Introduction and Speaker Background

Hi everyone! I'm doctors and Gargoyle and I hope you are enjoying the advanced Anti-Aging and Technology Summit. Today I'm interviewing Doctor Joseph Refaeli.

He's an expert in anti-aging medicine and has been practicing for over 25 years. He founded the Fazio Medical Group and has also developed a web based health and biomarker analytics data collection software called Physio Age.

He's really prominent in the whole field of clinical telomere biology research, has published four studies in that space. He lectures nationally, internationally on the clinical application of telomere biology.

You can find him at roughly medical.com as well as at roughly MD on Instagram. His website is also is physio.com. I think you're going to really enjoy it.

At his talk. Hi everyone. Welcome to the summit. Today I have Doctor Rafael with me. How are you? Job? I'm doing very well. Sanjeev. Nice to be on your summit.

I'm so thankful that you were able to get you in at the last moment. But I think it's so important, with the work you're doing and. And your expertise in this whole space of aging, that we couldn't have not had the summit without you.

So, I'd like to maybe before we can get into the viewers understand your background and how you know why you even went to this aging field. Because there's no, like, there's no specialty of aging.

I think, you know, necessarily. So it must have been something that kind of pushed you down this road. Yeah. So it's kind of a looking back on it at this point is kind of a long journey.

But I was trained in internal medicine, at, Cornell here in New York and then went, to practice primary care internal medicine in New Hampshire at the Dartmouth-Hitchcock clinic.

I sort of got my doctor legs, and I, saw patients for five years, you know, in a, an outpatient setting, but also saw patients in the hospital and saw a whole lot of patients.

So the whole gamut of things, but I guess at the same time, toward the end of that, my both my parents were getting older. They're a little bit older when they had me and they were starting to ill.

One of them was developing Alzheimer's disease. I was also starting to feel like I was just really kind of filling the holes in the dam and not really trying to, you know, sort of create a new way of, of holding the water back.

So I, I was looking around for other things to do, and it was a time in my life personally that I could sort of step back from internal medicine. I went to a few conferences in the field of the they call it back then, anti-aging medicine.

And saw that there was a lot of research going on in the field. I mean, not just do you have a disease or don't you have a disease or what do you do about it?

But what's the process, the sort of prodrome that leads up to a disease in an organ system before it's detectable? Sort of at the subclinical level? And I got really interested in that because that's what you want to do for Alzheimer's disease.

You know, once you have full blown Alzheimer's disease, it's kind of like trying to unscramble an egg that doesn't work so well. And, so I decided to switch my field.

I, came down to here to New York, and, you know, that movie Field of Dreams. Build it and they will come. I, opened up along with my partner, at that time, Anti-Aging Medicine Associates in Manhattan, and said that we're going to try to sort of look at you, even if you're healthy and try to slow down your aging process with the technologies that were available.

The thing that was happening at that time as well, which will tell you how old I am, is was in 1997, six, seven. I made the decision in 1898 when we opened up the internet was really coming into its own.

And so, you know, that fabulous thing, PubMed was a becoming available and we could start to do our research rather than having to go to the library and, you know, ask for the journals.

And so I just ravenously went at the material and started, offering a program of hormone optimization, diet, exercise, supplementation, you know, with vitamins and other nutrients.

And, you know, at first the phones did not ring much, but I actually did, and just a mood lighting it, urgent care to, to, sort of pay the bills. And then eventually they started to and we started to see, doctors.

I'm sorry. Patients doing better. Got a little bit of, say notoriety, I guess, the field was getting some media attention, so I was on some of the major, you know, national news outlets talking about slowing down the aging process and I was invited by Bob Butler, the founder of the National Institutes of Aging, to come to a roundtable.

And he sort of, wanted to know sort of what these practitioners were doing. There was other geriatricians. There were geriatricians or people that take care of the problems of old people.

And and it was gerontologist there. Who are the people who study aging, which I had no doubt had known that was even a field. And literally that I really no, I was kind of being invited as a sacrificial lamb, to say, you know, you're practicing snake oil.

What are you doing? But it turned out that we had actually a pretty good conversation. They were receptive, the group and Bob, said to me, look, Joe, sounds like your patients are doing well.

I mean, and at the same time, Nia was undergoing a series of studies looking at trophic factors in aging. And they were trying to determine whether estrogen in women, estrogen, testosterone in men, and growth hormone in women and men could help slow down aging and have improved outcomes.

So they were interested in it and what my clinical experience was with it. But ultimately, Bob said to me, you know, look, you seem like a relatively smart guy.

I'm not sure what they said, relatively or not at the time, but, he, he said, look, we'll call yourself an anti-aging doctor, you know, what are you doing to measure the aging process? You know, what do you what are you doing?

Biomarkers of Aging and Biological Age

You measure blood pressure. If you're giving an antihypertensive, you're given this stuff. What do you do? I'm like, you know, scratching my head, I don't know.

My patients are doing great. So that really started me in 2002 to look for biomarkers of aging and and to try to practice the kind of medicine that is objective, but personalized to look at what the effects are, what I'm doing on them.

And that's been my journey over the last, 20 odd years. Wow. You know, so I think you're really one of the pioneers in this whole in this whole field.

Let's just dive right into those biomarkers, because I know that you spent a, you know, probably last decade, working on refining our understanding of this.

Do you want to take us through, what what is the current knowledge base on on, on, what are the top biomarkers? You know, I guess traditionally. And now what's, you know, up and coming in, we can kind of go through each one.

Sure. So the biomarker marker is, is a measurement of a physiological or biological property in a body that, gives you information about that organ system or that part of the body.

People know. No, a cholesterol is that that's a biomarker, for, you know, the lipids floating around your blood that could potentially cause cardiovascular disease.

High blood pressure is a biomarker. Hemoglobin, A1C measurement of your blood, your biomarkers of aging are those measurements that can be done with an instrument, either a, you know, non blood or a blood, a blood test that correlate with chronological age, you know, relatively well.

We'll call Pearson correlation about 0.2, which is, you know, a correlation of one, which is a 1 to 1 correlation. So it absolutely goes in lockstep. A very good biomarker would be 0.5 or so.

But if 2.2 are above it does correlate with age. So biomarkers of aging are those measurements that that can predict sort of if you did that measurement on somebody plus or minus a certain number of years, how old they are based on that kind of marker.

They also then put together a quick question on that. You said 2.2, like so a one, a one would basically mean a right on, bang on. It's an exact correlation with age, something like a point eight or whatever would be much closer.

I would so, so point all the way down close to almost zero. Like zero would be no car, no correlation. Right. So we're saying we're accepting even a point two, which is not a doesn't seem like it's very far away.

But even that's like correlation is it's considered a if it's an important one. Right. So there are biological measures that are very important. Like for instance hemoglobin A1, C control your blood pressure.

That doesn't necessarily track with age. You don't have to have that get worse with age because not everybody gets insulin resistant or overweight or inactive or get early diabetes, but because it's so important, you know, at whatever it is 0.2 or so, it's still going to be, you know, useful as a biomarker, but it's not a great one.

So the ones that are very good, are sort of in the non blood category, things like we think about blood pressure. But what blood pressure really is, is a measure of your arterial stiffness.

And specifically the large arteries in your body, the aorta, the carotid arteries, the ones that go down into your legs called the iliac. Those arteries, when they get stiff, they cause problems.

They cause cardiovascular disease, stroke, heart failure. Because the function of the arterial system is to dampen the pulsations. And each time the blood is being pushed out of the heart.

And this pulsations, you have the top number systolic and bottom number diastolic. And the in between is that is that sort of pressure dampening stuff that's correlated around 0.5, that, that marker, which is done with a specialized instrument, blood pressure is pretty good.

Systolic blood pressure goes up. It's correlate around 0.3.4. And so then there's pulmonary function, how fast you can blow out air in that first second when you're doing that violent maneuver called the pulmonary function test, where you're taking a deep breath and blowing it out real fast.

There's huge databases showing that that's highly correlated with, with age, but also, correlated with pulmonary disease and other diseases as well as death.

So if you have that those two, you have a pretty good idea about what people are doing in terms of the aging process. We put it when you put those two together and you can add onto onto that cognitive functioning through a

battery of tests.

We use a company called CNS Vital Signs that does a, an online 25 minute series of sort of like video games that you have to do with memory and how fast you process and scanning, tapping, etc.

things that used to be done in a manual fashion, can now be done, you know, sort of a quick computerized test. And then we look at skin elasticity, both from sort of an unknown exposed area and also from a sun exposed area.

Those are sort of our biomarkers of aging that are non blood, and they're sort of in that mid range of correlation with chronological age. But but are measuring very important functions. Right.

Because it's not that important to measure. The chronological age is one part of it matters to actual biological age. Right. Does it really matter. Like if they measure technology and that's that's that's kind of the point.

So up until 2013, we had those for biomarkers and we had added to them telomere length and an immune function, which we can talk about more and more in detail.

But we put them into a, a panel that gave an overall, what we call the physio age, which is our way of thinking about physiological age. So, you know, you may be 60 years old, but physiologically, those markers are all saying you're a functioning more on average, like a 50 year old or like a seven year old.

And then 2013, Steve Horvath came along and kind of threw a wrench in the whole thing by doing his DNA methylation seminal studies, where he looked at, and I know you're interested in epigenetics.

And so, but he, he looked at blood and, and subsequently many other tissues and found that the pattern of methyl groups attached to your DNA, or what we call your epigenetics, changes highly characteristically with age, such that, you know, you can predict in two years, how old somebody is just by looking at their expression pattern in their, in their DNA, their epigenetics.

So some of those biomarkers are coming in at 0.9. I've seen some as high as.95. You have to understand, though, to your earlier point, if a marker is correlated at 0.95 and you're and you correlate with chronological age, you might as well just use chronological age, right?

You're not learning anything. People don't understand. They say, well, what's the best biomarker of aging? And I say, and they say, I've heard this high correlation.

Once I understand the Pearson R or the R squared, and I say if it's you want, you need to have spread on either side of that correlation of chronological age versus the marker to know whether you're doing better or worse, if it's exactly along that bisection of that square, you're not getting any information.

The original biomarkers, an epigenetic age, DNA methylation age were trained against chronological age subsequently. Now they start to train them against other markers, like the kind of biomarkers that are important.

And I think that they have they've become more useful markers other than just in forensics, which ones are using. I've heard about the groom just being, I guess, trained.

Yeah. Be. Yeah. Groom ages. Champ is trained on mortality. And, the fino age is the one that is, the Morgan Levine, originally that, us see, I believe, and now is a professor, associate professor at, Yale.

She is, sort of the biostatistician that was in Steve Horvath lab and has sort of been, working and producing a lot of great papers on this stuff. Fino age is is a number of tests that you can get in a routine CBC and chem panel, as well as, the addition of a CRP, which people may know is a C reactive protein, a marker for inflammation.

Right? Probably if you've been to a doctor, you're over 40. You've had that measured in you. And, you know, very fascinatingly, if you put those into what we call these sort of AI, deep learning, neural network kinds of things that

smarter people than I understand.

But, you know, the data scientists tell us, you know, this is real stuff. It spits out, you know, a high correlation between these 8 to 9 markers, and, and mortality, like the grim age, and, and can give you an age that is, you know, an R squared around 0.7 ish,.6.7.

So that's really interesting to me. So when that came out, we sort of had to start incorporating those things into our into our overall software package, where we measure these things and tell patients how well they're doing.

And the way I look at it now is this there's no single best biomarker of aging, each one looks at different aspects of the aging process that are important.

And I can tell you, having looked at hundreds of, you know, biomarkers of aging for some biomarkers and thousands for other biomarkers over the years, there is a wide inter individual and intra individual variation in those.

So you can, for instance, have one biomarkers that, you know, take the sequencing or 50 that shows you at 30 and another one in the same person that shows you at 60 people who say, well, you know, what's what's up with that?

I do. They're like, I have a patient sitting across from me going, should I believe, which one should I believe? Of course I want to believe the younger one. Right.

But but what it tells you is that people age differently in different tissues, at different rates, based on lifestyle, genetics, nutrition, epigenetics, many, many different factors.

We all have our weakest system. We have our strongest system, we have our in between systems. And it's important to know what what all of them are doing.

It's a very amongst people. Or is there like a general regression that, you know, first, our cardiovascular system aging markers begin and then the respiratory and then the immune system, is there a certain progression that happens or you think it is it, you know, depend on your genetic background?

Yeah. So that's a great question. And that brings up the, the, the concept I screen keeps on going off and do these things without touching it. Sorry.

That brings up the general concept of, rate of loss versus, what your, what you've inherited. So anytime you measure a biomarker, you're looking at what has happened since birth to that biomarker and then also what you inherited in that biomarker.

So you might for instance, like I have a patient that has this big barrel chest, he was he was a swimmer when he was younger. Great VO2 max, but now a cigaret smoking.

And his, he's losing faster and it's tracking him over time. M51 or pulmonary function because of inflammation from the cigaret smoke. But he inherited a huge reserve.

So his Como is what we call that number. That is how fast you can go. There is still 15 years younger than his age, but if you just looked at that one snapshot, you say no worries.

But no, you have to track them over time. The same thing goes for many other biomarkers. So which system start to age? Yeah, some don't start to age like cognitively mid to late 30s.

Even a little later than that. Handgrip actually continues to go up into your 40s and then starts to go down after that. Things like the arterial stiffness though that does start to decline at your peak, sort of what we call your peak reproductive age around age 25 or so, you reach your peak level of of of arterial elasticity, the obverse of system stiffness.

Telomeres and Their Role in Aging

And you lose about, you know, 1% per year on average. Most biomarkers of aging, you lose about half to one, something like 1.5% of your your inherited function per year.

So that's usually more certainly in a younger population. That's more what determines your what your biomarkers look like is your inheritance. And then as you get older, it's more what you've been doing with that inheritance that is going to be the determinant of it.

So, you know, you have to you have to look at them all and you have to track them over time. But if you're absolutely right, there are certain systems that start to age earlier.

Lungs also, they reach a peak at, about 25 or so and start to decline after that. Varying aspects of that whole process that goes into blowing air out really fast, start to, to, to age.

And that's and so if you want to sort of prevent lung aging, you want to know early on how much inheritance you had. So I'd love to have patients come in at 25, 20, or 25.

And I see that because most of my patients so my average age, my patient is around 48 to 52. So when they come in, they get started on a program. They oftentimes learning all this stuff about themselves, say, oh, would it be good if my son or daughter came in and I said, yeah, be fantastic at that baseline when they're at their peak function and we can know what's going on.

And sometimes you'll find things like particularly in biology, which will perhaps get into yes, inheritance is a big part of that, that, you know, you can inherit is about 70% heritable.

So if you don't choose your parents wisely, you can be, you know, on one end of the liver lottery versus the other. And, and so and knowing that early on allows you to do things to people.

When people have information, it really changes their behavior. So if you have really short telomeres, you don't want smoke anyhow, but you really don't want to smoke if you have really short years, let's just move right into talking about tumors.

I definitely want to get into that. An immune system and, you know, and even hormones after that. But let's maybe just for the viewer, just give us like a, you know, 30,000ft view, at least the value of the telomeres.

So why we think, there's such an important biomarker and, and then going from there. Yeah. So telomeres are the caps on the ends of your chromosomes. Your chromosomes are the packaging of your DNA.

And human chromosomes and all mammals have linear chromosomes. And so the ends of the chromosomes, if they're not kind of protected, the DNA repair system, DNA damage repair system will recognize them as a broken strand of DNA, and they'll try to go in there and fix it.

So telomeres have to be there. These repeats of non-coding DNA. So the most DNA codes for proteins, and then stranded RNA, this turned into proteins. If you have the end of your chromosomes, are non-coding.

It's this repeats of tag which doesn't make any proteins. There are about 10,000 or so between 8 to 10,000, that, young adulthood in life, the very ends of them, is no longer a double strand of DNA.

It's a single strand of DNA that curls back on itself so that it doesn't, it's not exposed as an as a naked end. That would be, cause the DNA damage response to occur.

So being fold up, folded up like that protects them. And that whole structure of the proteins that bind it up into that little, cap is is what a telomere is.

Now each time cells divide, right. You have to replicate your whole DNA, make another set of DNA. But the problem is the ends of the chromosomes. The enzyme that or the molecule that, duplicates them.

Coordinate polymerase can't do it at the very end, it falls off the end. So you need this enzyme called telomerase. It is an enzyme that puts the ends on the chromosomes.

And that is what keeps the tears from getting shorter when, remember, you go from a single cell, at conception to 13 trillion cells at mid adulthood. If you didn't replicate the ends of those chromosomes, you quickly run out of those 10,000 base pairs, right?

So it's rapidly reproducing the two of your ends during in utero. And then at birth, telomerase is suppressed. And that starts the gradual erosion of telomere length of about 50 base pairs per year or 0.05 kilo bases.

And that's sort of the average rate of loss. It why is it important that you, besides preventing this DNA damage repair? Because if the DNA damage repair mechanism goes into work, then it stops the cell from dividing, if the damage is bad enough, then.

And if telegrams get short enough to the cells will no longer divide. They become what's called senescence. Which in the sort of the Greek word for old person getting old, and they don't do their job and they secrete a lot of inflammatory molecules.

So there's, there's, the telomeres are sort of that molecular clock for how much you can repair damaged tissues by having the stem cells that reside in each of your organ systems, divide and then replenish those cells.

Other things that that happen is that is that besides just, you know, replenishing cells, once they particularly the immune system, once they become, senescent, they don't just sit there quietly.

I like to analogize it to a watchdog. A senescent cell is not like a healthy young watchdog. It knows when a burglar is coming, goes after and bites the burglar and gets rid of them.

And senescent cell is like an old blind, nasty watchdog that doesn't get the burglar, doesn't do his job, but also is snipping at the neighbors, causing problems and biting his own owner by secreting what we call these inflammatory cytokines or these molecules that cause inflammation, inflammation, which have been coined the media.

So, so that's sort of a 50,000ft view of what telomeres are. And, and they're really at the very top of the list of things, that are sort of the hallmarks of aging you probably heard of and maybe, maybe some of your other, guests have talked about the nine hallmarks of aging, but I think of that as our biological equivalent of the unified field theory in physics.

In biology, we now have sort of broken it down into the various things that occur. And one of the major things is loss of teleological. Well, yeah, I heard that that before.

That is, the telomere, part again is it's basically shown that, longer telomere length are associated with a longer life and, and, delayed cancer, less mortality and so on.

Right. That is that is that correct? And shortening appears critically. Shortening is associated with adverse and negative outcomes. Is that correct? That's that's absolutely true.

There's been hundreds of studies looking at, telomere length and link and know very well that you lose that 50 base pairs per year. And also, there's studies showing a very large study, showing that the shortest third versus the longest third of telomere length at 60 years of age is associated with a significantly increased risk of death.

And of, cardiovascular disease and of cancer. It's been sort of repeated in other studies, a large study out of Copenhagen looking at individuals between 45 and 75, up to 22 years of follow up.

They've seen that if you're in the bottom 10th, bottom decile of telomere length versus the top decile, you have about a 1 in 1 point five times or 50% increased risk of getting cardiovascular disease end up dying.

And that's sort of with each decile increase, it gets worse and worse and worse. So I think, you know, the data is very strong, large data sets, looking at longer telomeres being associated with better health and health span, in addition to longevity, lower disease burden and shorter telomeres being associated with the opposite.

There are also models of disease that are very rare, called the dilemma of these just keratosis congenital being sort of the initial one, which is thought to be a skin disorder, but actually is the skin that manifestations are really sort of just the tip of the iceberg.

What it really is, is they have 50% activity of telomerase. Not not going. They just have 50%. And the first generation of that mutation can live to be about 50, but not much longer than their lungs give out.

They get pulmonary fibrosis and die if they pass. If they have children before they pass away, that next generation, they have shorter telomeres and less active, telomerase.

So then they will make to maybe 30 and die of bone marrow failure, because the bone marrow of course has to keep on dividing to make new cells. So, after the three generations, they pretty much don't make it out of a uterus.

And that, that, that ends that lineage that is been recapitulated in mouse models and other, and it's, it's, you know, if you have critically short telomeres, you don't live very long.

Likewise. Yeah. Go ahead. Interesting is that, it looks like it's not just your like what you do in your life, but also what happened to in utero and what your parents gave you the correct.

But seems like that's almost a huge amount of the impact of your telomeres is what's up in other generations or trauma that happened to your parents or something like that.

Yeah, I mean, for sure, I mean, it's things that happen in utero, but also almost more importantly, well, so what you inherit from them is very important. It's that 70% number.

You know, I have a piece by piece to come in and. Yeah, there's ranges of between 8 and 12 kilo bases at age 20 to 25, so. But you only lose about point about three kilo basis over your whole life.

So let's say you start out at 12 and you get to nine. You're still great. You're like a 25 year old. I have some basis coming with yours. And likewise, I had a patient who came in at 40, and her two year length was less than five.

So she doesn't have that much room to lose telomere before they get critically short. So inheritance is huge. Early childhood stress causes shortening of telomeres virtually, which is what I love about liver biology.

Virtually everything that we know that is good for your health has been shown in studies to be associated with longer telomeres and everything. We know that's bad for you smoking, being overweight, being inactive is associated with longer telomerase.

And if you do things like if you have a lot of stress from taking care of an older patient or Alzheimer's disease patient, your telomeres are longer. But if you exercise, it mitigates that stress and delivers are in short, and what's even more fascinating as a physician studying this stuff is that, you know, we know that stress is associated with bad outcomes and shorter life.

Well, how is that? We know that cortisol is bad for you to write too high a cortisol. Chronic stress in bones. The you know, the Cushing's syndrome, which is the disease state, is a very bad thing to have.

But lo and behold, cortisol inhibits telomerase. It is the molecular link from between stress, shorter telomeres and bad outcomes. So it's really it's really fascinating, how it's all coming together.

I just want to jump jump in there that this question about, the what is what is, been shown that she left in tears. I mean, I know, exercise, I heard and the study came up, but hyperbaric oxygen therapy.

Yeah. So that's a that's a great question. So you have to you have to I think, be clear about things that have been shown to life and telomeres versus things that have been shown to keep them stable versus things that have slowed down the attrition.

A lot of the lifestyle stuff has does that because besides having to divide oxidative, stress free radical damage causes telomeres to be shorter, faster, not just when cells are dividing, but even when they're just sitting there, you can go and gosh, you cause shortening.

So if you do things to get rid of that oxidative stress like, diet high in fruits and vegetables and Mediterranean type diet or supplements, etc., those kinds of things can slow down the loss, but they're not going to lengthen telomeres, because the only thing that lengthens delimiters is telomerase.

Right. Now there's another way that telomerase can be, you know, for the molecular biologist out there that there is another pathway for lengthening telomeres, but we're not going to get involved.

That's a small, small part of it. So telomerase itself is what will lengthen. So there has been gene therapy in, in mouse models that have and in vitro that, you know, sort of same thing that we're looking at for other kinds of gene therapy.

You take an AV or you take a virus that carries the gene into the DNA, and it turns on telomerase. Those things have definitely been shown to turn on telomerase and lengthen telomeres.

The natural product molecule, derived from Astragalus member nations is traditional Chinese medicine that goes by the trade name 65, has been shown in studies that I've been fortunate to be involved in to lengthen telomeres, in a randomized controlled trial, much I mean, those computer keeps on going off here.

Okay. Sorry about that. And in a large randomized controlled trial, telomere lengthening. So and there's, so exercise itself doesn't link into the hyperbaric oxygen chambers.

Study your, your referring to was really fascinating study, that has shown some increase in telomere length and a decrease in senescent cells, which is associated with shortened telomeres.

It's a big increase. They've been reporting like 20% or something like that, which is pretty incredible. I, I'm not certain that the tailor like measurements were, you know, they didn't use the exact same technique that I typically use in my office in that, a number of studies they use. But.

So I'm waiting for more corroboration on that. But theoretically, what they're doing with that is they're giving a stress, of hyperbaric oxygen. And then, and then pure oxygen and then taking oxygen away and almost like exercise.

I mean, this is this is how the human body gets stronger. If you give a little stress, it repairs, recovers and it's a little stronger and you keep doing that.

Telomerase, T65, and Clinical Effects

And the protocol was like 50 sessions of an hour or so or more of, of this kind of protocol, so I could see how it might do it. I just would like to see a bigger data set for I'm sure that that, that does that.

So right now, you know, this small molecule, telomerase activator, gene therapy, I mean, and, and so far there's a couple other supplements that claim it, but they don't actually have the data to.

And I've seen to back it up for to 65, this telomerase activator. Do people actually notice, like an improvement, like,

I mean, when you said a person came in with, you know, five kilobyte, shortening, what did she notice anything like, you know, can you see something that you.

I don't think you necessarily noticed the increase, per se. T it's so telomerase T 65 turns on telomerase. And the main function of telomerase is to lengthen telomeres.

Lengthening telomeres, is good for allowing the cells to divide. You know, you have a reduction in senescent cells, which we showed in a study that I'll talk about in a little bit.

Those can have beneficial effects. But telomerase itself by reducing this, DNA damage response can increase mitochondrial biogenesis, meaning increase the number of mitochondria and the efficiency of mitochondria through these sort of what we call a non-canonical as things that aren't about lengthening telomeres, but are other functions of that telomerase enzyme within the cell.

And so those types of things could cause, things that you could feel by taking to 65. I have patients that report, you know, top athletes that report, endurance, you know, masters athletes report better times, better recovery.

That could be related to the improvement in mitochondrial function, perhaps reductions in inflammation to take place because there's fewer senescent cells.

Some patients report improved vision. Certainly that could occur because of the the retina have these cells called retinal epithelial cells, which divide a lot.

And if you can help them divide, like more like when you were younger, perhaps you could get Chris provision. I noticed that myself, 65 for 14 years I have noticed that myself.

Some patients have noticed improvement in, near us farsightedness, which is the ability to read closely, you know, go figure. But, that, so that's some of the you have a total things, some people notice improved energy.

There's no studies that have documented that yet. But there are reasons why that that could happen. But again, you know, if you're taking if you're doing a dietary measure or you're taking a cholesterol lowering that is medication to lower your cholesterol, cholesterol, you're not necessarily going to feel that, but you are going to decrease the likelihood that you're going to have a heart attack or stroke.

And so that's beneficial. I think like with hormone replacement therapy, you know, besides the immediate getting rid of the hot flashes and night sweats over time, you see, I mean, we're doing this for 20, 25 years now.

Patients telling me that their friends are like that, that they're are that are their age, they're saying, you just why are you looking better right now?

What are you doing? And I think these kind of gradual experiments, 1% per year that you're losing in function and appearance is kind of a gradual things are what happened.

So you kind of have to be be in this for the long term. I call your telomere length. Your biological 401 K is sort of your savings plan that you have for ability to divide, ability to keep your cells healthy as you get older, you know, to fund your retirement, which is what your health span is, the time of that.

You're alive and free of disease and functioning. Well. I think you're I think you're right about that. I mean, it looks like we have to do this over some time to see the type of phenotypic, changes, maybe that, you know, it hasn't been long enough because, you know, maybe that G6 developed, been around for, what, ten, ten years or so now?

14 now. I mean, well, actually available to the public about 14 years now. That's the other thing about today. 65 people ask me about it. You know why I think that it's safe and a good idea to to to give as a supplement because it's not a drug, but it was originally discovered by a company called a Geron Corporation.

Geron is Greek for old man. And they were looking for a natural products of about 5000 molecules to to find one that turned on telomerase because they knew the telomerase, that was an important thing to do.

And they got like three hits in this stream, from this traditional Chinese medicine, a single single molecule that's extracted from these fragments, free throw, a patented process.

And they were moving it through the new, new invention, the new investigational drug pathway. So you did all the safety testing that that a drug that's going to go become a pharmaceutical.

And then, they pivoted, a few years later towards cancer therapeutics and sold off the rights. So it has a lot of safety, built into it. Because of all these studies that were done, it's generally regarded as safe because it's been in the Chinese medicine for a long time.

So I think, you know, it's it's it's it's a it's a pretty safe supplement. It's been around for a while. I've been giving it to my patients for many years.

I've been lecturing about telomeres and tumor biology and the effective to 65, there's, I think nine studies published now. Three randomized controlled trials or more, showing that a lengthens telomerase, turns on telomerase, reduces senescent cells in a randomized controlled trial fashion.

So I think that, you know, that's why that's that's the one I use. Yeah. Yeah. Let's talk right about your study because that was actually blew me away.

And that's I was like, I wanted to reach out to you, that basically show people, randomized to take to you 65 or not. There's a difference. The immuno senescence is, is that correct, that that's, that was that was what the finding of the study was, that is that is correct.

So the, the study was looking at the 500 individuals taking 65 and varying doses from 100 to 500. I use, and the typical dose is between 250 and 500. I use.

And looking at this population of cells called senescent cells. And they are, you know, your, your white blood cells you have and then you have your granulocytes, you know, lymphocytes, the granular sites are sort of the ground forces to hit the ground.

You know, you know, sort of you're not smart about it. And the, the lymphocytes are sort of the, the part of the immune system that knows exactly what to attack.

And so it's more educated, these, these cells, the part of them are T cells. They become older if they have to divide and divide and divide, because they're fighting off, infections particularly, a certain type of herpes virus infection is very common.

And they lose that ability to divide and they become senescent. And as I mentioned before, they secrete all these inflammatory cytokines. And so that's a bad thing.

What they also do is they don't go away. So they accumulate. What they're supposed to do is go in there, knock out the enemy, be either a virus or a tumor, and then, you know, in order to do that, that, that one that's uniquely designed to fight off that particular virus or that particular tumor, expands into millions and millions of cells.

So it divides and divides. And then once the job is done, they die and a few cells are left behind, called the memory T cells, which then are ready to fight that off.

It comes back. Herpes viruses are you've heard the phrase the gift that keeps on getting right. Once you have them, you have them. They when you're under stress, comes out from your trigeminal ganglion.

If it's your if it's your if it's a cold or herpes virus, when it comes out on your lips. That's a repeat thing every time

that happens for a herpes virus, this whole process takes place.

The cell's telomere length gets shorter and shorter and shorter. Once they get critically short, they become senescent, giving CD 65 to this population that had this virus called CMV cytomegalovirus, which is herpes virus number five.

Not all of them have it about 60%, because about 60% of people in that age group will have it. And they don't even know, have they? They don't know they have it because it's been up.

It doesn't have any, symptoms. On it, we had a 20% reduction that was highly significant, a highly significant reduction. And not only did we have a reduction in the senescent cells, but we had an increase in the naive T cells.

Those are the ones that can fight off new infections. And we have a lot of them were young, but they start to dwindle as we age, which is one of the reasons why older people don't respond well to vaccinations like flu.

Response to flu vaccines in an older population is 50% or less. But if you have an increase in those numbers, more like when you're youthful. Another reason why individuals that are younger don't have a at as adverse outcome to Covid, as well as older people do.

So it was really, a complete remodeling of the immune system from an older immune system to a more youthful immune system. And the age of 28, is that correct?

Yeah. So CD 28. So you have to almost all cells when you're younger, all your T cells express CD 28. And that molecule helps it to really divide briskly and amount to great response.

If you don't have that, if a CD 28 negative that it doesn't. Now it's an anemic response. It's not as good at fighting off the infections, but again, sits there and secretes these inflammatory molecules that cause cardiovascular disease, osteoporosis, cancer.

I mean, CMV infection has been associated with many of the chronic diseases of aging. Herpes virus is in general our, stressors of the immune system. There's a whole theory of, of herpesvirus one being an important factor in increased risk for Alzheimer's disease, because it causes the cells to support the neurons, the cells called glial cells, they divide.

Neurons don't divide. But we will do a little bit. But the glial cells divide when they get senescent because they've been having to fight off these viruses.

They don't do their job. They don't support the the neurons. Well, then the neurons start to malfunction, producing that the amyloid beta plaque that we talk about and Alzheimer's disease.

So there's there's companies that are formed looking at turning on telomerase to help, treat and prevent Alzheimer's disease. So the immune system, you know, we think about it as being important for infection, but it really is a major factor in every disease of aging, every degenerative disease, because, again, it's a stressor.

So that's really the key is keeping inflammation to a a low level, basically. Our, our innate immunity to becomes less as we get older. That's what happens.

Immuno senescence as the aging of the immune system. And we end up, because of all this lifetime exposure to, to, to this, various pathogens that just basically stimulate our immune system.

So, so something like you're saying the CD eight CD 28, negative. Is that correct? That ends up increasing as time goes on. Is that correct? Yeah. Yes. So, for instance, we will just get back to the aging.

The innate immune system does age and does get less functional, but the adaptive immune system is actually the one who suffers the most with age. And that's the one that is, you know, the lymphocytes attacking, you know, in

an orchestrated fashion, not just going out there guns blazing, trying to kill everything.

So what happens? Is it, it the Cd28 molecule, then if you count, if you count them, it's about, you know, 99% of cells express it. As you get older, it can be as low as 20, 30% or even 10% express.

That's for the adverse being 80 to 90% or CMV, Cd28 negative, which takes up lots of space. So, in the study, people with CMV had about 220 cells per microliter or teenage CMV -60 cells per micro.

The huge difference in the statistically significant. And that was in a randomized controlled trial looking at it in the same group, the numbers were almost exactly in that cohort that came through my office where we, originally looked at, and 65 in those, in those, in the same cells.

So, but what is the major thing that causes it? It's chronic stimulation of the adaptive immune system, particularly the CD8 cells. And really the major factor is the herpes viruses, particularly CMV.

But even if you don't have CMV, the more herpes viruses you have good studies showing an association between the higher number of, herpes viruses. The shorter your telomeres are.

Because telomeres are that marker for how much stress the cells are undergoing, as they are required to divide to keep the herpes virus from coming out.

So that is, you know, one of the major has to know there's other aspects of aging, the immune system, the famous gland, which is sits behind your heart, in front of your heart, that where your T cells go to learn and be educated enough.

They create these 90 cells that shrinks to almost nothing. This at age 50, there was an interesting study that you're probably aware of. The trim trial, where they gave growth hormone metformin and DHEA, and they saw some increase in thymus gland.

That's the other side. I call that intrinsic immune aging because that's not from external forces, viruses, etc.. It's sort of loss of that, of that thymus gland, production of the T cells, extrinsic aging is when you get exposed to these viruses or certain head and neck tumors, any chronic stress of the immune system is going to have this effect on HIV.

Has that kind of an effect? It's not on the T cells, but it's not on the CDA. It's it's on C4'S helper cells. But now that we're seeing, you know, people with HIV living longer lives with low viral loads, what's causing them problems is CMV and an increase in those T cells.

And so we have to start. It would be fantastic if it were a vaccination for CMV. Because it is it is robbing people of, of, I think, quality years of life toward the end of life.

When, when, when it's caused more shortening of their telomeres, a greater increase in senescent cells than, than, than they would otherwise have to have, I call it a super, super slow HIV.

Do you see, think that, if you have less exposure to these allergens or things that stimulate the immune system will live longer? Yeah. So that's a really interesting question.

Immune Aging, CMV, and Future of Longevity

I mean, there's a whole kind of debate, research in immunology about what level of stimulation is good versus bad. I think if you live in a bubble, then, you know, your immune system then doesn't get educated about certain things.

And increases in autoimmune disorders have occurred. There's been very interesting books written about that, and I think that's true. You have to educate your immune system to certain pathogens.

And you know, everything we know in biology, there's a whole phrase, nothing, in biology makes sense except in light of evolution. And that's the this is key.

He was a famous biologist. And it's true. We evolved in an environment where we live to be 30, 40 years, but maybe not even. And we died from infection and starvation.

Next door neighbor trying to, you know, take over your plot of land. We didn't die of natural causes. We didn't die of old age. And so our immune systems evolved in that environment.

CMV was probably, you know, relatively helpful then, because it caused a little bit more robustness to the theory that's been written about in the immunology journals, a more robust immune response that may have been helpful for parasitic infections that we were, you know, were rapid in us.

So it might have had a beneficial effect. And that's why CMT has got a somewhat of a symbiotic relationship in the human body, has been in humans for a long time.

But in the past 5000 years, we've gone from living to 30, 40 on average to 7580. It is now having deleterious effects that weren't showing themselves because we weren't living that well.

That's a it's a it's a theory called antagonistic attraction, where, there's a beneficial effect usually, our response. So that increased inflammation to fight off infections that may have given those ancestors the ability to fight off that infection and get their genes into the next generation.

But then the prices increase in senescent cells as we get older. So if you ask me, would it be better to b c a, b negative c? And I'd say negative because if you want to live a long, healthy life, I mean you can still do it.

There's, there's I'm not going to say that that but your will, I think your chances of doing it are better if you, if you're CMV now, what can you do about it?

Look, you know, we've all learned germaphobe, since Covid came around, where you have your hands putting all sorts of stuff on. You know, that probably is helpful for not getting it, but, I have patients who are married, been married, good marriage, regular sex, 25 years, one CMV positive the other night.

So you only spread it when you're setting the virus. You know, just like when a cold sore, and most of the time, you're not doing that. I think there's probably some people that have a little bit more innate resistance to it than others.

So, you know, if you're in a subway, you know, you're shaking a bunch of people's hands. You know, don't take in your mouth right afterwards. Don't rub your nose, your face, wash your hands.

You know, there's been a massive drop in flu since Covid because of people wearing masks and doing that stuff. Same thing would go with CMV. The interesting thing about CMV is that it, seroconversion rates or, you know, some technical medical term for, you know, who've gotten infected in about an antibody response.

It's about 30% at age ten, and you get about a 1% conversion rate per year. So that between 10 and 90, you basically get to 90. What's about 90% CMV deposit that confuse them about these senescent cells because they thought that that, you know, this was just a normal aging process.

But if you're seeing me negative, I can see by practice. You see in the negative, they've got 15 to 28 negative cells, not 220. And yeah, they're dealing a little bit longer taking into consideration whatever they inherit.

They have more naive T cells because there's room for them. They're, they're not being crowded up on senescent cells. So, you know that that is, that's sort of the the short version of the CMV story.

You know, it's important, I don't I don't tell people to go crazy about it. I think it really helps us understand the

general concept, which is any stressor stresses a cell.

In this case, the immune cell has to divide to get shorter. That tissue, which is the immune system, gets older and doesn't function as well. That could be a cartilage cell in your knee.

You're running 50 marathons a year. I heard some crazy guy did one marathon a week for a year. I mean, God bless him that that takes some some guts and some skill.

But the stress on your joints, undoubtedly the condo sites, the cells that make cartilage or the stem cells that replace them are going through some stress.

The tumors are getting shorter. So you have to remember, you know the phrase in the UK, mind the gap, you got to mind your telomeres. And I think, you want to do what you can to keep it from getting shorter.

You want to, and then potentially do things that can lengthen then possibly to 65, for, you know, if that's something that you want to try, I think there's going to be genetic therapies for it in the future.

There are some companies looking at that right now. You know, potent, increasing telomerase activity that causes a 30, 40% increase that, you know, perhaps happened in the hyperbaric oxygen chamber.

I'm not saying it didn't, but it but but if it did, that's the thing that we're a little skeptical about. So in a study from Harvard with Rhonda Pinto is now, you know, he was at Harvard now, MD Anderson, he turned on until at first you knocked it out in these mouse models.

And it is more rapidly. They got gray testicles, shrank, their spleen shrunk, their brains got smaller. You know, they just they look at a whole bunch.

Then he was able to turn it on through this little genetic trick that he did. And then their fur grew back, explains Brubeck. They da. They almost did a Benjamin Button in the movie where you went from, you know, gold to young, and it was like a 30% increase in funerals.

So if we in fact, saw that, I would I would think we'd see more, on the outside, in the inside, in terms of people just looking a lot different, is that actually took place, which I think it will at the I mean, I'm at the point now where I think that aging is a technological problem.

It's not a theoretical problem to to cure. I wanted to ask you that exact question. How, how hopeful are you that, you know, we're going to be able to solve this, this, this aging problem?

Yeah. So, I mean, I'm very hopeful. I mean, there are people like Aubrey de gray, you know, they're, you know, the head of the Sands Foundation, you know, who talk.

These are very legitimate, very smart people. Talk about 150 years, or what's called longevity escape velocity, where you live long enough to get enough technology such that you just don't aging where there are species who don't age, you know that.

I mean, the general human, you know, some species of shark. They just they have active telomerase, they have strong tumor suppressors and don't get cancer.

And they just keep getting bigger and bigger and bigger and don't age. And what kills them is unnatural causes, you know, boat hits, or they get an infection or something like that.

So I think it's possible within humans, I think that that, you know, in the short term, with current technologies, we could see people living to 120 with a very robust level of health, depending on how soon and how early they start.

You know, imagine that, you know, I get another 60 years of, of life in this or better condition. Now, I mean, that's

that's a pretty that's a pretty big deal.

150, 200 or, you know, the vampire type thing. I don't know about that yet, but, you know, it's funny in science, you just can't predict. Back when I was growing up, he started the war on cancer and the and the, the mission to put a man on the moon, and people are like, cancer will be cured.

No problem. But you forget about what happened, you know, the other way around. So you just don't know what technology comes along that can really change things.

But it's a very exciting time, I think, to be in the field and to to be a part of this and watching this, it's it's made my, my career in medicine, you know, just fascinating.

And I get to see it in my practice, the things I do for my patients, the various things I apply, improving your health as you do as well. And just one last question.

I know that we're just wrapping up, but what ask you? You know, maybe when I was just going through med school, I had the whole idea of antioxidants was really big.

I remember watching a documentary by we, first of all, was taking, like, 15 pills. Oh, God. How can you take 15 pills? He said, right. I'm not going to die. Right?

And but I want to get your thoughts on this because our viewers are probably here inundated with, with, you know, antioxidants that, so good for you. Where's the research?

What's your thoughts on. Yeah. So the free radical theory of aging, you know, from denim that in denim, Harmon, posited that, you know, reactive oxygen species produced by the mitochondria and other inflammatory processes was a major driver of aging.

And that if you took antioxidants and quelled that those those reactive oxygen species, then you would fix the aging process. I mean, that's been largely debunked, because aging, as you can imagine, is much, much more complex than that.

These reactive oxygen species are actually some of them are very important as signaling molecules. But that's not to say that they weren't to something, I mean, inflammation from a, you know, attack from free radicals is definitely still a major part of the aging process.

But what we understand now is that the damage taking place, the more important thing is to repair the damage, being able to repair the damage, replace the damaged cells.

This is where the telomeres come in. So just flooding yourself with antioxidants isn't, you know, there have been studies have shown benefits and various things, you know, vitamin C and vitamin D combination and slight reduction, cardiovascular disease have been a lot of null studies as well.

They've shown, you know, no benefit. There's been some studies showing, you know, a worsening effect like beta carotene in lungs, lung cancer because just one antioxidant being thrown in there, even two isn't really working.

Now in mouse models, if you give a cocktail like sort of the cocktail that you and I prescribe, and then also various types of, complimentary antioxidants that, you know, regenerate your vitamin C or vitamin E of lipoic acid.

I think there's there's a role for that. And I use them in my practice. But you you need to. Aging is a more complex process than that. You need to look at the regeneration side.

You need to look at the senescence side. You need to look at those nine hallmarks of aging. You know, mitochondrial dysfunction is one of them. That's the major generator of of reactive oxygen species.

So for the listeners, don't just willy nilly take a whole bunch of supplements, and antioxidants, you want to make them targeted to do. There he goes. My computer again. Sorry about that.

I gotta get that fixed. You want to do it in a targeted fashion? I think under the guidance of a at least a nutritionist or a physician, or somebody that knows about the complexity of the aging process and then measures what's happening.

I mean, if you want something to help your cardiovascular system, you want to measure things like arterial stiffness, you want to measure, I mean, there's there's a whole bunch of supplements.

I have my patients taken. I thought I would be, but I am taking somewhere in the range of 20 pills a day. But they're all there for a reason, and I'm measuring to see whether they're working.

And I'm just dose with my patients and with myself that, you know, what we talked about before, before we came, became live. You know, I practice and you practice.

And what we all should be practicing is the end of one medicine, where each of us is unique from a genetic, epigenetic lifestyle standpoint. To apply the results of, you know, one theory or one study, you have to be exactly like the average person in that study or, to, to really make it applicable to you.

So you need to know what all the markers are doing, and you need to track what you're doing to those markers and see if they're going in direction. And that's perfect. Thank you.

I really appreciate we're just running out of time. But, I think looking at viewers who want to learn more about the work you're doing, and potentially contact you.

Yeah. So I have, two places where you can learn. One is, physio, dot com, physio, agent.com, which is where are software. The measuring agent is there for particularly for doctors.

I want to use that in their practices. And then at Rafael medical.com where I blog about things that's all relative medical. And then I try to put content up on Instagram weekly or at least sometimes twice a week.

But Rafael, MD, and keep, keep my, my followers, abreast of things that are happening in aging and occasionally, some exercise you ask them that I'm involved in.

But that's, that's where they can find me. Okay. That's awesome. Thank you so much. I really appreciate your time to great talk to you, Sanjeev. Thank you very much.