Cellular Senescence, Telomeres and Senolytic Therapies

Dr. Joseph M. Raffaele, M.D.
Joseph Cleaver, M.D.

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Hello, this is Dr. Joseph Raffaele, your host for the Telomere Summit. I'm very pleased to have today, Dr. Joseph Cleaver on the show to talk to him about what he does. Welcome, Joe.

Joseph Cleaver, MD
Thank you for having me, Joe, how are you today?

Dr. Joseph M. Raffaele, M.D.
I am well, looking forward to this conversation. Let me tell our listeners about your extensive background. Dr. Cleaver is a co-founder of the Paradigm Wellness Medical Group in Napa Valley in Dallas and is medical director at Boutique Wellness, LLC in Winston, North Carolina. And has been practicing medicine since 1990, just about the same as me. He is a rheumatologist and is board certified in internal medicine, a fellow of the American Board of Anti-Aging Regenerative Medicine. Dr. Cleaver is board certified also in anti-aging and regenerative medicine, and has achieved certification by ABAARM, in advanced metabolic endocrinology, specializing in bio-identical hormone therapy.

As a faculty member at A4M and the Metabolic Medicine Institute, he lectures nationally and internationally, and holds the position of adjunct clinical professor at George Washington School Of Medicine. Dr Cleaver lectures extensively on longevity, senolytic science, aesthetics, and scalp and hair restoration, and actively trains medical professionals for A4M at Locanda Renaissance group, LLC. He has authored and published research, textbook chapters, and articles for international sports and anti-aging magazines. While at the Cooper Clinic and Cooper Institute, he conducted Homeland Security, NIH Research. As a biologics expert with 15 years experience in regenerative aesthetics, he applies this cutting edge regenerative medicine science to minimally invasive aesthetics of the skin, face, scalp and hair rejuvenation. Again,

welcome Joe, looking forward to our conversation. Why don't you just start off by telling us a little bit about how you came to be in this field? I always like to hear the journey and then we'll get into a little bit more of what you're doing currently.

Joseph Cleaver, MD
So first thanks for having me. This is always an exciting topic, telomere biology, senolytics, longevity, it's a pursuit of mine probably for the last 20 plus years. And when I first was introduced to, for example, A4M, I guess it's 18 years ago now, and I interacted with a lot of colleagues and they all had a story that they were conventional physicians or medical practitioners, and they ended up with kind of a cryptic type of symptomatology, like chronic fatigue or whatever it might be and could not get the satisfaction or the answers from conventional medicine. And that's what drew them into regenerative or integrative medicine. And truth be told, I was educated in the University of Rome, in Rome, Italy, right in the heart of the Mediterranean. And that's really what started my integrative approach because the subject material in medical school, at least in my Alma Mater, University of Rome, already took an integrative approach.

And then when I got back to the States, and did my residency up in UMDNJ, and New Jersey and fellowship in Miami, down at the University of Miami in Miami, Florida. I ended up in Dallas, Texas, and it was at Baylor, I was a professor at UT Southwestern, and then went over to the Cooper Clinic one day, as a patient and ended up being hired actually on staff there. And the Cooper Clinic was one of the original, I think, integrative medicine, preventive medicine clinics, in the country, started back in 1970. And I was there for about 14 years. And the approach was always to embrace lifestyle as a preventive therapy. And so that mindset was always there. I never had any medical issues, and I've always was exposed to this all the way back to the medical school, then Cooper Clinic, Cooper Institute, doing research over there. And as a rheumatologist, I did a lot of sports medicine at the time. And that's what exposed me, if you will, or opened the door to using PRP, biologics for MSK injury, et cetera.

And you've been in practice, I think we've been in practice, we were just talking about that, probably about the same amount of time, and sometimes your practice, as much as you think you're steering it, sometimes it steers you. And it ends up morphing into something you never imagined. And that's how my practice has developed and evolved over the years, to a point today that I have taken integrated functional medicine, biologics, telomere biology, the hormone balancing, et cetera, and have expanded it into functional aesthetics. And that balance between the looking good and feeling good, really opened the door to senolytics and longevity. So longevity was always part of the practice, and the last five years have really taken a deep dive into senolytics and understanding the real drivers behind, or the most potent, if you

will, or important drivers behind premature aging, inflammaging, et cetera. And that's how my practice kind of morphed over the, especially the last five years. So I balance about 50/50 aesthetics, hair restoration, skin rejuvenation, sexual performance, et cetera, because all those things knit together beautifully in a longevity program.

Dr. Joseph M. Raffaele, M.D.
Yeah, I mean, that's a great story. And I was just thinking, when you said inflammaging, that you were you trained in Rome and that term was going by Claudio Franceschi, an Italian professor researching in longevity medicine, I think back in '96 or something like that. So, yeah, you came from that sort of a mindset. You talked about having a precision senolytic protocol, and I'm curious about how you put that together with peptides, telomere biology and TA-65. And we'll talk a little bit about how you got into that and what kind of things you do.

Joseph Cleaver, MD
So a real deep dive in the last five years has led me to that cell senescent burden and the impact that lifestyle, fundamentally, we're all first and foremost, lifestyle preventive medicine practitioners, and that's the purest form of medicine. If we can prevent through education and lifestyle, we're so far ahead of the curve, in maintaining quality of life and preventing the diseases of aging, that we see more and more in the literature, it's been around for quite a long time, the senolytics and the impact or what's senolytic do as a science, to initiate that apoptosis or destruction of zombie cells or senescent cells. My patients, when I call them a zombie cell, they never forget it, so I use that all the time, but especially the SASP cell, that secretory phenotype, that is the real bad boy on the block, that we need some of the healthy, short lived SASP cells, but those longer lived SASP cells that become very inflammatory, they create a lot of inflammatory substances, IL6 and TNF Alpha, et cetera, that are the real driver behind premature aging and those diseases related to aging, diabetes, dementia, et cetera, cancers, heart disease.

What we see with cell senescence is that lifestyle plays a huge role in increasing cell senescence burden in the body. So when I started, I was doing longevity for many years and I've used the TA-65 and telomerase activator as a cornerstone in my therapy. And we have a much better understanding, at least I do, and how I link the impact of what telomerase does and the impact it has in the non-canonical aspect or function it has in mitochondrial health. So we were kind of grasping if you will, 10, 15 years ago, it's like, oh, everything's mitochondria, everything's telomere length. And I think it took a while, at least, for me to understand how they integrate together and you can't separate them out. The science is there now that shows if you maintain telomere length, if you don't have dysfunctional telomeres, that mitochondria function better. The mitochondria in biogenesis is optimized. ROS, oxidative stress is decreased. And they all

interplay between each other. But the end result is when you read the literature, it's like, oh yeah, telomere shortening is very important for driving a cell into senescence. And mitochondrial dysfunction is very important in driving a cell into senescence. Epigenetics, you know, we can go through the list. But when I started using, for example, TA-65, I didn't know until I read the paper that you published recently. I had to kind of coax that patient and persuade them and say, give it some time, give it some time, give it six, nine, 12 months. And over you will see the impact it has on telomere shortening or telomere health and mitochondrial health on skin health, for example. And overall sense of wellbeing, overall sense of energy. And fast forward to 2021, I realized that maintaining telomere function, maintaining telomere health, has a huge impact on mitochondrial function. And so you had to get that patient over the hump. If he was like, hey doc, I've taken this for three months.

And you're telling me about these telomeres and telomerase and all this other stuff, but I don't feel much different. I say, well, stick it out, give it six, nine, 12 months and see how you feel. And if you don't think you feel any better, stop it, and then see how you feel because inevitably they do feel a difference, in the sense of well-being, that sense of really just energy every day. And it all started to make sense to me when we looked at the literature recently with this pandemic and the virus that is responsible for creating the pandemic and the impact it has, or that virus has in the acute infection, it destroys mitochondria. So in the literature, some of the literature that has been published, say, patients who have shortened telomeres do poorly if they contract this infection, this viral illness. And so if we have somebody with longer telomeres or somebody who may be on a telomerase activator, has improved mitochondrial health, mitochondrial function, they might fare better, because the cell function, system functions are going to be at I think, a different level of functionality than somebody who has shorter telomeres. So it all makes sense.

Dr. Joseph M. Raffaele, M.D.
Yeah, I think when those papers came out, I was really fascinated to see that it was sort of two mechanisms. One is your senescent cell burden determines what your inflammatory state is and people with cytokine storm, it occurs because of an overreaction of the immune system because of these cells that are producing the SASP molecules. On the other side, though, it's your ability for your lymphocytes to divide fast enough to fight off this viral infection, Abraham Aviv has hypothesized, and then subsequently I think Maria Glasgow in French Group have shown that you actually, people with shorter telomeres do have worst outcomes in bottom 10 versus the top 90th percentile, you have more severe disease. Because in the short term, the lymphocytes are not able to replicate enough to take it on. So it's those two mechanisms, both tied together through telomeres and through senescent cells, I think really kind of brought it home. So if someone is doing whether it's lifestyle, hormone replacements, we know estrogen

can turn on telomerase to a certain extent as well, or actual telomerase activation, if they can keep their telomeres longer, they could potentially be less susceptible. It can also be potentially used as a stratifying tool, which I'm doing in my practice to see, if you have really short telomeres, is it something that you need to be more careful about? I mean, it's obviously not backed by a large body of data right now, but I think that could be a direction to go in. We see people that are 25, 35 years old without any of these other risk factors, obviously age, not being at that age, succumbing to bad, or getting bad diseases, and sometimes succumbing to it, what's the reason for that? Well, probably because in some of those systems, your biological age is not that young. So it really, the pandemic has brought, I think us into this kind of area where we're looking at short term adverse effects because of something that's impacting the long-term aging process. And it's really fascinating. You employ, which I don't that much in my practice, so I'm curious to hear about your clinical stories about it and your approach to actual senolytic molecules like fisetin and quercetin, and some peptides, tell me a little bit more about how you go about that, what your patient choice is, what you monitor for, to give us our listeners an idea about how you approach that.

Joseph Cleaver, MD
So when I lecture I'm educating medical practitioners, excuse me, or in my office, trying to explain to a patient why they would embrace them and want to be interested and start a senolytic program, I explain to them there's two sides of this equation. We have a healthy stem cell, healthy cells in all our systems on this end of the equation. And on the other end of the equation is that senescent cell or basically an apoptotic cell. In the middle, we have a senescent cell. And we have two targets, one is preventive, and that's where I think actually telomerase activator TA-65 comes. It makes sense to me that the, especially in the data that you elucidated, looking at a decrease in senescent cells over a period of time, it makes sense to me that it's preventive. And that that's why TA-65 is a cornerstone in my senolytic program, that patients are on 365 days a year. Whereas early on, so that's the preventative part.

And some of these senolytics are, purely senolytics are going to create and induce apoptosis, but they have double duty, several of them have double duty, if you will. For example, fisetin, it has some preventive capacity, it also has a senolytic capacity. I use a lot of rapamycin rapalogs, same thing, a decrease in mTOR can have a benefit on both sides of that equation. So we want to prevent or maintain a healthy cell, and that's through telomere length, that's through mitochondrial function, minimizing oxidative stress, and maintaining those healthy numbers of the cells that we need to do to optimize organ and system function. Then inevitably, we're going to dump over, periodically, cyclically, we're going dump healthy cells into that senescent state. And then what we want to do is periodically rid the body of those senescent cells through a pure senolytic if you will.

Dr. Joseph M. Raffaele, M.D.
What's one of the pure senolytics?

Joseph Cleaver, MD
I'm sorry?

Dr. Joseph M. Raffaele, M.D.
The pure senolytics versus the ones that-

Joseph Cleaver, MD
So there are some fairly exotic senolytics that are not mainstream, that are not, honestly, are not FDA approved. We do a lot of things that are off label. We do a lot of therapies that aren't recognized as standard of care by the FDA or by other medical guidelines, if you will. But there are peptides that are senolytics, there are peptides that are mitochondrial peptides. So what has come to light recently is there are several publications that look at, everybody is embracing NAD, for example, everybody is like I'm gonna do IB NAD, because it's going to increase my mitochondrial function ATP, et cetera, and improve my stem cell function and health. That's probably true, but if we haven't removed the SASP cell that is also going to benefit from, for example, a NAD infusion, I think was an oversight, if you will, until more recently in my programs or in in my main protocol.

So what I'll do first I'll start setting up my senolytic program that is preventive, and that is the TA-65, the flavonoids such as fisetin, for example. And before I go come in with mitochondrial support to maintain a healthy stem cell presence, I'll move into the senolytics and then clean them out through intermittent fasting. We know that manipulating our caloric intake through intermittent fasting, et cetera, or fasting mimicking diets, certainly is beneficial up to a certain age. There's studies that show it's not that effective as we get later in life, and try to use intermittent fasting, but there's still probably some benefits.

So that plus certain peptides actually that drive P53 into that senescent cell, into that SASP cell and induce autophagy. Now that I've cleaned up those senescent cells, those SASP cells, then I'll come in with that really potent or that really focused, targeted mitochondrial support. And there are peptides that do that, there are other, you know, mainstream, if you will, very well-known nutraceuticals such as carnitine, ALA, et cetera, resveratrol, that support mitochondrial function. But all along, remembering that the mitochondrial DNA are so different as you know so well, than nuclear DNA. And they have that capacity to utilize, for example, TA-65 to shuttle back and forth between the nucleus and help improve telomere length and function. But non-canonical aspect of TA-65 or telomerase activator, it does

improve, or it will help mitochondrial DNA heal from damage. And there are other things out there, there's a fascinating article I just saw on intra-mitochondrial melatonin and its impact on mtDNA. And all my patients, I'm getting little off track here because I just thought of that, mitochondrial melatonin has a huge impact on mitochondrial function, mitochondrial biogenesis, and healing of that scarring mtDNA, and that mtDNA has so much more damage on a daily basis than our nuclear DNA. So we have to keep up with that. So it's just another on the list in addition to TA-65 or telomerase activator, to maintain mitochondrial health.

Dr. Joseph M. Raffaele, M.D.
And so you mentioned fisetin, you mentioned quercetin, as far as the peptides are concerned, which peptides, 'cause I'm not as knowledgeable about peptides as you are, which peptides do you have some senolytic activity?

Joseph Cleaver, MD
So one that has a lot of anecdotal evidence and experience is something called FOXO4-DRI. It's a pure senolytic peptide that shuttles P53 to that SASP cell to induce autophagy. So the FOXO04 blocks P53 autophagy. But the brilliant researcher out of Netherlands, can't remember his name right now, this was five, seven years ago or so, came upon this peptide that was engineered to induce apoptosis and it's very specific, only to senescence cells. And the mechanism is through P53. And P53 will induce apoptosis. So in my program, plus minus, I'll explain that to a patient where we are with the the development of peptides such FOXO4-DRI. We talk about and discuss the upsides and downsides of newer peptides and to date has been very, very effective.

And what I see now is, after we start those preventives, senolytics we'll call them, clean up our senescent cells, then we can move with mitochondrial support with other peptides, other nutraceuticals, et cetera, that fuel mitochondrial biogenesis and function, et cetera. The testing that we do now, thanks to you and UCLA, and we really didn't have testing before that is specific to immune senescent burden, that I believe is really the master switch of probably aging of all our other systems. So it's pivotal to, we can now get a senescent cell burden assessment that we couldn't get before. And I think that's the only commercial available lab test out there that does that at a clinical level.

Dr. Joseph M. Raffaele, M.D.
Yeah, you're referring to UCLA clinical immunology or immunophenotyping lab that we send samples to. I've been doing my practice now for about 13 years, and they look at the CD28 negative suppressor cell, so CD28 negative cells, which are in a pretty large body of literature, thought to be sort of senescent, or at least sort of late differentiated cells, that secrete nasty

cytokines and accumulate in large number in people with CMV infection and other stresses to their immune system. That's available through TA Sciences or through PhysioAge, my software company that looks at things, has a software for measuring these kinds of things. There's another company that has a SASP activity marker, Jinfiniti, that I not got much experience with, but I think more are coming down the pike, 'cause I think it will be, it's really, I was like to practice sort of evidence, medicine where you see what the effect is. Like you give a blood pressure medication, you see the blood pressure go down, you give a senolytic, you see the senolytic cell burden go down, as you kinda pointed out.

Our paper showed a reduction, about 20% in senescent T cells after taking TA-65. And that is, starting in three months, and then six months and nine months, so that's a good market to follow. And it's a shorter term one, it's three months, telomeres take a longer time, I think, to get a good idea about which direction they're going in. So those were the two that I'm aware of right now. There are other companies that are working on, Beta-Glucoside, ASA, markers to look to see, whether or not these things are going to be effective. But I think, one of the whole issues is sort of with senolysis as a therapy for aging, is the whole concept that if you're taking out the cells, other cells, stem cells within the tissue niches, that you're looking at, be it muscle, liver, brain, have to divide to replace those cells, their telomeres get shorter.

And then you're going to then get back to a senescent cell burden that may be even a little bit higher. Michael Fossil's written about this in recently, 2019. And so senolytics are great, but you then have to help the telomeres of the cells that need to replace them so that they don't go down that same pathway. And I think that's maybe behind some of the failures that have occurred in some of the earlier studies done by some of these biotechs where they removed a large number of senescent cells, but then later on the mouse died, which is not something you want to see happen. I don't know whether that's behind Unity Biotech's failure with their osteoarthritis drug. But I think that is something that they're going to have to start keeping in mind when they're looking at removing senescent cells. So is FOXO4-DRI an IV peptide, a sub-Q, oral, how do you take that and what kind of?

Joseph Cleaver, MD
Right now it's IV and it's a short course of three infusions. We've tried it sub-Q, but I think it may be the pH, but it's pretty painful. So we don't usually go do it sub-Q, diluted in a D5W and run it in over 30 minutes to an hour. If we extrapolate from the lab studies, lab animal studies and convert it to a human dosing, when I'm using a new, any therapy, I'm very cautious and conservative. So I'll cut that dosing in half. And I haven't had any side effects at all. I know that there are patients, or people have experienced that at too high a dose, they can experience a cell lysis syndrome, if we think about it, if we're destroying all these SASP cells too quickly, too

fast, that's a possibility. And I did have, I gave a talk, you were there actually at a Cell Surgical back in June or May in Vegas.

Dr. Joseph M. Raffaele, M.D.
June.

Joseph Cleaver, MD
Yeah. And I remember one doc raising his hand and he actually self administered, he had it done, and he experienced some similar side effects. So using it cautiously, it has a, I think so far, it looks like it has a significant impact on cleaning up that senescent burden. The studies in animals are pretty fascinating. They genetically engineered mice to age over a short period of time, as you know, pretty typical studies. And took the aged mice and treated them with FOXO4. And within 10 days, their gray fur that was falling out, started to restore. In about two to three weeks, they got on their exercise wheel and started exercising 50% greater time than they did before. And in about a month or so, these are aged mice, so all their systems are starting to decrease in function. Renal function that was diminished to about 50% was restored back to original 100% of renal function as similar the young mice in the study. So this is an animal study, and we're still very early, but it's a fascinating peptide as a pure senolytic, that if your patient understands the product and understands the therapy, and the physician understands the therapy, that's something that's a possibility to trial or have part of senolytic program.

Dr. Joseph M. Raffaele, M.D.
Go ahead.

Joseph Cleaver, MD
No, I was going to say the TA-65 and the rapamycin, you mentioned before, and if we wipe out these cells, our body's just going to come in and replace them faster, potentially, that's a theory. I don't know if it's true or not, I think it may be. So that's where that preventative part comes in, where I set that up first. So that's TA-65, the rapalogs, even fisetin, and there's a long list of things that help maintain healthy stem cells. There's certain other peptides, some of the thymosins can do it. Some of the secretagogues actually improve and maintain cell efficiency and function.

Dr. Joseph M. Raffaele, M.D.
Yes, so speaking of side effects, particularly with the rapalogs, there was recently a study published in IPF, looking at IPF patients, and they gave them senolytics, I think it was , they didn't see too many side effects. But I know that other practitioners like Peter has mentioned it whenever some of his patients take a rapalog, they get aphthous ulcers in their mouth. Have

you seen that with your patients? And I wonder if giving them TA-65 potentially prevents that from occurring.

Joseph Cleaver, MD
It's a good thought. I haven't seen it, I'm pretty conservative with rapamycin. I embraced it. I'm sorry.

Dr. Joseph M. Raffaele, M.D.
What's your dosing on rapamycin when you give it?

Joseph Cleaver, MD
I was just gonna mention the study is in the elderly with the vaccine response. I think they did one and a half milligrams daily, in three dosing schedules. One was five milligrams weekly, and then the last one was 20 milligrams weekly, if I'm not mistaken, I haven't looked at that study in a while. You get some immediate mTOR response with the daily dosing. You get some at the five milligrams. And then there's this 20 milligrams weekly. I don't dose anywhere near that, but that has probably the best benefit, if I recall correctly in the elderly patients, even having a improved immune response to vaccinations, I believe about 12 months out. That it was the higher dose actually. And one of the side effects was aphthous ulcers. So I'm using two to three milligrams about, weekly on my patients. And I haven't seen any side effects at all. I haven't seen aphthous ulcers at all. But he made a good point, I think I know the podcast you were referring to, where when he was in residency, he was injecting bupivacaine into this .

So he's already prone to it. But it makes me think, one of the adjustments I made based on your discovery of the immune burden from hidden viral loads, such as CMV, I think, may be part of the reason why, because I clean up those viral loads now, with the anticipation, somebody has a smoldering EBV, or CMV, HPV. And I learned this when treating these patients in our pandemic that we're struggling with right now to treat. And if we give an antiviral, I had two patients that came back about three or four, four to six months later and said, I've had HPV on my pap smear for four years now, and all of a sudden it's gone. And I was like, well, that made me think, why can't we develop a program, prior even, or build it into a senolytic program, that we'd want to clean up that viral load or that viral burden in our patients as part of a senolytic program, because CMV has such a huge burden on the immune system, shortens telomeres drastically, that it makes sense to me to try and to address that.

Dr. Joseph M. Raffaele, M.D.
Well, so which do you use, Valtrex or a Famvir? I mean, those are antivirals for, most of the herpes viruses are not necessarily effective against CMV, they're usually the more toxic ones like,

again, like Cycloverin that work for CMV and probably, so you're probably not using it. So do you see some benefit from, which are the antivirals that you're using?

Joseph Cleaver, MD
Some of the antivirals that are being used off label in the pandemic?

Dr. Joseph M. Raffaele, M.D.
Which ones I'm just curious.

Joseph Cleaver, MD
For example, Ivermectin is a very potent antiviral.

Dr. Joseph M. Raffaele, M.D.
Okay, okay, if I thought that was the one that you were referring to. Yeah, I mean, interestingly, whether that has effects. Ivermectin has had a colored history recently. I mean, starting out with being fantastic, and there's a biological plausibility for this antiviral in multiple biological mechanisms through which it might work, but then openly, depending on where you stand on this issue, not being necessarily proven to be effective. So it could be that it's helping to reduce viral burden in somebody that has, I measure all the herpes viruses in my patients to see because of a study that showed that the more herpes viruses you have, the faster your telomere attrition. So if you have, one and two, almost everybody has three, almost everybody has four, not everybody has five, but as you get older, you get more of them, a lot of people have six If you have four versus one, you have a much steeper attrition of your telomere length. And it would be great if we had, I mean, I don't know, is there anything published on Ivermectin and herpes viruses?

Joseph Cleaver, MD
I believe there are some publications, if you dig deep enough into the literature, that it has never been really of any interest up until more recently.

Dr. Joseph M. Raffaele, M.D.
Yeah, sure because of the...

Joseph Cleaver, MD
How it came to light. We're not talking about as a therapy in the pandemic, but as an off-label therapy for certain smoldering viral loads in your patients. We've seen patients improve. And there's a combination, there's various protocols, that may or may not use Ivermectin, and we use some homeopathic therapies sometimes, the equivalent of Acyclovir. Rutin is a potent

anti-viral. And we've treated patients for example, with chronic fatigue that have that wastebasket, the diagnosis that is a EBV, a chronic fatigue type patient with surprisingly good results. So it's kind of taken the cover off for me and being able to insert that therapy into a senolytic program. It just make sense to me if we can improve those telomeres, telomere length, certainly even in CMVs, you know better than anyone. But are we addressing that viral load in a longterm, longevity program?

Dr. Joseph M. Raffaele, M.D.
Yeah, you're absolutely right. The virome that people carry is I think very, certainly with regard to the immune system, very important on how rapidly your immune system and your telomere length is attacked. We talk about the microbiome, which is obviously very important, but the virome, I think is actually going to turn out to be almost equally important. And there's probably a whole bunch of other retroviruses, line viruses that we don't yet know enough about, but probably are having a significant impact on our aging trajectory. They're looking for a vaccination for CMV because of of the burden of infant death and deafness, et cetera. And then of course, in transplant patients, in immunocompromised, HIV patients, it would be great to be able to stop that virus in its tracks, but so far, it's eluded any vaccination program. It's a pandemic, it's just not as fast a pandemic as the one that has hit us recently. Which is kinda interesting. Slow moving pandemic. So and are there any other peptides that you work with that impact senolysis or, I know people have talked about Epitalon, being a telomerase activator and a telomere lengthener. I mean, I saw the data on that was from older Russian studies that I was surprised, when I remember looking at them, that the telomeric measurement technique was probably not great. But I've heard Ed Lee talk about using it, and some other people talk about using it, have you had any experience with that?

Joseph Cleaver, MD
You know, that comes up a lot. I certainly speak and lecture a lot on peptides and inevitably telomere length, longevity, creep into the discussion. And if we're talking about peptides, you'll always got a question on Epitalon. And what I referenced is a study from the Buck Institute, out in Marin County, was done about eight years ago, and they were looking at the telomere length and how quickly telomeres can lengthen, what is the mechanism or what is the therapy, if you will, that is used to lengthen telomeres. And then they went back and looked at the, they said, okay, we can lengthen telomeres in this rat to make them the equivalent of an old rat, to a 12 year old human equivalent of telomere length. But they went and looked at the fragility of those telomeres and realized that they may do be doing more harm than good, because you can grow telomeres, and the length is not necessarily, well, it's not the most important thing, it's the quality and the structure and the function of those telomeres that are, I think, the underlying most important aspect of telomere length. So their conclusion was if you lengthen

telomeres artificially in a short period of time, the quality of those telomeres can be impacted significantly and may cause more downside than upside. So when I create a program and we do TA-65, for example, it lengthens telomeres, but it's a natural telomere, it's a substance that improves telomere length and quality of length and function of telomeres. And it's done in conjunction with lifestyle, over a period of time. And if you look at a list of things that lengthens telomeres, you say, well, what's the difference? Arsenic can lengthen telomeres. So we have to be very careful of, and use a therapy, and something I'd say is use T-65 that has been studied quite extensively in lengthening telomeres in a healthy manner.

Dr. Joseph M. Raffaele, M.D.
I had Tom Dowel on recently, he's a that did the TA-65 study on macular degeneration. And I want to just ask you, because there's very plausible mechanisms for why it worked to improve the macular function through removing senescent cells and lengthening telomeres. But do you, I mean, you do a whole program, but do you see any benefit in eyes? I'm always curious to talk to doctors that prescribe a lot of TA-65, whether or not they see improvements in distance vision or presbyopia. He said that they did pick up a signal with presbyopia, but not so much with distance, anything from your patients anecdotally?

Joseph Cleaver, MD
Well, I can tell you as a, my experience, in a handful of patients that have been on TA-65 for a long period of time. Short term, no, I haven't, I haven't seen anything significant such as that, but after a certain age, when our vision starts to, it starts to accelerate in terms of our visual changes, and our visual acuity, seems to maintain that visual acuity. And I wear contacts, but I have not changed a power in my strength of my contacts in about eight years. And, you know, and I'm in the age group that usually this is annually, you keep changing the power and the strength of your corrective lenses.

Dr. Joseph M. Raffaele, M.D.
Yeah, I've noticed that myself.

Joseph Cleaver, MD
I can attest to that.

Dr. Joseph M. Raffaele, M.D.
Yeah, I mean, I've had patients say stuff like that. I've also had some actually documented cases of reversal of presbyopia, not to complete no glasses, but to significantly lower diopters. Well, this has been great. I wonder if there's anything, any closing thoughts, that you have about senolysis, your approach, and to tell our listeners any pearls to take away with them?

Joseph Cleaver, MD
You know, I think we hit on a lot of the pearls already. And just the more recent ones that brought to light, the viral issues and the focus on TA-65, it's a cornerstone, it's a workhorse, long-term. And I knew it, I know you knew it, but until that study came out, and you published it, that was something that you had to really assume that it had to be a hypothesis that I was always waiting to be, or to see the proof. And now we have that proof and it makes so much sense, chronologically timelined, the way telomerase, or telomere function works. It makes total sense to me. And if we're going to fare better in any, especially any infectious disease, if we have optimized, look, telomere length to me is a surrogate marker.

Certainly they have a inherent function, but I know it's an inherent, it's a marker of stem cell health, it's a marker of mitochondrial health and function. And they're certainly going to fare better, especially when we start looking at the impact of, for example, this pandemic, and how it destroys mitochondria in such a short period of time. So if you already have deficient mitochondria and mitochondrial dysfunction, the telomerase dysfunction leads to PGC-1alpha dysfunction, leads to decrease in mitochondrial function, et cetera, et cetera. And along with P53, I mean, there's a triad that few people address. There was a study back in 2011 looking at telomere function, that I just mentioned. So if we optimize our telomere function, we're optimizing our defenses immunologically and in every system in the body.

Dr. Joseph M. Raffaele, M.D.
Yeah, that study by Hagan, at Adam's lab, has been great to put the telomere health together with mitochondrial dysfunction, through the master regulators of biogenesis, BCG one alpha and beta, that's great, that helped me get things together too. Well, I also would say that have a little bit envious of you, because you talk about lifestyle medicine and you walk the walk and talk the talk. You have a great place out there in, is it Sonoma where Locanda is, where you enjoy wine, make wine, teach doctors about how to do aesthetic medicine and anti-aging medicine. And then also just really enjoy life the way you learn how the Europeans and the Italians do, some day I'd like to get out there and check you out.

Joseph Cleaver, MD
Well, the guest house is always open for you, Joe.

Dr. Joseph M. Raffaele, M.D.
All right, thanks, Joe. It's been a pleasure talking to you.

Joseph Cleaver, MD
You too, good seeing you, thank you so much for having me.

Dr. Joseph M. Raffaele, M.D.
All right, take care.