Sayief (00:00:03):

Okay. And it will take about 10 to 15 seconds for the attendees to load in.

Zan Fleming (00:00:09):

Alright. Now they will be able to chat with us? We won't see them, they won't be admitted to the discussion, but they will otherwise engage with us and Michael will

Michael Zemel (00:00:30):

Chat. You mean the chat transcript or side box?

Zan Fleming (00:00:34):

Yeah, that's right, the Zoom feature. Michael is going to be the master of questions and we've got a few good ones from registrants. Sure. There'll be others a little handful. Yeah. We won't be able to cover all of them. We try to answer questions that we do receive after the conference and we post them. And so we might go back to the panelists for help on that. We will be also posting the recording and you'll be the first to see it. So we're four minutes away from showtime, and Sayief, how many people do you have in the house right now? Nine people have arrived early. Okay. Well typically more people arrive after the start time, but for those who are already listening in, just

Michael Zemel (00:01:56):

There is a correlation when you finish speaking, there'll be more people.

Zan Fleming (00:02:01):

Right. So those who are joining us, we're just having our final moments in the warmup room. You're most welcome to send us messages in the chat both now and throughout the session.

Michael Zemel (00:02:33):

And were we able to get Ralph his credentials to join the webinar?

Zan Fleming (00:02:42):

Emma, could you let Kristi know to do that? Thank you. Well, James is right now in California though he looks like he's back home in Oxford and Josh is down in Miami. I presume. You're down home, and Chris is over in Lausanne.

Chris Rinsch (00:03:26):

Yes, indeed.

Zan Fleming (00:03:28):

In Switzerland. My favorite places. Roger Shi is in San Antonio. Los Angeles. Los Angeles. Oh, okay. So you're out of town today.

Roger Shi (00:03:43):

That's right.

Zan Fleming (00:03:46):

And Michael Zemel, our CSO, is down in Nashville, Tennessee.

Michael Zemel (00:03:54):

Indeed. The music city. Music city. It is the music city but none of the music comes out of me.

Zan Fleming (00:04:06):

Oh, the things that go on in Nashville. It's actually where I was born. I was born at Vanderbilt Hospital. Don't hold that against the university, but I do go back a way to Vanderbilt And we're a minute from showtime and we are at the top of the hour. Let's begin and welcome everybody around the world. We are at the top of the hour and so I welcome you our global audience to another session 2025 edition of Targeting Healthy Longevity, a conference that's been going since 2017. We've got a fascinating program for you today and we'll be discussing some of the most promising approaches for increasing health span. But I first want to welcome Kinexum CSO, Dr. Michael Zemel, who was preeminent in translating promising data into products. Michael is standing in for our usual co-host, Thomas Seoh, who is off in Hong Kong presenting at a neuroscience conference, and actually Thomas is still with us, but we thought we would make sure that we had somebody a little closer to comm moderate this session. So Thomas, great to have you joining on very late from Hong Kong. Michael, over to you for a few housekeeping announcements.

Michael Zemel (00:05:57):

Thanks Zan. So first major housekeeping reminder is to please enter your questions into the Zoom webinar Q and A as our panelists are presenting and then we will utilize them during the round table. A link to the recording will be circulated to everyone here, all registrants and actually made publicly available within the next business day or two. Also, we have the chat function enabled for audience interaction. Be great if those of you who are willing would just say hi in the chat, state your affiliation and perhaps where you're logged in from just to get the chat moving. And finally, thanks for those of you who have submitted questions. We've received several excellent questions to those. We will add those that we receive in real time using the Q and A function. So again, please do use that function and the panelists will try to get to as many as there's time for. At this point I'm going to throw the mic back to our moderator, Alexander or Zan Fleming, the founder and executive chairman of Kinexum. Kinexum's a regulatory, clinical and product development strategic advisory firm. Zan also serves as president and founder of the not-for-profit Kitalys Institute, whose mission is to catalyze science into solutions for preventing chronic diseases and extending healthy longevity for all. Back to you, Zan.

Zan Fleming (00:07:32):

Well thank you very much Michael. I want to start by explaining the reference to the THRIVE Act, and we won't get into details about the THRIVE Act today, but you can find them on the Kitalys website for sure. This act is intended to catalyze the development and availability of products that increase health span, but perhaps the most audacious feature of the act is that it applies to all categories of FDA regulated products, drugs and biologics of course, but also medical devices and even dietary supplements. And that is because all solutions for targeting healthy longevity should be encouraged and supported by strong scientific evidence. In other words, we are looking for products or for labels like this, for drug, for a biologic product, for a supplement and even a medical device. So that brings us to who I will call the THRIVE four. Each of our distinguished panelists represents one of these categories, and note that the companies that they lead span the spectrum from being preclinical to being marketed though without

health span claims. So note a timing bias. Each of these companies are targeting deep roots of aging biology in various ways they target the mitochondria, and so I think it's very interesting that we have these major differences, but this commonality is very intriguing. So without further ado, I'm going to introduce our first panelist who is being summoned to NIH for a important meeting and we're therefore going to put him first. Dr. Josh Hare who is a preeminent cardiologist and a medical scientist who is founder and executive chairman of Longeveron Company based in Miami. So Josh, go right ahead, and you can now share your slides if you see them, and you can go to presentation mode, and there we go.

Josh Hare (00:10:41):

Terrific. Can everybody see the slides and hear me? Wonderful. Well it's such a pleasure to be here with you all. Zan, thank you so much for including me on this very exciting panel. What I'd like to talk about today is the use of cell-based therapy for health span extension and I'll be addressing specifically two conditions, one known as aging frailty and the other Alzheimer's disease. These are clear cut diseases of aging and play a major impact on limiting health span. The work I'm going to talk about has been conducted at the company that I co-founded called Longeveron. You see my disclosure, they're below and these assets are actually at phase two getting ready for pivotal trials. So we're very excited about the possibility of bringing these products to market in the next five years. Here's a mandatory forward looking statement because Longeveron's publicly traded, and let me just jump right into it. So laromestrocel also known as Lomecel-B is the product by Longeveron.

(00:11:54):

The technology for this product was licensed from the University of Miami. It's a proprietary formulation of bone marrow derived mesenchymal stem cells. This product is designed to address one of the key hallmarks of aging, which is the loss of stem cell reservoirs and potency with aging. Laromestrocel is also capable of modulating inflammaging and mitochondrial deficiency, two other key hallmarks of aging. Collectively, laromestrocel can address pathobiology characterized by fibrosis, inflammation, vascular dysfunction and loss of healthy cells, in the aging scenario lost due to senescence. This is how laromestrocel is developed. Won't go into detail here in the interest of time, but it is isolated from young healthy donors and culture expanded in a specialized laboratory that is housed in Miami, Florida called the GMP Laboratory, and laromestrocel can be administered to patients intravenously with a 40 minute IV infusion that has been shown in hundreds of patients to be very safe.

(00:13:09):

Now laromestrocel, how does laromestrocel work? Well, although it's called a stem cell, it doesn't actually engraft in the body and form new tissue. Rather, laromestrocel is a very powerful factory that's capable of producing growth factors and cytokines that can immunomodulate. It can actually form cell cell interactions with host tissues. Perhaps one of the most important and increasingly recognized activities is the release of exosomes, which are microvesicles containing a rich abundance of microRNAs and other proteins that can traffic throughout the bloodstream and reach distant targets, thereby explaining why laromestrocel can be infused intravenously and can reach distant targets such as the brain. One of the very exciting features of this product is that it can also form what are known as nanotube bridges that are large enough to allow the transfer of mitochondria from the Lomecel-B to aged recipient senescent cells, meaning that the use of this product can also lead into a rejuvenation of mitochondrial dysfunction in a host. Collectively, these mechanisms of action, as I mentioned before, have a pro-vascular, pro endothelial-effect, an anti-inflammatory effect, an antifibrotic effect, and can stimulate intrinsic regenerative repair. These four mechanisms have been shown widely in multiple clinical trials and preclinical models throughout the world, again, in multiple laboratories.

(00:14:49):

We became very interested about 10 years ago in examining whether infusions of these cells could improve the condition known as aging frailty. To me, aging frailty is the prototypic clinical scenario that describes what poor health span is. I think we all know that poor health span is the divergence between lifespan and quality of life, such that the last in the United States decade plus of life is characterized by poor health and poor physical capacity. This is clinically described as frailty, whereby individuals get a disproportionate loss of physical functioning and other parameters. And this can be nicely measured with the six minute walk test. A normal six minute walk test is about 500 meters in healthy adults, and we enrolled subjects in the study who had frailty and had an average walk distance of about 300 meters, so a substantially impaired six minute walk test. We infused in these patients here, as you can see, five different doses, the lowest being placebo, so in inert material and then an increasing dose of laromestrocel.

(00:16:09):

And what you see is a time dependent increase in six minute walk distance that's time dependent and also dose dependent. This is very important because it speaks to the biological activity, the compound, the cell compound, and you could see that the clinically meaningfulness can be assessed by looking at the day 270, the nine month change in six minute walk test between 200 million cells and placebo is 63.4 meters. It's highly statistically significant, and a 63.4 meter increase in your ability to walk over nine months is very medically meaningful for an older individual with a poor health span. We went further in the study to show that the dose response was statistically significant in the left panel and moreover, the increase in a six minute walk test correlated with a patient's self-reported outcome called the Promise PF so that as patients could walk more, they also perceived feeling better.

(00:17:20):

As a result of that study, which was very, very exciting to us, we decided to tackle another disease of aging, which is Alzheimer's disease. Alzheimer's disease is a devastating neurocognitive disorder affecting 6.2 million Americans. expected to double by 2060, and you can see one of the hallmarks of Alzheimer's disease is substantial atrophy of the brain. You see in the right, the healthy brain slice compared with the marked atrophy that an Alzheimer's disease subject confronts. And one of the key areas that is markedly atrophied is a structure at the base of the brain known as the hippocampus, which is the structure that's responsible for new memory formation and for emotional regulation. In this study, which was just published in Nature Medicine in April of this year, we were very excited to see a very good safety profile as well as a statistically significant improvement in the pre-specified secondary endpoint, which was a CADs score, which is a composite of these four measures you see here on the right, the CDR-SB, the AD CADL, the ADAS-Cog and the left hippocampal volume.

(00:18:44):

Again, similar to what you see in the aging frailty, you see a time-dependent effect. There's a decline in the placebo group shown here in the black line and an offset in the subjects that received the laromestrocel. If we drill down deeper and looked at specific measures of cognitive function, you see that it's a very nice effect. In fact, the statistical significance is greater in the individual metric of cognitive function. This is the MoCA total score. It's a measure of cognitive function. You see in the placebo group over the 39 weeks, a tendency to be level or decline and you see the very nice offset by all three doses of laromestrocel. I should also mention that some of the groups here got multiple doses versus a single dose, so there's a dose dependence as well as a cumulative effect of giving a multiple doses.

(00:19:41):

We also see a similar tendency in the change in the Mini-Mental score. Now what about the biological underpinning of this? Well, I already mentioned atrophy and hippocampal atrophy. Fortunately we can measure this with great precision in humans using MRI. Here you see an MRI from one of the subjects in one of our studies, and you could see, you could delineate the hippocampus and all of its sub regions actually, and you can quantify their size. So we built this into the study. Remember I had mentioned that one of the things that laromestrocel does is renew tissue, rejuvenates tissue, and we were intrigued to ask the question, is the clinical effect derived from an association with a preservation of the hippocampus or other structures of the brain? And lo and behold,, it is. So we did what's called volumetric MRI where we overlay the MRIs over time from an individual subject as shown here in panel A.

(00:20:42):

This is published by the way if you want to get greater detail. And what you could see is that there's rather substantial atrophy in the placebo subjects as shown in the right panel. This is how it's measured in the left panel and you can see the offset created by the administration of the laromestrocel and there is a dose response here. The more we gave. the greater the effect to reduce the amount of atrophy, and you can see here at the highest dose at 16 weeks, it's actually prevented any decline in whole brain volume compared to the placebo group. So that early time point is very important and speaks to perhaps the continued needing to dose. Now what's the mechanism of action? Well, I gave you the general mechanisms of action, but we're trying to delve deeper and find a specific molecular mechanism of action and we believe we've uncovered a specific signaling pathway known as the TIE2 pathway.

(00:21:48):

TIE2 is, as you could see in this study, going back to the aging frailty, TIE2 tends to increase over time in placebo patients. This occurred both with aging frailty and with Alzheimer's disease and lamestrocel prevents or actually reverses the increased appearance of TIE2 in the circulation. Why is this important? Soluble TIE2 is the receptor that sits on endothelium that has a downstream regulation of both inflammatory responses and angiogenesis. When that receptor is cleaved, it released into the circulation and you can measure that cleavage by showing the increased appearance of TIE2 in the circulation. As we see in a placebo patients, we believe that lamestrocel is reducing the cleavage of tie two, thereby showing a decline in the soluble proportion suggesting a preservation of the tie two receptor on cells and tissues and enabling healthy downstream signaling that exerts an anti-inflammatory response and a vascular response. I'm thrilled to be here with you today. I look forward to the discussion. I must end by thanking my team at the University of Miami Longeveron and all of the numerous awards we've received from the federal government that has supported this work over time. Grants to both the University of Miami as well as Longeveron that has funded these studies. Again, thank you and I look forward to the rest of the program.

Zan Fleming (00:23:32):

Well Josh, thank you. These are just absolutely spectacular results and they should be wider known, very promising, and as you say, you're targeting now to the hallmark of aging. You've

Josh Hare (00:23:53):

Already, I'm going to jump off for 10 minutes and I'll be back to join you in just a few minutes.

Zan Fleming (00:23:58):

Alright, well do come back as soon as you can. You bet. Alright, well let us now go on to Dr. James Carroll, a scientist himself and no stranger to this conference. He is CEO of THOR Photomedicine, and he's going to provide a overview of how photobiomodulation could increase healthy longevity. So James, over to you.

James Carroll (00:24:32):

See my slide? Can you see my slides? Oh, people are nodding, right? I was expecting a verbal anyway. First of all, I should say that thanks for introducing me as Dr. James Carroll. I haven't even started my PhD yet., though I am actually writing a letter now for when to start that. So I will introduce my credentials also at the top of the present, not the presentation, but your introduction about 15 minutes ago. As then there was something, a future-looking thing that somebody wrote. It wasn't written by me and included an ambition to maybe prevent cancer or something, which is not something, none of the things, none of that was written by me, and they're not formally any ambitions of ours. But let me introduce what we are doing and where we think we're going. A disclaimer. So in the United States, our products are permitted to claim temporary increase on local blood circulation, temporary relief for minor muscle pain, joint pain, aches and stiffness, relaxation of muscles and muscle spams, minor pain and stiffness associated with arthritis.

(00:25:41):

Any other condition mentioned in this presentation is not cleared or approved by FDA for all products in the United States. FDA is not approved or cleared photobiomodulation as such, at least not by that name in the United States and the other countries where you've got approvals for treatment of tendinopathies, chronic joint pain, back pain and oral mucositis. What is photobiomodulation? It's something, and you all look old enough to have seen this show TV, Star Trek, and then somebody gets injured, get taken to the doctor who gets out a laser aims the laser of the injury, and the injury heals instantly. So we make those. Any questions?

(00:26:19):

So it's not as fast as on TV. We get the idea, we shine light on people, and they heal more quickly. By the way, instant healing is not an FDA-cleared indication for use for us. So in the field, not just thought, but there's over 1700 randomized placebo controlled clinical trials published in this over thousands of laboratory studies, over 11,000 academic papers in total published 174 papers have got my name on it and/or THOR's products in it. We calculate that our products have delivered more than 37 million treatments to date, yet most doctors have never heard of it. It has a wide range of applications. How can one medicine treat so many different conditions? You should never believe anything that appears to do everything. It doesn't do everything. It does one thing, it does it very well, and it is very good at regulating the production of reactive oxygen species which this audience will overcome mostly from mitochondria.

(00:27:18):

So when we're sick, stressed, injured or just old, our cells tend to be low in energy, ATP, tend to be high in the production of reactive oxygen species, and you all know that too many reactive species for too long, overwhelmed the body's natural antioxidant mechanisms leading to augmentative stress, leading to the inflammatory cytokines leading to inflammation and cell death and the like. When we put light into patients, it's absorbed in mitochondria, and it changes the balance from production of more energy ATP and fewer reactive oxygen species, reducing oxidative stress and having a lot of interesting effects on NRF2 pathways and regulatory T cells and production of stem cells and growth factors. But we

haven't got time to do with that and I haven't got time to take you through the full map, but it leads to faster repair of tissue, less edema, less inflammation, and less pain.

(00:28:11):

There's a dose response. If we don't put enough light in, we don't have any effect. If we have too much light in, we can have accidentally two inhibitory effects, and it's not as simple as just too much or too little. That could be either too much intensity or it could be too much time, but it's more to do with the balance of irradiance and time. So IRradiance is the physics word for intensity of light. So very low intensity for as long as you like could produce no effect at all if it's too low. But if too much intensity for a short period, you might get a bump in some positive effects, but you can actually end up slowing things down by accident if you're not careful. The holy grail is to find this curve here. This is where my area of expertise is in how much light is enough and how much is too much to get the optimal effects.

(00:28:59):

Just to give you some medical applications before we talk about health and longevity, oral mucositis a horrible side effect of high dose chemotherapy or radiotherapy. In severe cases people can't eat, drink or swallow, not even swallow their own spit, and you can't imagine it. We've been in multiple studies. Here's one at the largest treatment center in the UK, the Christie, treating base of tongue cancer or tonsil cancer patients preventatively. We apply this before people have any symptoms, and here it's showing a 63% reduction in the use of morphine and an 88.7% of patients who need to be hospitalized because they can't eat, drink or swallow because the side effects are so severe. That's about 30% of head and neck cancer patients have to be hospitalized for those reasons. We reduce that by 88.7%. This was a tiny NHS study. This has been repeated in other hospitals now in much larger studies, but only the Christie did the hospitalization measurements, but nothing else does that.

(00:30:04):

And that's the point I want to make over the next few slides. Fibromyalgia, nothing works for fibromyalgia. We did a randomized trial in 42 patients with placebo control. Patient just lie in this thing for 20 minutes three times a week and this study for four weeks, we have this reduction in pain. So these are baseline figures coming into the study. Two weeks of treatment, four weeks of treatment, two week follow-up with no treatment, six month follow-up and you see the benefits are maintained. That's for pain. Kinesiaphobia is fear of movement and you can see that continues to come down over even in the follow-up period. Self-efficacy is going up, quality of life is going up, and leisure activity is going up. But these are all very positive effects for people. About 30% of these patients are unemployed or cannot rather, they cannot maintain a job.

(00:31:00):

So severe is fibromyalgia and I'm hoping you've all heard of it, and nothing else does that. Age-related macular degeneration is another company I co-founded LumiThera. It's the leading cause of blindness in the developed world. There's two kinds. There's the wet form and the dry form, which is 90% of patients dry form is considered untreatable. The wet form, you can have injections in your eye to slow progression. If you don't have AMD, you can see four kids in my kitchen. If you develop AMD, you begin to lose central vision. You have distortions in your vision, you begin to lose contrast sensitivity. You develop these blind spots called geographic atrophy, which gradually get worse until you can't read, you can't drive, you lose your driving license and you can't enjoy TV. So it reduces or inhibits greatly independent living. So it's a great cost to social services.

(00:31:52):

We developed a device like this for ophthalmologists and we did a 10-center style across the United States here. This is a placebo group. I was surprised by how big the placebo response was. I say it was placebo. Actually, it was just a very low dose and maybe a very low dose contributed to this effect. But the active treatment group here, this is over 24 weeks, three times a week for three weeks. The three bursts of that in a year, another three bursts in the second year here. And it's obvious what's going on here. We have an average a mean score of 5.9 letters. If you're familiar with the Snellen chart here, there's five letters per line. To have 5.9 letters as an average is basically whole line more than one whole line further down the chart for a disease that only ever gets worse. So we had 5.4 letter gain at 12 months.

(00:32:51):

At two years, 5.9 58.2% of patients actually had an 8.5 letter gain. 18% had a 13 letter gain and 5% of patients actually had a 16. That's three lines of improvement for a disease that only ever gets worse and nothing else comes close to doing this. This is all done with photobiomodulation that had got its marketing authorization in November last year, and the company was purchased for a very large amount of money a few weeks ago from Alcon, which is the world's largest ophthalmology drug and device distribution company. Anyway, back to this topic today was about health and longevity. Photobiomodulation has been clinically proven to enhance exercise performance. It's like one of the strongest proven beneficial effects for improving health span is exercise. Some kinds of exercise like its own two exercise and lifting weights. But it's in both cases, PBM has been shown to help.

(00:33:55):

I'm going to show you some data. Improve sleep quality, I'm going to show you data on that. It reduces nocturnal hypertension, not showing you that today. Reduce oxidated damage is one of the fundamentals of photobiomodulation. Improves heart rate variability you're about to see that reduces resting heart rate and improves the VO2 max. Again, associated with all of these are associated with the reduced risk of all-cause mortality. So, in one study, all of these were covered. Sleep, resting, heart rate and heart rate variability. Recovery is critical for professional athletes, military forces who want to train hard. In a study on 12 elite female soccer players using the Oura ring, I know or has its imperfections in terms of you wouldn't use it in a hospital for a judging people's heart rate or heart rate variability, but it is reliable for individual uses. So you can see the changes.

(00:34:52):

The changes are reliable even if it's not a hospital-level metric. These players are only going to use the NovoTHOR a maximum of twice a month over a whole season. Most of the time they're just collecting baseline data. How do these patients wake up? What are their heart rate and their heart rate variability? What is their sleep like? A lot of baseline data. And then they use a NovoTHOR occasionally, like twice a month. So they went and they had like a two week washout period and you can see what happens when they wake up the morning after the night before they had a NovoTHOR treatment. NovoTHOR is a whole body treatment system. I forgot to introduce that. And this is what we see. The Y-axis here is showing total sleep time and the blue lines, the baseline data. This is the treatment the morning after treatments, and what you see is a reduction in sleep.

(00:35:44):

Now most people think, well that's a bad thing, surely we should be sleeping more. However, there is the bottom line here is the heart rate, resting heart rate, and you can see the resting heart rate has dropped. This is a sign of recovery in a professional hardworking athlete. This is a very interesting sign of what the army called readiness over here heart rate variability gain their sleep. This is the night after using the morning after the night before when they had NovoTHOR treatments. So one treatment shifts

heart rate variability to the right as well. So it is a very interesting one-shot only two weeks wash out before you try it again and then do it again consistently showing that you sleep better and have a better resting heart rate. And VO2 max after PBM. And this is a study on using photobiomodulation just on the front and the backs of the legs here, doing lots of individual points.

(00:36:48):

This is before we had the NovoTHOR and the changes in VO2 max. Another good indicator for all -ause mortality here is increasing here and speaking to elite forces as we do because the Army, Navy, and Air Force are big customers of ours, we get this significant improvement in VO2 max, which they tell us is very hard to move without a lot of training to get this improvement. And yet photo-biomodulation does this after a single shot. I saw mention of stem cells, I thought I'd show that when you put light into bone marrow, these are the baseline figures of healthy volunteers. This is 24 hours later, a mean score of 378% increase in the number of circulating stem cells 24 hours later. And in a randomized trial on acute myocardial infarction patients treated within hours of their first heart attack here and then they get multiple treatments over the first few days and then they're doing blood tests. And what you see here is a reduction in creatine kinase, non-significant, reached 0.08 as a P value, but troponin T was significantly reduced in this study just by putting photobiomodulation into the bone marrow treating the tibia. And that's all folks. Whoa.

Zan Fleming (00:38:11):

Well James, again, very impressive data and also under-recognized community what PBM has the potential for. So it's very exciting and we thank you for your wonderful presentation including Star Trek, one of my favorites.

James Carroll (00:38:34):

There you go.

Zan Fleming (00:38:35):

We'll come back to you in a moment, but let's go on to Dr. Chris Rinsch who is and was on Switzerland, beautiful part of the world and is founder and CEO of Amazentis. Chris himself is a highfalutin scientist and will have a lot to talk about from a scientific standpoint. So Chris, thank you for joining us later in the day.

Chris Rinsch (00:39:08):

Thank you very much.

Zan Fleming (00:39:10):

Go right ahead.

Chris Rinsch (00:39:11):

Okay. Let's see.

(00:39:28):

Okay, great. Thank you Zan for having me. Yes. So today I'm going to be speaking about nutritional interventions and how we can impact our health span. And we've been working here at timeline now for, gosh, it's been over 15 years doing the research that I'll be showing today and just a few minutes. So

really exciting stuff when we start talking about health-span. I love sharing this slide here because it shows basically what's happening with our muscles as we get older and our muscles are peaking their function as we get into our thirties and they're declining. And then some of us remain very active until we get old, but then others start to have problems in muscle degeneration. And this is a good arc that shows what our health span is all about. What we want to do is maintain our health at its peak, which I would qualify as the green line here in this figure.

(00:40:45):

And the nice thing with muscle function is it's a great proxy for overall health as we get older. So we're really focused here at timeline on the impact of mitochondria in terms of improving overall functionality of our body. And if we think about mitochondria as one of the key elements of aging, basically what happens, the mitochondria as you were hearing in the previous presentation is all about being the energy source of our cell. It's basically the power plant or battery inside of all of our cell, keeping our cells functioning healthy. And as we get older what happens is that the mitochondria stops functioning as we'd like it to function. And consequently what happens is that the cells, our cells stop functioning in an optimal way and this gradually becomes apparent to us as the organs stop functioning as they should and they're not functioning at an optimal way.

(00:41:56):

And then we start feeling our age and we feel the decline in muscle function. And there's all kinds of other age related declines in biological function that are linked to a decline in mitochondrial function. So today I'm going to be speaking about a nutrient called urolithin A that we've been working on now for about 15 plus years. What is urolithin A? It's a naturally occurring postbiotic that's produced by the gut microbiome. So inside of pomegranates and walnuts and different types of nuts and berries, you have this class of compounds that are called ellagitannins. And when a person consumes one of these foods, the ellagitannins are transformed by the gut microbiota into a compound called urolithin A And this transformation is something that is not a universally transformation in everybody because only about a third of the population has the right gut microflora to make this transformation.

(00:43:09):

And it can be either a high level of transformation or a low level of transformation or somewhere in between or not at all, which makes it very unlikely in general for somebody just consuming a pomegranate or pomegranate juice to actually get exposure to adequate levels of the compound or nutrient urolithin A. And what we discovered was that v is more than just a byproduct of the pomegranate in other foods, but it actually acts at the level of the cell and it stimulates and improved mitochondria health. And it does this by stimulating a recycling of the damaged mitochondria. And this recycling is called mitophagy. And so this is a little cartoon that shows you sort of a mitochondria lifecycle and as your mitochondria are functioning in your cell and they're producing energy, they do get damaged by reactive oxygen species. And what happens is the cell naturally pulls these damaged mitochondria into a pathway that's called mitophagy, which is this recycling process whereby the mitochondria are engulfed, they're digested, and then healthy mitochondria are then replacing the damaged ones.

(00:44:39):

And this is how our body and all of the cells that our body with the exception of our red blood cells, basically maintains a healthy cell with optimal bioenergetics. So we've tested urolithin A for its effects on mitochondria function. And I'll be showing you a few of these slides here. But I think one of the interesting things when we talk about health healthspan is thinking about these model organisms called C. elgans, and they're little worms, and they're a great tool to assess the effect on healthspan and

particularly on lifespan. So we see here when we feed worms, it improves their lifespan by about 45%. And the only intervention that is not a genetic intervention that improves the lifespan of these worms greater is through caloric restriction. Caloric restriction is also another means of stimulating this whole autophagy mitophagy pathway inside of an organism.

(00:45:57):

So one of our first publications was in nature medicine now a while ago and this publication we detail how urolithin A is able to impact the mitochondria function and cell function. And we see that on the left here on the slide you can see ellagic acid, which is one of the precursors during the digestive process of the ellagitannins prior to being converted by the gut microflora into urolithin A. And so we can see how that really unlocks the ability to stimulate and enhance lifespan. But I think what's more interesting is when we go into rodents and we take a look at the effect on actual muscle function and what we can see here is when we're administering for a long-term to rodents, we can see an improvement in both the muscle strength and running distance and endurance in the rodents. And that was something that really struck us as very interesting and encouraged us to develop urolithin A further for human use.

(00:47:11):

And so this slide, there's a lot of information on it, but I'll walk you through it. It's essentially three separate double-blind placebo controlled randomized studies in which we evaluate urolithin A in healthy adults. And on the left we have our very first study that was published in Nature Metabolism. And in this study here we administered either placebo and then we also administered an increasing doses of urolithin A, 500 milligrams and one gram. And then we followed people over a 28 day period and we looked at the impact on cells and the tissue of the muscle and the legs before and after this 28 day period. What we see and what you can see here on these columns is each column is an individual, and each line is a different mitochondria related gene. What we can see is that as we increase the dose, there is an upregulation of mitochondria-related genes in the muscle tissue of these individuals after only a four week period of time, which was very exciting and caused us to advance and initiate the second and third trial here and other trials that I won't be presenting here today.

(00:48:40):

But, and in the second trial we administered for a period of four months and what we saw was that we were able to improve leg muscle strength by over 10% during a period of four months just by administering 500 milligrams of urolithin A, which is what we call Mitopure. And that was very exciting. And then we took a larger, and that population was a population of 40 to 65 overweight sedentary individuals. And then, in trial three, this is basically an average age of around 70-ish. And what we did is we followed these people, and what you see here is after a period of two months, a dose of one gram of Mitopure improved the muscle endurance in these individuals, and we showed an improvement in muscle endurance in the hand muscle and the first interosseous as well as in the leg muscle. So over the years we've been doing a lot of science here and so we're a very science-focused nutrition company which really distinguishes us from many other companies acting in the whole nutrition and dietary supplement space. And we've published a number of articles whether it's Nature Medicine, Translational Medicine and Metabolism, all the way to some more recent publications that we expect to come out very, very soon.

(00:50:24):

And what's even more exciting is these publications have inspired other scientists to explore and understand further benefits of urolithin A and different models of cellular health and physiological parameters. So all of this work is destined to go into actual commercial products. And so it's not only looking at mice and humans, but it's also developing products. And so we've gone through a very robust

process to take our ingredient, which we call Mitopure and bring it through the FDA approval process to show that it's very safe and then develop it into products. And so we've developed into different types of nutritional products. We have gummies, we have soft gels, we have powders, and we've also, we've been focusing here on more nutritional aspects in this short presentation but also another organ. Our largest organ of our body, which we hold dear to our heart is our skin.

(00:51:41):

And the skin is bombarded by all kinds of insults, daily UV light and other types of insults that we might encounter like pollution. And this also has an impact on the overall functioning of the skin and the aging of the skin. And so we've also developed products that are for topical application as well and with the aim of creating a holistic approach to healthspan and longevity that includes both oral nutrition products and topical products. And on my last slide here, I just show you some pictures of our nutritional products on the left as well as the new line of skincare products that we've recently introduced in a new and been rebranded just this last month. So thank you very much for your attention.

Zan Fleming (00:52:50):

Well Chris, thank you. You truly are a unicorn in the dietary supplement space. You are developing clinical data on a regular basis and publishing them, and that really is unusual, and the data are quite impressive. It's just really remarkable. And so we will want to come back to you to talk about your long-term goals for developing your platform. Again, thank you so much.

Chris Rinsch (00:53:23):

Of course. Delighted.

Zan Fleming (00:53:26):

Good. Well questions to follow, but let's now go to Dr. Roger, Shi who is a professor of pharmacology, the University of Texas at San Antonio. Roger has a remarkable history in therapeutic development. He was at Lilly before going down to San Antonio and involved with some very important products there. And he has what I believe is maybe the most promising approach that is not yet in the clinic, but I think soon will be. And so as a means of representing up and coming products, we wanted to bring Roger on to show again another way the mitochondria. So Roger, delighted to have you and we give you the floor.

Roger Shi (00:54:28):

Alright, can you see my screen? See our screen?

(00:54:30):

I do, yeah. All right. First of all, it is really my honor to present our work. I want to thank Zan for the opportunity. It is a rare moment. The previous speaker already highlighted importance of mitochondria, so I don't give you any more further information. So let me see to advance slide, yeah, so aging is going to kill all of us. Age itself does not, but aging related diseases are going to kill us. Aging-related diseases selectively affect tissues that are highly dependent on mitochondrial function, which is our brain, the heart, eyelid, beta cell, retina, and part of our ear. So, they are basically one disease which is aging, manifested by different tissue. That's all. So the question is can we treat all aging related diseases? One disease. Currently most of-aging related diseases are not, you know, the treatment for most of aging-related diseases other than diabetes, obesity, are not that highly effective. For example, heart failure, there is no effective treatment other than stent and stroke. In other case, this is no effective treatment,

and they kill most of us, actually more than cancer does. Alzheimer disease, which is another example. So if you understand aging-related diseases, we must understand aging itself. So Denham Harman proposed a long time ago that mitochondrial control the aging clock. The clock is turned on by free radical. The free radical generated by mitochondria damage, mitochondrial protein, DNA and phospholipid. One of the phospholipids, which has been understudied for decades is the mitochondrial signature phospholipid, it's called the cardiolipin. Cardiolipin is sensitive to oxidative damage and oxidative cardiolipin itself is a new form of free radical, which turn on this clock and speed it up when we reach to a threshold like middle age, then set us into the trouble for whole family of aging related diseases.

(00:56:59):

So what is cardiolipin? Well, it is initially discovered in the heart, but it's a lipid. It is the most complex lipid that has four fatty ether chains. It is the godsend of mitochondria. Every aspect of mitochondria require cardiolipin from curvature of inner membrane to mitochondrial fusion, fusion tology, every part of it, all the, that's why cardiolipin is so important. But the function of cardiolipin is determined by fatty ether conformation. Okay, so if you change the structure, which aging does, you're gonna change the entire behavior of mitochondria. So here's a pretty good example. The are two type of clam, one live 50 years, another live 500 years. Then the research find out that the major difference between these two type of clam is the mitochondria cardiolipin structure. The short-living clam has high content of polyunsaturated fatty acid in cardiolipin fatty ether chains. It's called the DHA.

(00:58:07):

The long-lived one, 500 years, has very little or very low level DHA. So here's a structure of typical cardiolipin. The healthy cardiolipin has the linoleic acid as a backbone and the DHA cardiolipin has six double bone. And this make cardiolipin highly sensitive to oxidate damage. So interestingly enough, the DHA content is inversely correlated with longevity. This is published a long time ago, people don't know why. So we pioneered, well we co-founded the field of cardiolipin synthesis and remodeling. Those are the enzyme we clone, cardiolipin synthetic enzyme, cardiolipin remodeling enzymes. The enzyme we've been working on for 20 years since I left Eli Lilly is this enzyme. So this enzyme involved in cardiolipin remodeling, so cardiolipin gets bombarded with free radical, and this bombardment accelerate by obesity and aging, and then the oxidized cardiolipin must be repaired, otherwise the cell will go to apoptosis. The repair process take two different pathway.

(00:59:28):

One repair is physiological repair. Basically, take away the oxidized cardiolipin and re-insulate it with linoleic acid, which recover the healthy structure. The enzyme we cloned actually involved in pathological repair. It actually well enrich the DHA content which mimics the effect of aging. So we use the animal knockout model, we knock out our enzyme, and we also knock out the telomere guiding RNA, which we know telomere length shortening, which is a golden marker for aging. Remarkably, if we knock out our enzyme, at same time, knock out the telomere guiding RNA, the lifespan of double knockout is doubled. And this remarkable effect is due to the fact that, this is all the measurement from cardiac function to cellular, every part of it being recovered by knockout our enzyme. And we spend almost over 15 years to work on aging-related diseases. Initially, we study obesity, diabetes, fatty liver, diabetic complication, and different model of heart failure In every cases.

(01:00:48):

If you knock out the disease enzyme, the mice are protected from those onset diseases. The most remarkable one is the mouse model Alzheimer's disease. If you knock out our enzyme, the PLoc number is reduced. The cognitive functions restored. So here's our model. So aging, obesity, generated Ras, Ras

induce our enzyme, our enzyme promote cardiolipin peroxidation, which is oxidation by changing the cardiolipin structure. That set off a whole game of mitochondrial dysfunction, then onset of whole family diseases. So this is the holy grail I try to present to you. So naturally I spend over a decade time at Eli Lilly, lead their early-stage drug pipeline. Like I was in charge of the very first generation of GLP-1 analog called Exendin type four. So I'm a drug hunter. So, after the validation, these enzyme is drug target for aging and aging related diseases.

(01:01:56):

We started doing the typical drug development process. We did high-throughput screening. We raised funds from angel investor. We spent last almost 10 years, improved the inhibitors structure and potency. Now we have three clinical candidate to be moving forward. One of it is called Dafaglitapin. So Dafa is very potent, and with IC50 is about seven animal. By this stage the drug company would be very excited to move forward for clinical trial. But, as a small biotech company, we run out of cash and I'm fully involved with university jobs. So the company basically is at a pre -IND stage. So, working for university, we have a platform allow us to test a different mouse model for this compound. One model is aging. So we treat mice. This is 18 months old mice with our inhibitor, which is equivalent to 10 milligram per kg by supplement it in the food.

(01:03:05):

After three months treatment, remarkable things happen. You can see the treated group, they look very different. The fur colors dense and blackened and more importantly, they live longer. They live significantly longer, they have much better glucose tolerance. Those are all fresh data, even Zan has not seen. One of the golden marker, which is what call cholesterol level go higher after treatment. And their cardiac output is like, your mice, significantly improved, their bridge strengths, their full limb and full limb running time, all significantly improved. Remarkable. So here's the treated mice. One effect that when we get older we are afraid of a cold because our thermogenic activity go down. And this is what happened when we get old, our mitochondria die in, this is brown fat. All mitochondria are dead, actually. This is after treatment. Completely restored. Another remarkable effect is the cellular senescence biomarkers.

(01:04:28):

After treatment, this is actually a much older mice, 24 months, near the death. After three months treatment, all the biomarkers in different tissue of cellular senescence is attenuated. Now the holy grail question is can we target aging for the treatment of age-related diseases as one disease? So the first model we tested is the coronary artery disease with permanent ligation of left descending coronary artery. Same day we give them compound or a vehicle. So this is what happens with the vehicle treatment. By the way, a third of mice die within 48 hours because it's heart failure, a heart attack. So the other treated not only no, zero deaths but prevented dilated cardiomyopathy and heart failure. This is the morphology. This is the volume. This is left ventricle function. Remarkable. Think about it, people consider that heart failure is a vascular disease. Here you permanently ligated left descending artery and minimize the damage to mitochondria because our enzyme promote mitochondrial damage in response to hypoxia.

(01:05:50):

So another model is the hypertension model. This aortic constriction. After two months they develop the same thing, dilated cardiomyopathy. The treatment also restore. This is measurement cardiac function. The most horrible disease is Alzheimer's disease. We analyze the expression of this enzyme. So, later stage of Alzheimer disease patient, this expression level of this enzyme goes sky-high. In rodents, this is AD PPS mice. Though brain has very little AO cat, but in the AD mice the expression level

goes sky high. So what happens if you treat the mice with this compound? So this is after two months or I think it's a three months treatment. This is the water maze test. You can see the AD mice have trouble to have a memory. This is the compound.

(01:07:01):

This is a control mice, or this is a control mice. This is our compound-treated mice. This is quantification. So the water maze test showing that this compound restored memory. This open field test, the same thing restored the activity. Most remarkable. You can see tau phosphorylation after treatment, completely attenuated. I never see any compound to do so remarkable change tau phosphorylation. The other mice develop prophecy. It's called tau tangle. So those data actually speak very loud that age-related diseases is one disease manufactured in different tissue. And cardiolipin remodeling by this enzyme is root cause for aging and linked aging to aging-related diseases. Oh, this is the cellular senescence. These mice has huge accumulation of somatic cell in the abdominal. This is after two months of treatment. So in summary, using Dafaglitapin, each disease, I could spend an hour to present the mechanism including mitochondrial fusion, fission, mitophagies, senescence, you name it. But I will summarize. Dafaglitapin treating whole family of aging-related disease as one disease, which I'm hoping to accelerate, to move to human clinical trial. It will save a lot of life. And with that, I'm closing with this graph. So Zam Fleming saved all of us.

(01:08:47):

This is extended Fleming. He is my hero because without penicillin, we probably, most of us are not here. So within few years it doubled our lifespan. But now aging is getting us into trouble because aging is a new disease, aging is a completely new disease. We had not entitled have a aging a hundred years ago before Alexander Fleming. So I'm hoping Dafa would liberate us and at least live a healthier life. And aging is not a new story. 2000 years ago, the Chinese emperor began to do research on aging, trying to find longevity medicine and send his missionary to Japan, to East China Sea, but they never returned. Hopefully, Dafa would fulfill this role. With that, I want to thank you for the opportunity to present our work.

Zan Fleming (01:09:42):

Well, Roger, thank you very much. The data are just amazing. Like all the other data we've heard, the promise is spectacular. I think we all want to see you go as fast as you can. By the way, thank you for mentioning Uncle Alex. Glad to be associated with that name. But let's do now go to questions and we've got many, many good questions that could be asked. I'm going to ask Michael Zemel to start off, and he can maybe direct a question back to Roger.

Michael Zemel (01:10:23):

Sure. Roger, you've got really terrific data, very impressive data in disease models with the next step, or I wouldn't ask it as the next step. Have you done any work on prevention of disease in normal animals or in animals that are in a pre disease-state? Or is that contemplated?

Roger Shi (01:10:47):

Yeah, I'm a drug hunter. Prevention would be something for nutritionist. We do have a whole body in mice, which is preventive because the gene was knock out in from embryonic day one. And those mice live longer. They are completely protected from every age-related diseases. So I think prevention surely work. Actually one of my colleague proposed say, "Hey Roger, this will be a huge market for nutraceutical. If you could get an FDA a approval." I said, no, most people will not take a medicine until

they're sick. But it's a good direction. I think billionaire should pay for it because they always want to live longer. This probably will most likely compare with all others like a v plus, Metformin, rapamycin, you name it. But this one sticks every direction we look. That's how remarkable. I was shocked by the phenotype of the mice after treatment. Yeah.

Zan Fleming (01:12:00):

Thank you. Thank you Roger. And we'll come back in a moment, but why don't we go over to Josh Hare. Glad you're back from NIH. And just again to say you've got data, you're in late stage, you've got an agreement for a seamless phase two, phase three adaptive trial made agreement with FDA. And so you're well underway for these targeting immediate hallmarks of aging. But can you imagine Lomecel being used in a relatively healthy population? What would be the feasibility of that? And I might mention that we notice in your frailty study that you're using TNF-alpha to select presumably higher risk patients with frailty. And so perhaps you could talk about strategies for targeting products to people who would be likely to respond.

Josh Hare (01:13:05):

Thanks Zan. Those are collectively great questions. A lot of points to address there. Basically the use of these types of products as pharmaceutical or a preventative therapy. There's a tremendous enthusiasm for this, especially amongst patients themselves. This is something that has been sought out for a long time. There's the strong perception, I think validated by evidence that one of the key points to make about mesenchymal stem cell infusions is the safety profile. It's incredibly safe. If you compare mesenchymal stem cell infusions to standard pharmaceuticals, the safety profile is better. And I think this makes sense that these are derivatives of the human body itself. And in a way we're taking a cell population out of the human body, amplifying it and giving it back. Of course, it has to be with the proper quality control by properly trained individuals. The risk would be that if untrained individuals or improper facilities are used, that there could be a risk of transmission of infection.

(01:14:26):

So long as those never, so long as that is attended to, then there is no risk. And there are large safety data sets that prove that. So this has led to a demand for these products. The problem is the supply that they are expensive to manufacture, and the amounts require large scale production. Now having said that, there lots of individuals seeking these treatments and lots of states are adjusting state laws to allow for the use without FDA approval. Florida has passed a law as that. So I think we got two societal issues here. One is I think that the FDA needs to start approving these as drugs to those individual organizations that are applying such as Longeveron. And we work very closely with FDA. We have RMAT designation around the Alzheimer's. We're hoping to get through that phase two, phase three trial. It will be very expensive though, and the expense of that trial will necessarily delay the conduct of that trial and the approval.

(01:15:59):

So if that could be hastened somehow, if FDA regulations are changed for this particular indication or this particular product, we'd love to see it get to market as soon as possible. Now the flip side of is, okay, let's say we get approval to treat a disease, should people be taking it as prevention? And again, I think the safety plays a key role. There are some people seeking these types of products and are taking them for prevention. It appears to be safe. It's harder to gather the clinical data in that kind of scenario relative to a well conducted phase three clinical trial. On the other hand, I think what you will see is more and more usage in the state of Florida. It's now going to be legal for athletes who have any kind of

athletic problem to seek treatments. And I think you'll see that they'll be used more and more for prevention. I was very intrigued by James's data also on his intervention for athletics and potential prevention of damage in high performance athletes. So this is an exciting fast-moving field and it's going to be changing year by year.

Zan Fleming (01:17:30):

Well thank you very much Josh. Well hope to come back. And Chris, you do have another product that we've got plenty of data that improves multiple health. Michael, over to you to ask Chris.

Michael Zemel (01:17:45):

Sure. So first of all, Chris, kudos for bringing outstanding scientific rigor to the supplement space. It's something that is sorely needed and rarely done, so kudos for that. What is the role of evidence-based supplements overall in extending healthspan? Urolithin A, but supplements writ, large evidence-based supplements in extending healthspan.

Chris Rinsch (01:18:19):

Well, I think we're really at the early stages on taking, as you said, advanced science and really exploring the use of supplements and validating them in the clinic with of course we've focused on really, really trying to show in humans the various benefits at the cellular level and the tissue showing that we're actually able to stimulate improved mitochondrial function, stimulate mitophagy, and actually stimulate an improved functionality of the tissues, whether it's muscle function, muscle endurance. Recently we've been looking also at immune health, and so we have a paper that should be coming out soon on immune health where we looked at people, average age around mid-fifties of individuals who are healthy, taking our product one gram of Mitopure during a month period. And we were able to show a change in the immune health of these participants and I thought that was very exciting.

(01:19:41):

We showed basically an improvement in mitochondrial function in immune cells. We took cells before in cells after we did a very deep phenotyping together with the Buck Institute and Eric over there. And this was done with professor Dr. Florian Greten over in Germany who was the principal investigator for this. And what they showed was that over a month long period they were able to increase the number of CD8T naive cells in the overall populations, which was really quite phenomenal and they were able to see an improvement in mitochondria function and that was able to be measured just by drawing a blood draw. And so this is something that is very exciting to see, that we can take nutritional interventions and then validate them clinically and show that they can have an important effect on various attributes of our health that are very important to our health span, whether it's muscle function, which I spoke about as being very important and the bedrock really of our health.

(01:21:05):

And then as well as immune function. I see this continuing and I see nutritional interventions as being a very important element but not a replacement for good diet exercise and lots that we all talk about now, the importance of sleep that having a holistic approach is key for healthspan, but if you can take the right supplements that are acting on key pathways of aging, like in our case mitochondria dysfunction, I think that's really exciting and we've been very fortunate to have identified urolithin A as a very important nutrient that acts on mitochondrial health ,and we're also very pleased to be able to offer that to people through our Timeline brand, that you can go online and just order that and have

that come to your home. So it makes it very easy for people to have that nutritional intervention and breaking down those barriers is very important.

Michael Zemel (01:22:27):

Very exciting, really, back to you Zan.

Zan Fleming (01:22:32):

Well, and thank you Chris. It's remarkable what you can now do with a product that is on the market and available to people and we really are excited about what you're doing and committed to doing and thanks again for emphasizing the foundational approaches to targeting healthy longevity. It's lifestyle, safe and effective. It needs to be done first and foremost, and then all these other modalities can help. And by the way, it's conceivable that the four products that we've been talking about could be used together or at least in some combination. So anything that works and presumably if it works, it will tend to work or another product with a different mechanism, it'd be even better. And so that's yet another prospect. But let's go back to James Carroll, and James, likewise, you have so many compelling data in treating disease conditions, but for a medical device, doing a prevention trial is a daunting proposition. So what is your thinking about pursuing a so-called healthspan claim that would be going that you can actually prevent two or more chronic conditions or at least improve them in some way?

James Carroll (01:24:10):

Given that as Jian said, if you maintain a healthy lifestyle, so that obviously involves, as I said in our pre-meeting yesterday, the first rule of longevity is to not die, and then the leading cause of death is cardiovascular disease relateded to atherosclerosis and obviously diabetes and cancer and Alzheimer's sort of following up. And we know that exercise is a major component of that. So we contribute to people's ability to do exercise and so their outcomes are better if they're using light as part of their exercise regime. As I also showed, when we treat the side effects of chemotherapy and radiation, that is a pre-treatment before they have any symptoms, we are doing something to cells sufficient that they become resilient to the effects of radiation and chemotherapy, the adverse effects of it. And there's no sign that these things are reducing efficacy of chemotherapy and radiation.

(01:25:17):

If anything, there's some hints of a trend that maybe the cancer treats are better, so we're doing something to healthy people that makes tissues more resilient. Now I can't explain what we don't know exactly what that is. We think there's NF-KB and AP1 are both involved as the transcription factors, but we don't know more than that. There are fruit fly studies that show longevity. You can give these flies light every single day and they seem to have a much better health and lifespan. They die off more slowly than a control group that doesn't receive any of it. There's studies on the brain or mice where they apply photobiomodulation four to five month old mice for, seven month old mice for five consecutive months every single day for the treatment and there's a reduction in the microglia and astrocytes in the brain of aged mice compared with untreated mice and compared, they compare well with three month old mice that didn't receive any treatment. So I think absolutely this is an area for it to be considered. Obviously it's hard to do a hundred year long studies in humans, but in short living creatures, this seems to be working.

(01:26:41):

Did I answer the question?

Zan Fleming (01:26:43):

Well, I think mostly, I guess there's a practical question here, and that is could a medical device company with all the considerations involved without having sort of a corner on the market so to speak, afford to do a prevention trial that could cost many millions of dollars?

James Carroll (01:27:08):

Yeah, that is a difficulty, isn't it? I suppose the true answer is for as long as, I mean how long do these have to be to prove longevity? I suppose you'd be using, yeah, you'd have to prove if there were liable biomarkers that FDA would recognize markers of health. If we can show those and if that means that it takes three or five years, then I think that's something the industry could consider. But if it's going to be just going to be 10, 20 years, I mean it's not that industry can't have a registry and start looking at early biomarkers and keep following patients for decades, but if you can get it on the market with earlier with some kind of health and longevity claim, healthspans claim and obviously that would be nice.

Zan Fleming (01:28:02):

Well, thank you. That actually is exactly what the THRIVE Act tends to facilitate. So again, I urge everybody to take a look at the details of the THRIVE Act that's available on the Kitalys website and I wish that we had much more time for questions, but we've only got about seven minutes, so I wonder if you can provide some other questions, Michael, that the audience has been putting to the panelist. Absolutely. Lemme just cue up Thomas in case he's fallen asleep. Oh, we'll put him on to ask a question or make a point in just a moment.

Michael Zemel (01:28:51):

Excellent. He's awake. There he is. So Thomas, before I jump into questions.

Thomas Seoh (01:29:03):

Yes, what was the question? I've been fascinated by this discussion and struck by the fact that this would be of enormous interest to the people who are attending this conference. This is actually Suzanne, not a geroscience conference but APAC, Asian Pacific Longevity Medicine International Summit in Hong Kong. And I've been just surprised, I dunno if shocked is the right word, but I was unexpected to see this huge rise, rapid rise over the last five years in the phenomenon of longevity medicine clinics. We've been looking at product development and on the back end there's this enormous exploding interest in applying things that science is demonstrating on behalf of patients. So obviously we want to be sure that regulatory requirements are met, but with marketed products such as urolithin A supplement and with photobiomodulation, I think that these kinds of data are going to be a great interest to actually, we have a huge mass delegation from China, so we have 50 or 60 longevity clinic sort of groups that are wanting to push these kinds of solutions through to thousands of patients. So we're going to see a lot of data I think if they can be captured instead of just part of a medical treatment.

Zan Fleming (01:30:33):

Thank you Thomas. Josh's cellular approach will also be of great interest to these clinics and he mentioned that as a,

Josh Hare (01:30:43):

Yeah, this has become a major trend around various geographic locations, particularly in Asia and Latin America. There are quite a large numbers of US residents leaving the US to seek these therapies and this is a growing trend, and it'll be of great interest to see how this plays out over the next few years.

Zan Fleming (01:31:14):

Well that is both an opportunity and a challenge. We want these to be evidence-based and as you know, that's not always the case. That is one other feature of the THRIVE Act to encourage investment in acquiring data that all of you are part of and we therefore applaud all of your efforts that regard. Michael?

Michael Zemel (01:31:52):

Yeah, so I have a question for James from John Ferber and I'm to expand on it a little bit. He asked about light color range and frequency. And just to expand on that, James, is it a single wavelength or wavelength range for all the different applications, and are there applications for which that require specifically laser perhaps for depth of penetration and others that would require LED or would do with LED? Can you comment on the uniformity I guess, of treatment across applications?

James Carroll (01:32:34):

So that's wavelength and lasers, the main topic. So in the question there, so it seems that you can look at the absorbed from spectra of any molecule and that includes cytochrome shock studies in mitochondria, which seems to be the main target for photobiomodulation. Not saying there aren't others, there are certainly some membrane changes which occur with infrared light, but sticking to the one where we have the most evidence is in mitochondria specifically its effect on cytochrome oxidase and we see the oxygen consumption and the ATP changes and the better behavior of the electron transport chain, fewer reactive oxygen species. The why is when looking at the absorption and the absorption spectra of cytochrome shock studies, it looks like there's some very specific targets and the best ones are in wavelengths, which you start moving through to the green area and blue areas of the spectrum look like those should be the wavelengths for PBM.

(01:33:43):

The problem is the light doesn't penetrate the tissue very well. The reason we can all see each other today is because visible radiation is bouncing off of our faces into the camera and that's why those wavelengths are unlikely to have any useful clinical utility and yet they seem to be optimal for absorption. In cytochrome shock studies, there is some absorbed in the red and in the near infrared spectrum, so in the middle of the red range and the middle of the 800 range, at least those are the ones that have been published. There may be others. And it seems that even though they're relatively small in terms of absorption and action spectrum, we see in those wavelengths they seem to work. How sharp are those peaks? How accurate do you need to be? It's very clear that in the 800 spectrum it's quite broad. It's narrower in the red spectrum.

(01:34:38):

So we're talking about several tens of nanometers spectrum via the peak, which is around 835 nanometers, but through to 850, 860 and much shorter down to 800 nanometers, people are getting effects. I've seen many wavelengths used way outside where the peaks are for it ,and they too seem to work. And the thing that most people, even in industry, people who make these things don't realize. Certainly when you're using lasers, lasers are never the wavelength they say they are because even if you turn when you turn them on, by the way, when you purchase one, they can be plus or minus five or

10 nanometers, you can spend extra money, get them closer within five nanometers as you switch them on, let's say you do have one of your preferred wavelength, it moves as it warms up. So the wavelength changes. S, if you haven't specified a wavelength, it's not the one you probably see the published, because nobody tests these things and it moves anyway.

(01:35:38):

And yet all these positive studies seem to occur. So I'm uncertain about really how accurate the importance of wavelength it is somewhat important, but there's precision. Oh dear, this one's two nanometers different from that study there. I think that's unimportant. If you are talking a range of 10 nanometers, then it becomes more important. Tens of nanometers then becomes important in terms of, and you want one that penetrates red is better than any other part of the visible spectrum. Near infrared is better. And I'm talking about in the sort of sub, I dunno just about in the eight to 900 range is the best sort of penetrating. There is another part in the spectrum. We get beyond 1,015 nanometers and there's another good penetrating spectrum that needs more investigation to compare efficacy with the other near infrared ones, sorry, that's long and it's nerdy and it's outside people's most confidence and they've used a lot of words that are new to people.

(01:36:39):

There's something with lasers. It's just to get that one out of the way in terms of penetration, it's the wavelength that counts, not whether it was coherent or not. Laser light is coherent and LED light is not coherent. There are people who argue that because when you have coherent light you can see speckles in the visible spectrum, you can see speckles and it's an interference pattern. It's a trick of the light on the back of the eye. And the idea is that somehow as these waves somehow maybe photons are reaching the same molecules simultaneously and having double the effect actually one molecule can only absorb or one atom can only absorb one photon at one time. So this seems unlikely to be true. Nobody has done adequate study comparing laser with LED to absolutely compare light for light. All other parameters the same, the wavelength, the intensity, that means the beam area, everything identical only difference was coherence. Nobody's done that study. Anybody goes around and clean lasers better than the LEDs with all the way around. Is it? It's not true. A perfect study has not been done, and there's studies that prove LEDs are better, there're study approved that lasers are better.

Zan Fleming (01:37:50):

Well James, thank you for those details.

James Carroll (01:37:54):

Killing you with the details.

Zan Fleming (01:37:55):

Yeah, well it's fascinating and gosh, we have run out of time, we have done over 90 minutes and we always let the formal audience go or the formal part of the program go, but those folks that are willing, both panelists and the audience who want to stay on will keep going. But before we completely end, we'll turn it back to Michael for just some final comments. But first I want to thank the panelists for an amazing discussion and presentations. It's just incredible what all of you are doing and it's so important. We want to keep encouraging you to keep going. Michael, thank you.

Michael Zemel (01:38:44):

Absolutely. And I also want to thank you. I'm sorry we've run out of time because in addition to the questions that were in the chat that we haven't gotten to, I've got a list of my own, this has been a fascinating set of presentations, but in order to finish up the formal part and we'll stay on afterwards, just a little bit of additional housekeeping, just a reminder, everyone will receive all registrants anyway, we'll receive a link to this recording within the next day or two along with additional announcements, the future targeting healthy longevity sessions, including the October 15th fireside chat between Bill Haseltine and Larry Steinman on pursuing healthy longevity. That is going to be one for the ages and should not be missed. With that, the formal portion of this event will close with many thanks to the panelists and to you the audience for your attendance. We will be leaving this webinar open for a period of time for those speakers and audience members who are able to stay chat, ask some more informal questions. Thank you.

Zan Fleming (01:40:01):

Thank you Michael, and thank you all in our audience and for those who can stay on, let's keep going.

James Carroll (01:40:12):

We all want to know what happens when we combine all of our optimal molecules and therapies together.

Michael Zemel (01:40:20):

Yes. Have you done that experiment?

James Carroll (01:40:22):

Not with these guys. No.

Zan Fleming (01:40:26):

Joshua, what were you gonna say?

Josh Hare (01:40:28):

I think the fascinating thing is that we should all recognize that we are all endorsing and validating this concept of the hallmarks of aging, right? All if not most, all of our interventions do hit mitochondrial biology. There's the linked inflammaging. So these are very important take homes and I think the notion of combinatorial therapy or tailored therapies emerging as it has for all serious chronic diseases, there is not one magic bullet for any known human disease. It's always a combinatorial approach and they're always individual susceptibility. So I think that multiple approaches we've seen here today endorse that concept very nicely.

Zan Fleming (01:41:23):

Well, and Josh, you also are developing an approach for hypoplastic heart and heart failure and that's the combination with surgery, just as another example. Yes. All great stuff. Thomas, you wanted to say something?

Thomas Seoh (01:41:44):

Just a logistical point, James, I see you posting stuff in the chat. You might want to choose a "For Everyone" option. You're sending your information to the panel, but if you're wanting it to be spread more broadly to the panels, choose the everyone option. Sorry, go ahead.

James Carroll (01:42:02):

Oh, right. I dunno how I do that. Oh, host them to panelists. Yeah. Got it. So I've responding to somebody's question.

Michael Zemel (01:42:10):

Yes. I am wondering if I can ask Roger a question. Roger, can you tell me, and forgive my ignorance on this, what else does ALCAT1 do that we might, I mean I understand the target and the purpose of the target, but what else does the enzyme do that we ought to think about when thinking about inhibiting it?

Roger Shi (01:42:37):

Yes, good question. People often ask after my presentation say, well, it is such a bad gene. Why in the modern nature has not gone rid of it? We have to put this question in perspective. What is the function of these enzyme? The function of these enzyme is part of the cellular senescence response. So very early on when we try to establish a stable cell line overexpresses protein. Most of the cells basically not survive and those cells who can struggle to survive is because they already attenuated the inflammatory response. They are also attenuated the cellular senescence response. So that's the basic function. These enzyme promote inflammation. These enzyme promote cellular senescence. Both are quite important when we are young. Cellular senescence will be triggered by telomereome shortening.

(01:43:44):

So, and telomere shortening exposed double-strand DNA, also induce inflammation by the cGAS-STING pathway. So when we are young, our body do everything, prevent us develop cancer. So if there's tumor shortening, the cell will likely to become cancerous. So the cellular senescence is preventing cancer development. As we get older, those cellular, the senescent cell accumulate in our body, and we pay the price when we live longer because Mother Nature really does not select for longevity. It is actually, human out live most mammals because human has a brain. So the brain actually contributes to the race. Actually, you think about it for woman, menopause is basically a mark line that Mother Nature said you no longer need it. So menopause basically is a milestone for aging. For man, it is a different story. Man is the conqueror of the world. So man's productivity can continue if you are the king or if you are strong just like a natural one.

(01:45:08):

So to cut it short, this enzyme is involving cellular and enzymes, probably anti-cancer response when we are young. So it's not bad. Mother Nature does not select for longevity. So this enzyme has not shown its ugly side when we get old. So when we get old, when we pass our reproductive age, that's when this enzyme is showing the ugly part, which is promoting cellular enzyme and mitochondrial dysfunction. By the way, this enzyme is sitting at the junction between ER and the mitochondria. Most molecule, including nutraceutical, cannot penetrate mitochondria because mitochondria is double membrane. So that's where I don't understand some of the nutraceutical, how it works in antioxidant response because if antioxidant is highly effective in treating aging, then we should take a lot of antioxidant. But most of the antioxidant does not penetrate the double mitochondrial membrane. So fortunately our enzyme is sitting outside the mitochondria. It's at the ER-mitochondrial junction. That's where remodel, the

phospholipid being transferred. That's why this enzyme is fully druggable. And I answer more than you ask, I hope clear about some of the issues. Yeah.

Zan Fleming (01:46:33):

That's a really elegant explanation.

Michael Zemel (01:46:36):

Absolutely. Looks like Chris has a comment about it.

Chris Rinsch (01:46:40):

Well, I just wanted to thank you for organizing such an amazing conference today and this cross-functionality here. I mean we can really see how all the different products that each and every one of us here are working on to develop, to bring to humans are very synergistic. Whether it is nutrition, whether it's light therapy, whether it's stem cells or even pharmaceutical intervention acting at different stages of our life for our health span. I think we're covering here basically early on, early prevention with nutrition and with hitting with different frequencies of red light as James was talking about. And then as Joshua was talking about all of the stem cells and how important that's going to be throughout your life to try and help reconstruct the body. And then as you get into serious diseases, what Roger's working on. It is just a very nice combination of different tools and I'm really excited to see how that all comes together in the future and benefits all of us. But thank you. Thank you very much for inviting me today and it was really great to participate with all of you.

Zan Fleming (01:48:07):

Well Chris, that's a beautiful summation, much appreciated. We've got it recorded, we'll point it back multiple times, so thank you for that. I know it's late there in Lausanne, but we sure appreciate your being with us.

Thomas Seoh (01:48:27):

Can I just follow up to you, Chris? Thank you so much, Zan. Can I just follow up something that Roger said. I've sort of been faciley making the assumption that for healthy longevity, health plan products to be even optimally effective, their highest and best use is to supply them, administer them to healthier younger people. But Roger's comment about Dafa suggests that actually, you don't necessarily want to give certain kinds of interventions to younger, healthier people at least until they crossed over into the senescent side, the post-reproductive age side. So just something that I guess I've learned something here or hadn't really thought about that before.

Zan Fleming (01:49:18):

Good, thank you. And Josh?

Josh Hare (01:49:23):

I also want to give my thanks and appreciation for the meeting and really learned a lot from my colleagues. Look forward to interacting with everybody again in the future and following the progress of the THRIVE Act very closely.

Zan Fleming (01:49:43):

Josh, many thanks. You brought so much to the discussion and we're going to be looking for new data soon.

Josh Hare (01:49:53):

We're going to have our readout of our pivotal trial in HLHS next summer, so under 12 months and that'll be Longeveron's first pivotal BLA potential enabling study. So, be on the lookout, and it will be announced.

Zan Fleming (01:50:15):

And you've got others. They're looking them.Thank you Josh.

Josh Hare (01:50:19):

All the best to everybody.

Michael Zemel (01:50:27):

You know, Zan, there was a question, I know, before we go, there was a question following on what I just said about the THRIVE Act. One of the first questions in the chat was from Scott Faulkner who simply wanted to know, and we'd all want to know, whether it has been introduced in Congress yet.

Zan Fleming (01:50:47):

Well, we need to get Scott Faulkner's help. He is a political and quite an accomplished one. He was CEO of the House of Representatives so he knows where the bodies are buried, literally,in in Washington. And Scott, we'll double back with you about getting your guidance on how to approach the Hill. We have done that to some extent, but we're not experts in that domain. We're just coming up with what we think will be very attractive, bipartisan support. This is something everybody wants. They want to be able to do something about preventing multiple chronic diseases, and all solutions that work should be made available as soon as we have the evidence that they do. So that in a nutshell is what the THRIVE Act is about, and yes, indeed, we'll double back with you Scott. Thank you for the question.

James Carroll (01:51:59):

Begs the question, what level of evidence is going to be required? Many of us here, and we are all biased in favor of the fact that we spent a lot of time and a lot of money working on evidence, and therefore we like the complexity, the challenge in that it keeps other people out in that the people who haven't paid the money, done the work and have the evidence, and how's FDA going to, what bar are they going to set for health and longevity? I'm sure it's a conversation they've been in before, so we've got to figure it out.

Zan Fleming (01:52:43):

That is a key balance to strike ,and as Josh was referring to in Florida, you can hang up your shingle and start injecting so-called stem cells, and they help. It may not, and it may hurt. So we're not for that. We are not for getting ahead of the data products that work. On the other hand, we want to see incentives to encourage companies and investors to get into the hunt for evidence-based product development. Just as all of you are doing with that. We believe balance can be struck, but we see a lot of good, bad, and ugly in this field. We don't like the bad and the ugly.

Roger Shi (01:53:55):

There's a question in the audience ask about DHA is being beneficial as a supplement. Can I answer that question?

Zan Fleming (01:54:04):

Yes ahead, Roger.

Roger Shi (01:54:05):

Yeah. This boil down to the fundamental issues why DHA is beneficiary in the food supplement but is so bad in cardiolipin. Remember, our body never trusts anything we eat. If we eat the protein, it'll be digesting into amino acid. It is not absorbed, the whole protein to be used our body part. So is all the fatty acid we take. DHA is used to supplement. It does probably benefit to the brain because brain has very high content of DHA. That's why aging affect brain so much. DHA is enriched with double bonds, highly sensitive to oxidative stress damage. However, what incorporated into our lipid is not determined by what we eat. It's regulated by mitochondrial behavior, function. So the remodeling place, take place in the ER. The ER is the fuel depot, is like our fuel tank. All the fatty acid is synthesized, they're all stored there.

(01:55:18):

The availability and how these enzyme choose DHA, our enzyme choose DHA, is the million dollar question because we found that early on that this enzyme preferred DHA, remember during onset of aging human being the DHA content in cardiolipin is gradually enrich as get older and older. It's almost like the fuel gauge. You have very little fuel left. That's why I showed a graph where DHA content is inversely correlated with longevity. So when we get, let's say 60-year-old, our mitochondria has, if you analyze cardiolipin structure, which was pioneered by Shahin in our institute, he was a lipidomics expert. It's very few lab can analyze the cardiolipin structure. Shahin's lab pioneered that. So he actually reported very early on, almost like 15 years ago, if a person developed type two diabetes and later on other people find that heart failure, in every cases, it accelerated incorporation of DHA content, DHA into cardiolipin. So that means accelerated aging. If you have diabetes, you have heart failure, you age faster. I hope that answered all the question, is what we take is completely different from what our body use, especially this enzyme have a preference at ER.

Zan Fleming (01:56:53):

That's a great point.

Michael Zemel (01:56:54):

Well put.

Zan Fleming (01:56:55):

It's getting the defector to a target receptor signaling pathway, and that doesn't happen just because you put it in your mouth. Yeah, so very well said. Gosh. Well, Thomas, you're still up. You got a big day ahead of you tomorrow. And we also understand that you're going to accept ana award for the product that is currently also on the market. You want to say a word about that?

Thomas Seoh (01:57:36):

Sure. We're very gratified. This is a dietary supplement that Michael Zemel invented I believe. And it's housed in a subsidiary of Kinexum called NuSirt. That's a long story, won't go into that now, but, Michael, do you want say something about LEUSIX, the supplement? We have a pharma side and the supplement side, we have the supplement on the market. We have clinical data and we're also working. Am I still connected?

James Carroll (01:58:06):

Yeah, you are.

Thomas Seoh (01:58:08):

I just got a disconnected notice. I don't know what that was. We have a phase two program on the pharma side, and we have a supplement on the market now available on our website and on Amazon. Michael, do you want to comment on it?

Michael Zemel (01:58:23):

Sure. The pharma and the nutri side are distinct different products, clearly different products. On the nutri side, the product Thomas is referring to is one for weight management, and it is built on a combination of catabolic signaling through SIRT1 as well as inhibition of adipocyte lipid synthesis. And it's an interesting combination. It worked well in cells, it worked well in rodents, it worked well in humans, if we took it through three clinical trials, the first of which was short term, just to show increased fat oxidation as well as improvement in inflammatory biomarkers. And then put two additional companion trials, two additional trials that were run concurrently. One in individuals under caloric restriction, one in individuals without caloric restriction. And we're able to show very nice weight loss, very nice fat loss with really minimal lean mass loss improvements in insulin sensitivity and inflammatory biomarkers. We then used the human as a model for the dog. We went ahead, we said if it works in people, maybe it'll work in companion animals. And actually we had a vet school do this, and it actually worked out quite well in fat dogs. So it does not have drug-like efficacy or GLP-1-like efficacy, but we think it could be pretty interesting for those people who are rotating off the GLP-1s, as they typically do after a year or slightly over a year to help preserve what they've worked hard, the weight loss they've worked hard to get to.

Zan Fleming (02:00:26):

And there is a drug product that, as you mentioned, will be in a phase two trial in the near future.

Michael Zemel (02:00:37):

We actually have completed several phase two trials, but we're working on a new indication and so we'll be starting that phase two trial before long

Thomas Seoh (02:00:51):

A combination. The lucid supplement is a combination of the essential amino acid leucine and vitamin D6. It was Michael's seminal discovery. Who would've thought that adding leucine would be synergistic with various healthful compounds? I think we have data, some a little clinical, mostly preclinical with resveratrol, NAD+ donors, berberine, other compounds like that. But on the pharma side, it's a low dose combination of metformin, sildenafil, and leucine. So something that we think would be a great, if it works, it'd be a great contribution to global accessible medicine.

Michael Zemel (02:01:33):

Exactly.

James Carroll (02:01:35):

You've synthesizing leucine or something? What's the source of it?

Michael Zemel (02:01:39):

Oh, so we purchased, I mean, there's GMP leucine, pharma-grade GMP leucine, which the best leucine, which is what we use, is produced by fermentation.

Zan Fleming (02:01:53):

And one question that comes up is that there's plenty of leucine in the diet. And so what's the difference between just eating a good, healthy, full or leucine diet and taking this product?

Michael Zemel (02:02:09):

It's a great question. I'd like to pretend that wasn't planted, but it probably was.

(02:02:17):

It's a great question. And the answer is this, your fasting leucine is on the order of a 10th of a millimolar, a hundred nanomolar, give or take. If you have a really protein-rich meal of high-quality protein, that will go up two and a half or maybe even threefold, it's 250, a quarter of a millimolar, up to maybe three tenths of a millimolar. That's not enough to do anything. We've done the PK work, we need to get it up to approximately 0.5 millimolar, which does require the supplement and it needs to be taken in one fell swoop, not over the course of a long meal in order to get to sirtuin signaling. And the follow-up question for that sort of thing usually is, ooh, leucine, doesn't that stimulate mTOR signaling? That's something we'd like to avoid. And the answer is yes, but you have to get really high concentrations of leucine.

(02:03:25):

You can do it in a laboratory, in a lab or in mice or rats. It takes somewhere between one and a half and two millimolar to get to increased mTOR signaling or mTORC1 signaling. We don't go anywhere near that range. We've got a nice plateau that occurs well at 0.5 and you have to take a lot more leucine to get to that anabolic range. And, while we have not measured in clinic, for example, taking muscle biopsies to show that mTORC is not activated, we have done it in our animal studies, and there's absolutely no effect

(02:04:14):

As in many cases it's finding the Goldilocks zone that makes the medicine or the supplements work

James Carroll (02:04:23):

For every medicine. And that includes light as well.

Zan Fleming (02:04:27):

That's right. Paracelsus said all drugs are poisons. It's the dose that makes the poison a drug.

James Carroll (02:04:36):

Absolutely.

Zan Fleming (02:04:38):

I would've said that in Latin. But

Roger Shi (02:04:44):

I have a question for the panelists about the fundamental issue of aging. So despite the fact that our average lifespan has increased, our maximum lifespan has not surpassed the previous record set by a French lady. So what is the fundamental issue behind this is the human genome, whatever built for the maximum usage or longevity is about a hundred twenty, twenty two years, 25 years. Why is that? It's fascinating.

Zan Fleming (02:05:22):

There is a dogma that is built in that is related to telomeres and other biologic phenomena that just lock our or make a ceiling to our survival. But there is a school of thought that we can hack these different targets to be able to even live longer, not just have greater healthspan. And that in theory is feasible. If we can think it that eventually can probably be done. I don't know of any safe and effective approaches that will help us to live beyond 125, but

Roger Shi (02:06:14):

Then that's why I ask the question, because we often hear a scientists comment with the commercial interest, say, baby lived 200 years already born today. I just don't believe that. That's cool.

Zan Fleming (02:06:29):

Yeah, I think that's harmful for that kind of assertion to be put out. It's just not based on evidence that we've got something that can do that. Now, it's not to say that we shouldn't be looking for it and shouldn't use it if we found it, but it's a disservice to tell folks that we're right around the corner for living to be 200 years old.

Michael Zemel (02:07:00):

Well, ZZanI look forward to discussing that in the 2075 edition of THL.

Zan Fleming (02:07:07):

Indeed, I'll see you there. And I guess maybe that's the signal, Michael, to bring down the curtain on this session. It has been a great discussion. I really appreciate Roger and James hanging on this long and to Thomas for staying up so late. Thank you out in Palo Alto, Emma Snyder, our great new associate, and to Sayief our Zoom master for getting us all on the screen. So with that, maybe we'll close the show and a recording will be coming out shortly to those who would like to look at it or pass it on to their friends.

Michael Zemel (02:07:51):

Thank you.

Zan Fleming (02:07:52):

Thank you. Thanks everybody. Thank you.

Michael Zemel (02:07:57):

Bye now.

Zan Fleming (02:07:58):
Bye.