belmonte for showing that you can reverse the age of cells that you take out of a mouse and put them back in and that also is so beneficial, so you don't just have to reprogram cells that are in existence.

Dr. David Sinclair:

Ultimately, where is this going? Well, it would be like asking the Wright Brothers, "How soon do we get to Mars?" It's doable, I just don't know when, but I can say now, if the information theory of aging is correctly that we will be able to one day, perhaps have an injection of a virus that carries these reprogramming genes and turn them on with an antibiotic. In the mice, we used doxycycline. It's pretty inert drug and turn on these genes for four to six weeks, reverse the age of the body. And then your doctor will say, "Come back in another decade, we'll do another treatment."

Dr. Lee Hood:

Yeah, yeah. So, you, in your book, discussed longevity genes. You want to describe what this does and their role in this information theory of aging?

Dr. David Sinclair:

Yeah. These are fascinating genes. They came mostly out of the 1990s and early 2000s discoveries in yeast and worms and flies. Labs like Cynthia Kenyon, Gary Ruvkun, Lenny Guarante, of course, where I was. And these are genes that you might not suspect are actually controlling aging, but were discovered through just looking across the genomes of these organisms. And what we've discovered is that they do, is that they're built for survival. They're not built for longevity, but what they do is they respond to when organisms are perceiving adversity or future adversity.

Dr. David Sinclair:

For instance, in yeast, we showed in a nature paper 2003, that if you restrict the amount of calories that a yeast cell gets or raise the temperature or give it a little bit too much salt or lack amino acids, it will live longer through a set of longevity genes. These are the two ones, I alluded to, and that is a defense response trying to survive. And so, you can think of longevity genes in that way. These are like the Pentagon that you can call up and say, "There's an emergency, send out the troops," even if there isn't an emergency. And that's what our bodies are actually doing when we exercise and we go hungry, we're making a call to our body's Pentagon to send out the repair troops. And if you do that, routinely, you're going to have longer life. This is what has been shown time and time again.

Dr. David Sinclair:

Question is, when should you start? Well, we're starting to age from actually even before we're born, this clock is ticking. So, even if you look in the mirror and you don't have wrinkles yet, trust me, you are getting older, and you're heading towards decrepitude. So, I'm not saying to have intermittent fasting if you're a teenager or a young adult, you've got a lot of activity for your longevity genes. But for me, by the time I hit my 30s, I was already feeling like I needed something to assist me. And so, that's when I started.

Dr. David Sinclair:

So, there are two answers. It's good to start early, the animal studies suggest and what we actually show. But it's also, I wouldn't say it's never too late, but it's, you can start late. We can intervene in a mouse that's equivalent of a 70-year-old and have a lifespan extension of 15 or more percent, so it's in that window, but I wouldn't go too old. I don't think once you're 100 years old, you're going to go back to 20 unless our science improves.

Dr. Lee Hood:

So, how does the longevity genes then relate to these now classic nine hallmarks of aging? Again, that seems that whole process is a part of this simplicity we spoke about, that marks aging as a contrast with something more complicated like cancer.

Dr. David Sinclair:

Right. So, yeah, cancer has been described as 100 different diseases. Aging is really just, in my view, a relatively simple process. There are three levels: We've got the environment and what we eat and how we live, so this is external and internal inputs. And I've already mentioned that putting yourself in a state of adversity, walking, not eating, this kind of stuff does that.

Dr. David Sinclair:

Second layer are the longevity genes that sense that adversity and control the systems below it. So, what's below that at the very fundamental level? Well, of course, there's the epi-genome, which I've explained is my best theory, so far to explain the fundamental causes, but tied up with that perhaps influenced, if not controlled, by the epigenetic changes are what you mentioned, which are the hallmarks of aging. Many viewers will remember telomere loss, the ends of chromosomes get shorter, we lose stem cells, we have senescent cells, the zombie cells that accumulate in the body to make us old. These, about 10 years ago, we in the field agreed on nine hallmarks that contribute to aging primarily. And what they do is they control the troops. They are the various divisions in the Pentagon that go out. There's the Army, the Navy, the Air Force, Space Force. That's what these longevity genes will control.

Dr. David Sinclair:

Now, what I don't know yet, but what's exciting is that maybe if we can reset the age of the cell through the epigenome, these other hallmarks of aging will vanish. And we have some evidence that some of them do actually go away. Meaning that the information theory is perhaps valid. But that doesn't mean that we're just going to be able to, I think, just tackle the epigenome, these other things need to be addressed. And so, there are many researchers and companies working towards finding ways to address each of the individual hallmarks as well.

Dr. Lee Hood:

Yeah. So you spoke about the environment being the higher level that starts the whole chain of the aging process. What are the environmental manipulations that we can use to influence the hallmarks of aging, that ordinary people, you and me, can actually incorporate into the way we live?

Dr. David Sinclair:

Yeah. Well, it's not that hard to live another 14 years, on average. If you just do the right things, which is don't become obese, do some exercise, eat good food. What are the other ones? I think it's get sleep and don't stress, the basic stuff. That in itself will give you 14 years. It's been calculated. Bad luck notwithstanding, but you can go beyond that. That's just the minimal. If I could recommend one thing for people to try, it would be to eat less often.

Dr. David Sinclair:

I've totally changed my life around this, so has my father, who's 81, without any medical issues at all. We now eat one meal a day. I might have a bit of lunch, but not much and the rest is just warm drinks, which I love anyway. There's some really good experiments that show in many different species. And we've known this for 80 years that reducing the amount of calorie intake, particularly if you're restricted during certain times of the day, it's beneficial.

Dr. David Sinclair:

One of the best experiments I could point to or it's a set of experiments is by Rafael de Cabo at the NIA, which is the National Institute on Aging in Bethesda. And he did a very interesting set of experiments in mice, admittedly, but it was really telling. He was trying to figure out what are the differences between diets and you can give mice more calories in form of fat, or protein, or carbohydrate. And he did all those combinations 10,000 mice, but he did something also interesting, which was fed the mice either

all during the night, when they typically eat, called ad libitum feeding or only at for a little window during the day, or during the night, I should say.

Dr. David Sinclair:

And the mice ate almost the same amount of food, because you can imagine if you're a hungry mouse, you're going to gobble it down really quickly within that hour of feeding. The only ones that lived longer were the ones that had the time restricted feeding. It didn't matter what they were eating, so what that tells me, most likely and there's epidemiological evidence, this is true in humans, that it's not as important about what you eat, of course, you can't eat a terribly horrible diet and expect to live longer, but within reason. It's more important when and how often you eat.

Dr. David Sinclair:

And so that's what I do. I've really cut back. In the lot, during COVID, I've lost, what is it? Nine kilos, what's that? It's a lot of pounds. I'm down to the weight that I was when I was 20 now, and I feel great. There are plenty of other things you should be doing. Lifting weights, especially if you're male, an older male, keeping up the muscle strength, but even for women, keep your muscles toned, because falling over is the quickest way to dying actually. Somebody in the U.S. falls over every 19 seconds and breaks their leg or their hip and that's eventually fatal for most elderly people.

Dr. Lee Hood:

So, a really interesting question. I mean, intermittent dieting, intermittent fasting is presumably stressing the body and it activates some longevity genes and sets in place this whole anti-aging process. So, my question to you, it seems to me the most challenging aspect of that is how do you persuade people to change their behavior and adopt activities that are really good for them in the long term? I mean, that is, I'm very interested in wellness.

Dr. David Sinclair:

I know you are, yeah.

Dr. Lee Hood:

And an issue was exactly, the same there. So, I'd be curious about your thoughts on how can we get people to change?

Dr. David Sinclair:

Yeah, yeah, right. You and I, we've talked about this and it's really difficult. What I find is helpful is information and even thinking about my own life. If I didn't get any feedback, positive or negative, I gave up. You step on the scales, but that's about it. Once you start measuring things and in getting feedback, I find it makes the world of difference.

Dr. David Sinclair:

Not everyone does this, but I were in an aura ring for sleep and motion. I monitor my blood work as well, just to know what's happening. So, that's the future, so that people won't just go for an annual checkup, they'll actually be constantly seeing when they did this or they took that supplement if things are working.

Dr. David Sinclair:

Now, that's still futuristic. We still have close to 50% of the U.S. overweight. So, how do you reach those people? It's really hard. And it's one of the reasons I wrote my book is to hopefully reach more people and make those people that hear or read my book realize that 80% of our longevity in our health, in old age is based on how we live and only 20% is genetic. So, you really can control how long and how healthy you are in old age. So, there's the education part. There's the feedback, positive feedback, hopefully. But other than that, Lee, I'd be interested in hearing what your thoughts on how to have people more interested in this.

Dr. Lee Hood:

Well, I would agree with you. I think there are two really important aspects. One is you have to give people a metric that show they're succeeding or failing and the metric can show they can change their behavior. And I think being able to measure something like biological age, the age your body says you are as opposed to your birthday, I think is one of the most valuable tools we're going to have in convincing people that this is a unique opportunity. Did you want to talk a little bit about that?

Dr. David Sinclair:

I'd love to. Yeah, so we've been working behind the scenes in my lab on trying to democratize that test. Now that test, if you haven't heard of it, I mentioned it earlier, It's Horvath clock, typically, it's called. What we can measure are the chemical changes on the DNA itself in blood or in a cheek swab. And that will quite accurately tell you real age, not your birthday candles. I like to joke that, I mean, who cares how many times the work has gone around the sun. That's not what's determining your health. It's really more about your true biological age.

Dr. David Sinclair:

And so, in my lab, we've been able to develop new technologies to be able to read that test. And I'll say publicly for the first time that we're planning on making this commercially available to the public, because I think it's so important that everyone who wants this test should have a cheap way to do that. And I totally agree. It changes your mindset when you can really measure how well you're doing and also see if you can improve it.

Dr. Lee Hood:

Well, I'll tell you the second thing, David, I think is really important is education at the K through 12 level. So, for example, ISB is putting together a program on health, where we have 20 units that are based on this vision of a health that's predictive and preventive and personalized and participatory. And one of those units is going to be on aging, and wouldn't be wonderful if all high school seniors came out of school with an understanding of the kinds of things we're talking about now. And for young people, it's easy to change. For a lot of things in older people, the easiest way to get them to change is to have them die off and let their kids change.

Dr. Lee Hood:

So, anyway, but I think education and I think metrics are, but there is a third really interesting opportunity that I'd love you to talk about and that is, Americans really like the idea... no, I mean, your big new idea is that aging is really a disease and we know how we can deal with the disease. And the

way Americans like to deal with disease is with pills. So, do you want to talk about pills and aging and where that's going in the future?

Dr. David Sinclair:

Yeah, it's a really hot area right now. Going back when I started my first company in 19... no, 2004. It was crazy to think that you could develop a medicine that would tackle the root causes of aging or slow down and people didn't even understand how to think about it, let alone know build companies out of it. I think we showed that it was possible. And we're now in a world actually where longevity research and longevity development of drugs, development of longevity drugs is one of the hottest areas in biotechnology.

Dr. David Sinclair:

I sit in in the center of a tornado of activity. And I see that it's really gone almost vertical, in a graph of interest of investors. I'm part of a group actually that recently said we're going to invest in a company related to longevity. We haven't picked out which company yet and there was a billion dollars of interest. So this is, we're in a zeitgeist. In other words, I think the science has reached a point where Wall Street and hopefully, Main Street, increasingly has realized that the science has come of age, and that we can truly develop medicines that will use this knowledge, not only to treat aging, but to treat the effects of aging.

Dr. David Sinclair:

And actually 85% of all suffering on the planet, including most major diseases, are due to aging. We are in denial that aging is not important, but actually it's far more important for lung cancer than smoking is, for example, by at least an order of magnitude. So, this is a major issue, but I'm optimistic now that we've seemingly turned the corner, similar to, yeah, I used the Wright Brothers as a good example. And we're talking, we're now in the 1920s, where people have seen that the Wright flyer works and there's a lot of interest in building, eventually a Boeing 747.

Dr. Lee Hood:

I think one of the most exciting ideas I extracted from your book was this idea that aging is the dominant cause of virtually all chronic diseases. Let's say, you can control aging then we can begin to think about controlling all these diseases. So, the argument is, why don't we spend the $6 or $7 billion on cancer and the $11 billion on whatever else? Why don't we spend it on figuring out how to control aging? Wouldn't that be more efficient than taking diseases one at a time? It's, as I would say, systems integrative global approach and very powerful than when you're advocating.

Dr. David Sinclair:

Right. Well, what I wrote in my book, I still believe, which is, "I'm not going to try to rob Peter to pay Paul." I think that all medical research is important and there isn't enough of the funding. The amount of money we spend on aging research, though, if you just look at the biology of aging, and if you don't include Alzheimer's and other things, which is sometimes included, unfairly, I think. It's really just a few fighter jets in the U.S. to spend on this. And so, I would say that as a country, U.S. can afford to put more money into understanding the biology of aging, even without robbing, or not robbing, but taking from other places. But I definitely agree with you that the impact of this could be far greater than tackling one disease at a time.

Dr. David Sinclair:

One of the problems with the approach that we have right now is that we've been effective at treating some areas of aging, such as heart disease. We got the statins for cholesterol. We've got very good blood-pressure lowering medicines. And so we're generally living longer because of that, but the brain still ages. And now, there's an increase in dementias. And that's the wrong way to approach Medicine. I would rather try to keep all parts of the body younger and healthier for longer and have an extension of our health span rather than just our lifespan.

Dr. Lee Hood:

Yeah. Well, this discussion really brings us to a fascinating point, you and I have discussed before. And that is our determination to push forward in the vision, we have, your vision for aging, and so forth. So, my question is to you, where do we go beyond government funding to get the resources to be able to do the science that really is going to transform aging?

Dr. David Sinclair:

Well, I've seen a lot more interest from philanthropists and nonprofit organizations. So, I think that's an area where people can make a big difference. George Church and I talk a lot about this. Just for a couple of million dollars, you can have a big impact in a lab, you can develop basically, a drug that's almost ready to go into humans if you're very efficient with capital. And often people who have the wealth to fund these kind of things are shocked that such a relatively small amount can have such a big difference.

Dr. David Sinclair:

But it really can at the early stages, discoveries can be made just by graduate student who's staying up at night dreaming. And this is what changes the planet, not a billion dollars of investment at the late stage of technology.

Dr. Lee Hood:

Yeah, yeah. Well, I think another approach that you and I share is this idea, we can take useful knowledge and spin it off to companies, which can generate enormous resources for the maturation of the ideas and that amplifies enormously the kinds of things that you can get done. And you've certainly been very successful in taking that approach as well.

Dr. David Sinclair:

Thanks. I have a few idols and you're one of them, Lee. I'm not kidding. It was very difficult as a young scientist in my 30s at Harvard, spinning up companies. In the 1990s, especially 1990s and even in the 2000s, it was just not something that assistant professors did. How could you do that? Let alone go in the media and talk directly to the public that was totally frowned upon. I look to people like you as inspiration and to give me the courage to do that, and I'm so glad I did. Unfortunately now, we live in a world where it's quite acceptable for us to do that.

Dr. Lee Hood:

It's pretty common. Yeah.

Dr. David Sinclair:

But it wasn't always the case and you were doing it before me. And you had the courage to do that. And I assume it's because you didn't want to just publish papers, you wanted to change the world.

Dr. Lee Hood:

And that's where we both are, I think. So, one of the things that's utterly necessary for changing the world is convincing the CEOs at every level, in healthcare industry, the high level people in government of the validity of the vision. And you have ideas about how to do because that is one of the most challenging, if you can get to leaders, you can change organizations. But getting to leaders and changing their thinking is enormously challenging. Yet, there are approaches one can use, obviously.

Dr. David Sinclair:

Yeah, so there are leaders in industry, there are leaders in government, leaders in regulatory authorities such as the FDA. And I think we have to talk to all of them. And you and I have been doing that. Actually, in my estimation, I haven't been that good at it. It's been quite difficult to change the world from the top down. I'm actually having better success from the bottom up. But I do think we have to take both approaches to be...

Dr. Lee Hood:

Both approaches, yeah, yeah, yeah.

Dr. David Sinclair:

... more successful. And the FDA, surprisingly, a few years ago said that they were open to calling aging a treatable disorder, if we could just prove that it was. And that those experiments are actually ongoing with a drug called metformin, which many of you will have heard of. It's a frontline diabetes, type 2 diabetes, drug for the elderly and people who have had high blood sugar. And that drug, seems at least based on tens of thousands of patients who have taken that drug, had protection not just against their blood sugar, but also cancer and heart disease and even Alzheimer's frailty for sure.

Dr. David Sinclair:

And so, this could already be a drug for longevity, that's available. It's very cheap. It's probably a few cents per pill. It's available over the counter in many countries, not here in the U.S., unfortunately. But if the FDA allowed doctors to prescribe metformin before you had type 2 diabetes. That would be revolutionary. This would be the equivalent of having the statins for heart disease or blood pressure medicine. This would be a new massive change. But right now, most doctors are either ignorant or reticent to prescribe such a medicine that would prevent multiple diseases.

Dr. Lee Hood:

How would you categorize rapamycin in that regard? Another drug that it manipulates a major, one of the central systems, to set up the defense that leads to reducing aging.

Dr. David Sinclair:

Yeah. Well, what you said really resonated earlier, which is that you and I believe, well, I certainly believe. I think you believe that aging is simpler and easier to treat than cancer, which is a bunch of different diseases. When it comes down to it, aging is not that complicated. Yes, the effects downstream

and all of the various things you see in old people, older people are complicated. But at the core of what's controlling all of that are really just three main systems that we've discovered.

Dr. David Sinclair:

There may be a few more, but we know three. One is the sirtuins that I work on. Another is called AMPK or AMP-kinase, which metformin works on. And now, Lee, you brought up the third leg of the stool, which is a protein complex that senses amino acid intake, called mTOR and so, mTOR, which is little m, capital T-O-R. If you eat a steak that's full of leucine, isoleucine, and Valine, this protein complex will sense that and say, "Oh, times are good. We just killed a mammoth. Let's build more skin. Let's make more whatever."

Dr. Lee Hood:

It's reproduced. Yeah.

Dr. David Sinclair:

Exactly. "Let's reproduce." But there's a trade-off. The trade-off is that the body shuts down its defenses, such as recycling proteins called autophagy, a very important hallmark of aging that declines with time. And so, by taking this drug rapamycin, which is definitively shown to or selectively shown or shown to selectively target mTOR, which is used actually to modulate the immune system. It's in low doses, it looks really promising as a longevity molecule. In rodents, it's probably the most successful molecule for extending lifespan even later in life.

Dr. David Sinclair:

The problem with rapamycin the way it turns out, is that if you take doses that are high, I think higher than 10 milligrams for a long time, it can damage kidneys among other things. It's not a perfectly safe drug, which you'd want for something that you'd use for longevity. That said, rapamycin taken once a week or in low doses, 3 milligrams are things that people are talking about and I'm aware of people who are trying it. You might say, "Well, why would you try something if it's not proven to work?" "Well, if we wait until it's all proven to work, a lot of people listening to this and watching will be dead."

Dr. David Sinclair:

There's a risk-reward ratio calculation that goes on in people's minds and it's all done under doctor's supervision because it's a prescribed medicine, but we're actually at that turning point, I think, in human history where we are able to say that there's a pretty good likelihood that some medicines that are already approved could affect the aging process in a positive way, right?

Dr. Lee Hood:

Right. Well, one thing, we promised to have a conversation with one another about it in the future is my idea if we can measure in patients enormous amounts of data that assay all the major systems and everything, in clinical trials like we're talking about with aging, we can, one, reduce the number of patients and give you have compelling results, and, two, we can see results much more quickly because we're looking at many more features to see if there are subtle changes and so forth. It seems to me this is going to be a really key part for accelerating the acceptance of some of the kinds of things that we've talked about here.

Dr. Lee Hood:

My last question, because we've got to turn to the audience now, is if you had to prioritize for the audience things that they could do now, what would be your priority list for them to live in a healthy aging manner?

Dr. David Sinclair:

Well, I've mentioned eat less often. I think the three meals a day plus snacks is misguided and I'm happy to debate a nutritionist on that. Other things you can do is make sure that you keep your muscle mass. We lose a percent also every year as older males, females too as well. Females have to particularly watch their bone loss as well. Doing exercise was-

Dr. Lee Hood:

Is the exercise primarily to keep up muscle mass or does it do other things too?

Dr. David Sinclair:

It does lots of good things, some of which I'm not even going to mention, but testosterone will go way up if you build up the big muscles in your body. I exercise my quads. My leg muscles, my back muscles are the main ones. The rest is just probably mostly just for vanity, but the big muscles are really important in males and females, if you have strong hips and there's a piriformis muscle which holds your hips, basically your legs together. The problem with current lifestyle is that sitting all the time causes those muscles to degenerate and it's very easy to just be weak there. Most people don't realize they're weak.

Dr. David Sinclair:

One of the things, I'll get back to the question, Lee, in a second, but there's an easy way to tell how old you are, roughly. It's called the sitting-standing test and it'll test these muscles. You sit cross legged, and if you can get up without touching the floor with your hands and stand up, you're young. A middle aged person like me might need to use a hand to get up and an elderly person will have to get on one knee to get up. That's really just testing your muscle strength. I think doing 20 pushups is considered really good at my age too, but those are not very accurate compared to the other things we talked about.

Dr. David Sinclair:

You're right that making your muscles stronger has multiple benefits. It's increased testosterone for males, and to a lesser extent, females. The muscles give out hormones that are beneficial. There are what, Lee, are called myokines, which we think circulate throughout the body and provide improved health as well. I don't know all of them, but I know some of them. The other thing that muscle strength and aerobic exercise in particular will do is it'll make sure that blood glucose levels don't get high in your body, and when you eat a meal, the levels of sugar in your blood don't spike. Having high blood glucose levels is one of the rapid ways to suffering in death.

Dr. David Sinclair:

Anyone who's had type two diabetes in a bad way will tell you that including lack of circulation, heart disease, et cetera and dementia. There's all those benefits besides just feeling great and being able to still walk in old age and make sure that, if you fall over, you'll bounce back up.

Dr. Lee Hood:

Well, with that, I'll start reading some questions from the chat box that the audience has asked. The first is, "When do you plan to have the Horvath clock test available for consumers?"

Dr. David Sinclair:

That's hilarious, only because that that's one of the questions that somebody was just asking me before I got on. All right, so this is public information, so let me think what I can say. We are right in the process of making that happen. The test will be coming down a lot in price. I hope to be able to have something available, conservatively speaking, before the end of this year. That's probably all I should say at this point, but it is coming. It will be it'll be backed by my science and it'll be backed by my reputation. I'll also provide feedback and suggestions on how to improve your score.

Dr. Lee Hood:

Well, I will make one comment on a, I guess, competitor now called Onegevity, that has a test for biological age that uses blood analytes. Again, it is now available, so you can look up Onegevity and read about that, but I think both possibilities are absolutely fascinating. Second question, "What is the ideal window for eating with intermittent fasting? You eat just a single meal, does that mean the window is just one to two hours of eating per day?"

Dr. David Sinclair:

Not even that. I'm like everybody. I'm a regular person. I like eating cheesecake, but what I've realized is that I feel so much better, I'm more alert, I'm excited, I've a better outlook, I'm optimistic if I don't constantly eat. I've never been big on breakfast, so that's just my physiology. Some people need breakfast, I don't, but I then I started skipping lunch and having a hot tea instead. I might eat a piece of fruit, but that's about it. Then at dinnertime, I'll look at dinner, if I go out to dinner socially, I'll just eat normally. That's fine. I'm not going to reduce my joy in life, but most dinners are small. They are more like what a rabbit would eat than a lion. I eat fish. I try not to eat big steaks, but generally I've reduced the portion sizes really way down. I've never felt better.

Dr. David Sinclair:

I boasted probably a little too much that I've got my 20-year-old body back, but I really do and it's invigorating to be like this. It wasn't that hard. I really started, in earnest, in February. We're now in April. It wasn't that hard. I hope that everybody can consider it, if they are not already doing it. I would encourage you to do it for at least two weeks before you give up because it takes two weeks to get used to it. We've all got habits, we go to the fridge, we eat snacks. Once you get over that psychological thing, just have one drink, hot water or tea, whatever you feel like, then it's easy. I definitely don't feel hungry. In fact, I feel way better not having all these meals.

Dr. David Sinclair:

One question I get though is, "Should I fast longer than 18 hours which is what I tend to go for?" You can do that. I'm not that good at it actually. I don't have a lot of willpower to be honest. A lot of people are better than me. Some people go for three days. Maybe every few weeks. If you go for three days, you get real deep cleansing by this process called autophagy. The body will start to recycle more proteins that it normally would using a system called chaperone mediated autophagy or CMA. I would love to try three days. I just haven't been able to do that yet.

Dr. David Sinclair:

Then there's the extreme version which is a colleague of ours, Dr. Peter Attia, who's become pretty well known for this, he does a week of fasting, just with water and he does that I think every few months and apparently that's extremely good for you according to his estimations, but it's hard to do. I would say at least try not to eat three meals a day. That's a good start.

Dr. Lee Hood:

Then if you can get to one, that's even better.

Dr. David Sinclair:

Yeah, you really do start to appreciate food, that's for sure, but it doesn't dominate your life. I lived a childhood where my mother used every meal to discuss what was the next meal? I'm pretty happy that I don't live like that anymore.

Dr. Lee Hood:

Great. In your book, you write about resveratrol, NMN and other supplements. What does latest research say about these? Would you give advice to people that are... What advice would you give to people interested in adopting them?

Dr. David Sinclair:

All right. The technology in my lab has been improving steadily. Resveratrol was a very early discovery back in the early 2000s. What we were trying to understand was, "Can you activate these longevity pathways, mechanisms with a safe molecule?" At the time, we didn't know that. Now, it seems obvious, of course, because everyone's talking about it, but we didn't know. What we discovered, co-discovered with my coauthors, was that plant polyphenols, these are a variety of molecules that are made by plants when they're also under adversity, and one of which is resveratrol which is found in grapevines and red wine, was pretty effective at activating one of the sirtuin enzymes that my lab and others has shown to be beneficial for health in mammals and even in humans.

Dr. David Sinclair:

Resveratrol got a lot of hype actually. It was unavoidable. There were a couple of things going on. The red wine industry loved it. Sales of red wine went up 30-plus percent and have stayed up. Then there was the commercial entity, so I started a company called Sirtris which had a professional team of people talking to the media. All of that, no, 60 Minutes, Barbara Walters' interview, all that was pretty fun, but what really came out of it was the realization that a safe small molecule could be used to mimic the benefits of fasting. We fed resveratrol to mice that were on a high-fat Western diet and they lived as long and were just as healthy as the mice that were lean. That in itself was, I think, a radical departure from what people were thinking.

Dr. David Sinclair:

Would I take resveratrol? Well, I do still take resveratrol. I, at least, take a teaspoonful of it every morning. I take it with a tiny bit of yogurt just because it needs to dissolve. It's like brick dust. Otherwise, it doesn't dissolve. I've been doing that since my 30s. I'm still alive. We don't know if it's going to make me live longer, but certainly-

Dr. Lee Hood:

You're the good test subject.

Dr. David Sinclair:

Well, I'm an Australian. There's a tradition of Australian scientists experimenting on themselves like Barry Marshall discovering that the ulcers in the stomach are caused by bacteria. He actually drank the bacteria [inaudible 00:52:50] himself and then cured himself.

Dr. Lee Hood:

But he won a Nobel Prize. Sometimes, it works.

Dr. David Sinclair:

Well, instead of waiting 30 years for the clinical evidence. I'm not doing this to try and live forever. I don't really worry about that, but I am very curious and I do like to learn things quickly. My father's been on resveratrol for the same amount of time. As I mentioned, he's 81 and is fit or fitter than I am, but I don't recommend supplements. I'm not an MD and we don't know if these are going to work, but there is a lot of evidence, I would say, in animal studies that resveratrol is relatively benign and also can be beneficial to your metabolism and protecting the organs. I continue to take it until I see evidence that could be dangerous. I haven't seen anything like that in 20 years.

Dr. David Sinclair:

I do take another molecule that's fairly prominent in the media of which is called an NAD Booster. You can buy these. They're call either NR or NMN. I certainly don't sell anything at all. I don't promote anything, but I find that a lot of people are interested in it, so I'm mentioning it tonight. NAD Boosters came out of research out of my lab as well as [inaudible 00:54:09]. We discovered that the sirtuin enzymes are controlled by the level of NAD. There's a molecule that our bodies make for metabolic reactions but also control the sirtuin's activity. When you're hungry, if you're yeast cell or a human, your levels of NAD will rise, but as you get older, it declines.

Dr. David Sinclair:

What we're trying to do is to artificially boost up the levels of NAD in the body and that's why I take the molecule called NMN which is a precursor to NAD. Interestingly and what's very rarely recognized is that one of the companies that I founded, cofounded, called MetroBiotech has been doing clinical trials in people for over two years now with an NAD-boosting molecule that is related to NMN and found you know really great results so far. I'm not at liberty to say what they are yet, but I'm still taking NMN, having seen all the data. I don't want anyone to get the impression that I'm a cowboy who's just experimenting on himself. It's not that. I only take very calculated daily risks, but I also at the same time do clinical trials on these molecules to try and rapidly find out, a, "Are they safe?" and, b, "Are they effective?"

Dr. Lee Hood:

I love this question. "Is it totally a good thing to get younger? Wouldn't that over populate the world with a bunch of newly young people?"

Dr. David Sinclair:

Well, I don't think that the world is a pie that has only a certain number of slices. I think we can keep growing the pie. Now the world has limited resources, of course. We can't keep burning oil and we can't keep overpopulating or continuing to populate, growing in population, but as I explained in the last part of my book, when you actually do the math, and we're actually going to publish a mathematical model in the journal Nature Aging soon on this, what happens is if you stop aging or slow it down, certainly if you slow it down, it doesn't appreciably contribute to global population, despite what you might think. There aren't that many people dying from old age actually.

Dr. David Sinclair:

The problem is birth. Unfortunately, fertility rates or at least reproductive numbers in families is steadily declining across the planet and is even in the negative for most developing countries or developed countries. The US would go negative if it didn't have immigration. I don't think you should worry about population. World Resources, yeah, we need to solve that, but I'm hugely encouraged by, for instance, the energy transition to renewable resources. I drive a Tesla for good reason. I think that humans are capable of engineering themselves and innovating themselves out of really any problem. It's just a matter of will and the investment. We can solve any problem.

Dr. Lee Hood:

I think the other point is to be younger means you're vital, energetic, curious, creative. It's hard to believe that virtually anybody wouldn't like those traits. Another question, "If someone were interested career changing into a field of aging from a business related field, where would you recommend starting?"

Dr. David Sinclair:

Let me start, if you're in high school, have a great interest in science. You want mathematics, you want a bit of physics, you want chemistry, you want biology. When you get to college, I would do some basic biology. I'll do some philosophy. I'll do some history if you're interested. Get a broad education. It will help you greatly in the rest of your life. When you get to my age, it's very difficult to do those kinds of broad thinking and learning, so do that, but then start to focus maybe in your second, third year on genetics which now covers molecular biology as well as even nanotechnology kind of stuff that Lee has developed in his career.

Dr. David Sinclair:

We're now in a revolution, both in our ability to read and write the genome, to read and write the epigenome and to do experiments by the millions per day, just as one person, something that took me a whole PhD which was to discover three genes and read the code can now be done, well, it wouldn't even be done. The whole genome could be done in an hour by a graduate student of yeast cell. We're at a point where it's a great time to join molecular biology and genetics and science in general because we've got these tools that people like Lee have built for us that we can now do a million experiments today.

Dr. David Sinclair:

That's a long way of saying, also get some experience in bioinformatics because being able to analyze all of that data is invaluable and I cannot find enough good bioinformaticians at this point.

Dr. Lee Hood:

Absolutely. "Presumably, you currently do your own sequencing for your methylation age calculations, is this the kind of things somebody could do themselves today on a regular basis with their own DNA sequencer?"

Dr. David Sinclair:

Who has their own DNA sequencer for goodness sakes? If you had a DNA sequencer-

Dr. Lee Hood:

well, with Olink, you can actually have a little DNA sequencer that doesn't cost... With the single cell sequencing technology from England.

Dr. David Sinclair:

MinION you mean or is this-

Dr. Lee Hood:

Yeah, the MinION. That's right.

Dr. David Sinclair:

Right, a little candy bar-sized sequencer, you can do that for sure. I think you can do your own test at home, but you'd need a bench and you'd need a centrifuge and you'd need a pipette and a kit. Probably don't want to make your own reagents, but-

Dr. Lee Hood:

It would probably cost you a thousand times as much as getting it from somebody who is a pro.

Dr. David Sinclair:

It would. It would. Come to Lee or come to me. We'll get it done routinely and be able to help you interpret the results as well, but I think it's an interesting point that genetics has reached a point where you can edit the genome and read the genome, even in your garage or your kitchen if you want.

Dr. Lee Hood:

Absolutely, you can take a DNA sequencer out on field tests and look at organisms in the field, so it's amazing. "What is the most accurate way to measure NAD levels after consumption of precursors? What is your perspective on NAD+ via IV for longevity, similar to what we've done for addiction detoxification?

Dr. David Sinclair:

Well, for IV NAD, I haven't seen any solid data yet. I'm aware of it being offered. I went to one of the hotels in Hollywood and they offered it to me at the reception desk which was funny, but also it seems to be helpful, at least anecdotally, with helping with addiction and there are clinics around the country, particularly in Florida, but I can't say as a scientist that I've seen convincing, placebo-controlled experiments that would tell you if that's working or not. I'm open to it. I certainly think it's possible. If anyone has data that they'd to share with me, please go ahead and send it to me and I'll judge it as I would any other study. Go ahead, Lee.

Dr. Lee Hood:

I think we have to close down with the last question I'll ask you, David. I know from our conversation that you're writing another book and I'll offer you a chance to make some comments about it or to decline at this point in time, whichever you choose.

Dr. David Sinclair:

Right. Well, it's late in the night over here on the east coast, so maybe I'm in a talkative mood, but yeah, I'm excited. The first book, Lifespan, was a New York Times bestseller. It was super exciting. I've enjoyed the process. The feedback that I've received from you, Lee, and many others, but particularly your voice was very meaningful to me, has prompted me to want to do it again, right? You get enjoyment, you find fulfillment, you do it again. I am writing another book with my coauthor, Matt LaPlante, who's a genius that bringing together a whole bunch of disparate crazy stuff in my mind. I know, Lee, you work with Matt, so you know what I'm talking about.

Dr. David Sinclair:

My new book, we're still not disclosing exactly what it's about, but I can tell you that, a, I'm very excited about it. It's going to be as interesting and revolutionary as the first book. We like to take what seems obvious to the world and look at it from behind the mirror and actually see what's going on. It's going to be a journey of understanding where we've come over the last few million years as humans, "Why do we exist with crazy hands like this? Why do we look like this? Why are we a lollipop physique? That's pathetic. You put us in a cage with a chimpanzee and one hit and we're dead. We're pathetic as a species. Why did we evolve genetically to be this pathetic and then what happened to the world that we've made around us?"

Dr. David Sinclair:

Obviously, we've got technology to try and make our lives easier to cope with all of the faculties that we've lost over time since we've been out in the wild, but we built a world that that isn't perfect for our physiology. I'm staring here into lights. I'm not going to sleep well tonight. We suffer from social media. We've got a lot of depression and anxiety in our young kids. We've got other problems. We sit all day. Time and time again, our technology solves one problem and causes another. I call this the treadmill that we're on. Really, ever since humans have picked up a rock and used it to bang an animal on the head or maybe one of their enemies on the head, we've been on this treadmill and the question is, can we ever get off? What does the future hold? That's what I'm writing about.

Dr. Lee Hood:

Well, David, I want to thank you for an absolutely stimulating and wonderful conversation. I thought you did a terrific job in bringing the world of aging to everyone. I just say a few lessons that I took home when I read your book was something we haven't talked about is that this aging process, David and others have discovered, is conserved all the way back to the simplest of single-celled organisms. I think there are two interests with regard to that conservation. One is it underscores the idea of simplicity and elegance and something that's shared in all creatures. Number two is the idea we can use model organisms like mice and yeast to discover fundamental things that apply in very straightforward fashion to humans. That's really an exciting idea.

Dr. Lee Hood:

I think, number two, the idea that aging is a disease and that we really have powerful tools for curing and slowing and even potentially reversing that disease. I think number three, if we can do that, we can begin to think of a very powerful way for attacking the broad set of chronic diseases whose major predisposing factor is, in fact, aging itself. I think, finally, with all of the revolutionary changes that David has discovered, in the next 10 years, we're going to see remarkable opportunities presented to each of us for fundamentally changing our lives and presumably moving us into the 80s and 90s and 100s, physically capable and mentally alert, enthusiastic about life.

Dr. Lee Hood:

Now, that poses other really interesting issues about, "Where are we going to get enough money to do all the fun things we'd like? Are we going to have multiple jobs?" all sorts of exciting things. Anyway, I want to thank Town Hall for allowing us to do these wonderful exciting programs. I think to the audience, please, we'll have other exciting programs in the future that combine together ISB and Town Hall. If you're interested in keeping up with all of these, go to our website at ISB which is isbscience.org. Thank you, and especially you, David. We have a great evening. We really appreciate your contributions and your expression of them.

Dr. David Sinclair:

Well, thank you, Lee, and thanks to everybody, the Town Hall folks and everyone who tuned in tonight. I thought it was a wonderful discussion. Lee, thanks for everything you've done for science and technology as well as.

Dr. Lee Hood:

Pleasure.