Targeting Biological Aging With Rapamycin

Robert Lufkin, MD
with Matt Kaeberlein, PhD

Robert Lufkin, MD
Welcome back to another episode of the reverse Inflammaging Summit body and mind longevity medicine. And today we're gonna talk about arguably one of the most promising medicines for longevity among other things. And we're going to talk with one of the world's experts in the area. I'm so delighted to have Dr. Matt Kaeberlein who's a professor at the University of Washington School of Medicine. Matt, thanks for joining us today.

Matt Kaeberlein, PhD
Sure, thank you. It's a pleasure to be here

Robert Lufkin, MD
Before we dive in. Maybe you could tell us a little bit about your background and how you came to be interested in this fascinating space.

Matt Kaeberlein, PhD
Yeah. So I actually got interested in the biology of aging at the beginning of my graduate career. So I went to M. I. T. Where I did my PhD and and during my first year here at M. I. T. I heard a seminar by a professor there named Lenny guarantee and he was talking about how his lab had just within the last couple of years started studying the biological mechanisms of aging. And I I don't to this day I don't really know why that resonated with me. But I was so fascinated by the idea that you could use genetics and molecular biology and biochemistry to study something as complicated as aging that I went and I talked to Lenny and ended up joining his lab for my PhD thesis and and really haven't looked back and so you know the specifics of what I've been studying in in my own work have evolved. I would stay over that, you know the 20 plus years since since I heard that seminar, but it's all been related to the biology of aging and you know I would say the one thing that has changed is back then, I was young enough that I didn't really appreciate the sort of personal importance of this. But I would say that as I've as I've gone

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through my my career and gotten a little bit older, I have also transitioned my interest into you know, maybe a little bit more of the immediacy of what can we do about the biology of aging in people to improve health span, hopefully lifespan, but but really you know keep people healthy as long as possible by modifying the aging process in a positive way.

Robert Lufkin, MD
Yeah that's a great observation how many people in this space that are in you know medicine or health care that as they get older and older they sort of transition their interest to longevity and there's an inordinate focus on it out of self interest

Matt Kaeberlein, PhD
Becomes a little more personal. Absolutely.

Robert Lufkin, MD
Well the lab you worked in at M. I. T. Lenny Grandes lab has an amazing reputation, a history of great workers in that great people in the lab who have gone on to have amazing careers on themselves, including yourself, Dave Sinclair, Brian Kennedy Gil Blander. I wonder what do you think? What was what about that lab, was it, was it Lenny, was it you guys were just especially smart guys or was there the timing was right or what, what was the magic sauce you think?

Matt Kaeberlein, PhD
Well I certainly would not claim that it's because I'm particularly, you know, a genius or anything, I think that, so, so what I would say is I think it's a combination of factors, right? I think Lenny absolutely ran the lab and was a visionary in lots of ways, but ran the lab anyway, that allowed people who were very self motivated and risk takers to flourish, right, I think. And so I think that was part of it, I think it was also, you know, when I was in the lab, it was really an amazing time because Brian had just left, but I knew Brian, he was still in Boston, we interacted, David was in the lab at the time, Heidi Kestenbaum who went on to do some really important work, was in the lab at the time, Brad Johnson who went on to do really important work was in the lab at the time.

So there are all these really creative and smart people in this environment that was, you know, a little bit competitive, very supportive as well and it was that mix, I think that really had an impact on me. And it was also a time in the field when, you know, the field was growing rapidly, new tools to come online that for the first time really allowed people to do true mechanistic molecular work and identify some of the foundational mechanisms around the biology of aging. So I think it was a combination of all of those things that you know, that allowed several of us to

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really become immersed in the field and go on and have successful careers. And I hope my career, I hope I would like to think that maybe my biggest successes aren't behind me, but I think it was a combination of all of those things that allowed several of us to make a mark. But I think we also because of that environment and because of the where the field was at at the time, we got hooked and stayed in the field. I think often times you'll see people, you know, as graduate students who go on and do something completely different when they get to their postdoctoral research and they're independent careers. Several of us who were in Lenny's lab around that time stayed in the field and didn't go work on something else. And so that's probably part of it as well.

Robert Lufkin, MD
And it's so great that many of you have your own labs now and you're creating a future generation of experts in this field that will hopefully, you know, go on and do even even greater things.

Matt Kaeberlein, PhD
Yeah, I think they definitely will. I, you know, I say this whenever I'm talking to junior people in the field right now and I think this is such an exciting time to be a graduate student, post doc junior faculty in the field of aging, biology or neuroscience or whatever you wanna call it because there are so much renewed interest and resources coming into the field Right now that I think the opportunities are just huge. You know, I truly wish I was 25, 30 years younger and coming into the field now because I think the opportunities to make, you know, just just amazing discoveries that are there of high impact you know, they're almost unlimited right now. And so it's a really, really exciting time to be a young person coming into the field and doing science around the biology of aging.

Robert Lufkin, MD
Yeah, it was a great time when you were starting out, but arguably it might even be a better time now. One of the things in doing this summit, it's interesting talking to experts on longevity from coming from all different places. One question I like to ask them is, what is your view of longevity, aging? Why do we age? What are the mechanisms? Is it wear and tear? Is it hyper function all these things? And it's very interesting because there's no clear consensus from the experts. Everybody has a slightly different take on it.

Matt Kaeberlein, PhD
Well, so and I think that there's a lot actually to unpack there. So if the first thing I would say is when I think it's important to recognize that the word aging means different things to different

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people. And so often times, I think the disagreements that come up around is aging a disease. What is aging really? You can track that back to how the individual person is defining aging, right? So, I try to be precise in my language and talk about biological aging. That's the way I think about it. You know, there's chronological aging, which is just the passage of time. That's pretty easy definitionaly to agree on. But biological aging is something different. And I I think of biological aging as the physiological processes, molecular biochemical processes that result in at least a permissive physiology as we get older for all of the different functional declines and diseases that go along with old age. And again, I try to be precise, I'm not saying necessarily that biological aging causes cancer. Alzheimer's disease.

Heart disease, I think it does to some extent mechanistic lee but you can argue about that because we really haven't proven that. I do. Don't think you can argue about whether or not biological aging creates a permissive physiology for all of those functional declines and diseases. And given that I would say that biological aging is really where we should be focusing our attention if our goal is to keep people healthy as long as possible. So that's kind of the way I think about, I think about aging now. What are the mechanisms of aging that I think the reason why there's so much disagreement or difference of opinion is we really are still figuring that out, Right. So I think it's important to appreciate in the last 2030 years.

Scientifically, we've learned a lot about the mechanisms of aging again, molecular biochemical genetic mechanisms, but we've also really only scratched the surface. So we've gotten to the point where we can put some names to these things. I'm sure many of your listeners are familiar with the hallmarks of aging and really the hallmarks of aging are just sort of a set of nine or 10 depending on who you talk to, conserved processes that seem to be related to the biology of aging in every animal where we've looked. And so we can put names on these things. These are things like DNA damage, telomere, shortening, epigenetic changes, senescent cells, those are aspects of biological aging, but there's a lot that we don't understand underneath the hallmarks. And I would argue also outside of the hallmarks of aging still yet to be figured out.

And I think that's why you get differences of opinion or disagreements over what is aging what causes aging and that leads to some of the different theories that you alluded to, Like hyper function rate of living theory. Right again, I think we don't know enough to really be able to say with a high degree of confidence, you know, why did aging evolve? How did aging evolve? And what are all of the underlying mechanisms that are associated with biological aging? There's a lot to be learned. The last thing I will say on that though is we don't have to understand everything about biological aging to be able to have an impact on it. I think we know enough today that we can start to develop and test interventions that modify the biology of aging

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anyway that we predict will keep human beings and potentially companion animals healthier longer by targeting the biology of aging slowing it maybe even partially river some of the aspects of aging. So, I don't think we have to understand the whole thing in order to be able to have an impact on it.

Robert Lufkin, MD
Yeah, you've made the point in several of your presentation. So you've understood the point that aging is the single greatest risk factor for most of the chronic diseases that we face and small improvements in aging and longevity will dramatically multiply over all the chronic diseases. And so by that line of reasoning then, if we come up with interventions to improve longevity and aging, we should expect to see those interventions applied not only to the phenotype of aging and improvement, but also by the chronic diseases that determine longevity. So, and we'll talk about that in a moment as we get into one of the drugs here.

Matt Kaeberlein, PhD
Yeah, but I would say we already know that. I mean, the funny thing to me is people will sometimes push back against that. Well, you don't really know that. I'm like, yes, we do. We absolutely know about lifestyle change that will reduce your risk for all of the chronic diseases of aging and improve your function as you get older. So there's really shouldn't be any debate about whether the biology of aging exists and whether it's modifiable. We already know you can do that. You can do that through exercise, you can do that through nutrition. Right? So, I think it's there's a little bit of a disconnect and some people just want to argue right, but I don't think we need to argue about this.

This is a solved question whether or not there is a biology of aging. I think the other way to think about it is you can also just look across the animal kingdom if you're at all skeptical that there is an underlying biology that regulates the rate at which animals age. Just look at dogs, right? Everybody is familiar with the idea that, you know, one human year is about seven dog years. All that means is dogs age about seven times biologically faster than people do. They get all of the same diseases of aging that we do, they're all age related in dogs. They get all of the same functional declines that we do. It just happens about 7 to 10 times faster in dogs than it does in people. And that's 7 to 10 depends on body size. So there's clearly this biology of aging and it is determined by genetics and environment. And if we can understand what those genetic and environmental factors are, we can modify them in ways that will improve aging. Trajectories. Keep people healthier longer. Probably alive longer as well.

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Robert Lufkin, MD
So let's talk about wrap a mission. What is rap a mission And why is it important for our understanding of aging and longevity?

Matt Kaeberlein, PhD
Yeah. So wrap emissions. It's a small molecule drug that was first discovered on easter Island, also called Rapa Nui. That's where the drug gets its name from. And it's produced by a bacterium found in the soil there. And we know the biochemical mechanism of rapid and it's it's a small molecule inhibitor of a protein called M. Two or M. Two or M. T. O. R. Actually stands for mechanistic target of rapamycin. So they named the protein after the drug. So rapid missin inhibits M two or so. I think really the question to answer is what is enter and why is it in so enter plays this fundamental role in every eukaryotic cell that we know of. So again for people who maybe haven't taken biology for many, many years right there are bacteria which are typically pro chorionic cells. And then there are eukaryotic cells which are all the cells in our bodies and and and in all animals.

So every eukaryotic cell that we know of has enter and enter plays this fundamentally important role or or one of its roles is in sensing the environment and then helping the cell or the organism make a decision about whether the environment is suitable for growth and reproduction. And one of the main things that enter censuses nutrient availability in the environment. And so from an evolutionary perspective this is really important. Every organism that has ever existed has had to do this has had to sense the environment, sense how much food is available and then make a decision. Is it a good time to grow and reproduce or not? And when there's lots of food around from an evolutionary perspective, that's usually the successful strategy is to grow as fast as possible develop, reproduce because you want to have babies when you have food to give them the flip side of that is when there's not much food around, it's a bad decision to have babies.

And so what it does is it senses the amount of food and the environment and then when there's lots of food around. Em targets turned on and that tells the cell in the organism. Okay, now's a good time to grow and reproduce when there's not much food around. Em targets turned down and that tells the cell in the organism. Okay, we need to shut down growth and become stress resistant. And the mechanisms are pretty well known for how this works. But fundamentally that's kind of the important gatekeeper role that tor plays. So wrap a mission. Is this drug that that tells tor to get turned down To sort of ignore the nutrient sensing cues and get turned down regardless of how much food is around and what we and many other people in the field sort of found out, many many years ago this was back in the early 2000s when several of us sort of

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independently and in our case accidentally discovered that when we turned down tor we increased lifespan. And at that point Brian Kennedy and I were working in you Pankaj papa, he was working in flies, a couple of other labs working in c elegans and all of us independently found out that enter was this really potent regulator of lifespan and all of these different cellular and animal models. And then around 2009 study from the interventions testing program showed that turning down enter and mice and in that case they used Rapa missin was enough to increase lifespan in mice. So this picture emerged that across a very wide range of different organisms from single celled budding yeast all the way up to mammals like mice, you could turn down enter and that was enough to increase lifespan.

And in mice. What we've learned since then is you can do this starting in middle age, which is really interesting and we can talk more about that and that you're not only increasing lifespan but in pretty much every tissue and organ where scientists have looked, you can improve function during aging. So it's not only that they're living longer, but you're actually maintaining function of tissues and organs much later in life. And what's really exciting to me is that in at least some cases you can reverse functional declines that have already happened with old age. So in my lab we've shown this in the oral cavity, we can reverse periodontal disease with rapid mice and mice. Others have shown that you can reverse immune dysfunction. Age associated immune dysfunction in mice.

Others have shown you can reverse ovarian dysfunction. Others have shown you can reverse cognitive decline. So, and I keep saying others, this is the other great thing about rap and it's not one lab, it's not only one lab doing this work, there are dozens of different labs around the world who all get the same answer. And so that provides a lot of confidence that this is a real and robust effect that is highly reproducible. And you know, having been in this field for a long time. I'll just say that's often not the case with a lot of what gets popular attention. It turns out to not be highly reproducible. Everybody agrees enter and wrap a mission is a robust and reproducible target to modify the aging process in a positive way.

Robert Lufkin, MD
Now. M Tour let me get this straight is the arguably the single most important signaling molecule protein in the animal kingdom conserved biologically over billions of years. And it wasn't discovered until 1990 and 90.

Matt Kaeberlein, PhD
I'm hesitant to state it quite that way. So here's the way I think about it. So look personally I agree with that but I don't say it that way. But I actually I think the way I would, the way I would frame

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it is we know that enter is a key node in this network of interacting proteins. Right? And so other things in that nutrient and growth promoting network includes things like insulin like growth factor one growth hormone, insulin fox. So transcription factors, there's a bunch of important factors in this pathway. It just turns out that there are that some of them seem to be more amenable to to modification in ways that have a positive impact on health span and lifespan and enter seems to be a particularly good node in this network to tweak to positively impact health span and lifespan at least in in laboratory animals now you're asking why wasn't it discovered Or at least in the context of aging.

Wasn't discovered till until the early two thousands. And even before that was sort of understudied, you know, in the sort of broader biological world. I mean sometimes that's just the way these things evolve. Right? So part of the res and why enter became highly studied. And we learned a lot about it was because of this accidental discovery of rapa mission. Right? So again, the and and people, I think, I think a lot of times the general public doesn't appreciate how much of science is serendipity, right? It's not so much that we are really smart a lot of the times and go find the answer is that, you know, we're doing experiments and something unexpected happens. And it's those unexpected things that then lead to the big discovery. And so this molecule rapid mission was discovered.

Nobody knew how it worked. But what was observed was you put it on cells and they stopped growing. And so people thought, oh that might be a really useful anti cancer drug or a really useful antifungal. I wonder how it works. And so people started doing biochemistry and genetics to figure out when we put on these cells, why did they stop growing? And that's how people identified tour. And then once once tour was identified then many, many labs started studying it and we learned lot about how it interacts with all the other players in that network. And the same thing was true with discovering the TOr and RAP were important for aging biology. You know, at least in our case we were doing what's called an unbiased genetic screen for factors that influence lifespan.

So it's not like Brian. And I went into this thinking, oh, tor must be really important for aging. It was because we had a tool that allowed us to look one by one at individual genes in the genome and ask which genes affect lifespan. And we got lucky that in the 1st 500 that we looked at torre was there. If it wasn't, it would have taken us longer to figure it out. But tor happened to be in that first set of 500. And we saw that when we turned down tour all of a sudden lifespan was extended. And then, you know, I was like, well, what's Tour? I didn't know anything about tor. And it turned out there was this drug that inhibits store and well, maybe wrapping my son would have the same effect. So, you know, it's really this serendipitous sort of process that led us to

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discover that rapid mission could increase lifespan. And I think that's probably true for these other labs that we're looking at as well. Around the same time

Robert Lufkin, MD
You mentioned that caloric restriction is reliably the most reliable way to improve longevity over the years. And in studies. And now intermittent fasting is getting a lot of publicity on that. How does wrap a mission work? You know, suppressing m tour as nutrient sensing compared to caloric restriction or intermittent fasting. Are we looking at the same mechanism there?

Matt Kaeberlein, PhD
Really good question. I would say again. You know, there's a little bit of debate about to what extent does wrap a mission mimic caloric restriction. So here's the way I think about it. They are overlapping but distinct interventions. So We know that one of the most potent things that caloric restriction does is turns down. And this gets back to what I was talking about before. The nutrient sensors. So when people or animals fast or are chronically calorically restricted interactivity goes down. And we know wrap a mission turns down the difference I think arises from the fact that caloric restriction does about 10 million other things. In addition to turning down enter while wrap a mission is a very specific. Now there are lots of effects of rapid mission that are downstream of them because it regulates a bunch of stuff.

But caloric restriction in some ways is what I would call a much dirtier drug. It has many, many other effects that rapid mission doesn't have. And I think it's still an open question. You know, to what extent are the effects of caloric restriction on lifespan and health Spahn in laboratory animals due to inhibition of versus non m Torres. And then there's this interaction between these other things that caloric restriction does, that happens in the context of being turned down and that still hasn't been figured out. I think there are a couple of things to say about caloric restriction and fasting though that most people don't appreciate.

So caloric restriction is definitely the most robust and by robust. I mean the largest effect size intervention for increasing lifespan. And you could argue health span a little bit. But I'm just gonna make a blanket statement that's not completely precise that arc restriction improves health span in laboratory animals as well. It has the biggest effect. I don't think anybody would argue that for non genetic interventions you can get up to about a 60% increase in lifespan in mice if you restrict calories by 60%. What's often not talked about or appreciated is in about one third of genetic backgrounds where caloric restriction has been tested. It has no effect on lifespan or actually shortens lifespan. So there's a genetic component to whether or not. And again, this is in mice. Whether or not caloric restriction increases lifespan. The fasting sort of

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myth that people don't understand is in laboratory animals at least fasting only increases lifespan if the animals are also calorically restricted if you do intermittent fasting in an ice? A caloric setting. The impact on lifespan is somewhere between zero and 4%. So it's tiny. So there's this idea out there popularized by certain people that intermittent fasting is universally going to be good for health in humans. I think intermittent fasting is a very useful strategy for some people to lose weight or maintain weight. It's unclear whether or not intermittent fasting in the absence of caloric restriction. Does anything in laboratory animals or will do anything positive in humans? That's my personal view of the literature but just unfortunately gets communicated in a very misleading way. I think often for the general public this idea that intermittent fasting is this really potent way to target the biology of aging. That's only true in laboratory animals if you also restrict calories by between 30 and 50%.

Robert Lufkin, MD
So the given that as you mentioned in laboratory animal studies that wrap a missin not only in some cases slows the hallmarks of aging or phenotype of aging but in some cases actually reverses it. And given the fact that it can be delivered at least in the I. T. P. Model at middle aged mice rather than a lifetime exposure. And this is in animals. Now what is the push back to people using that for humans? Obviously more work needs to be done but why aren't more people aware of the potential of this drug?

Matt Kaeberlein, PhD
So I think you know I would say there are really two things that are a barrier to sort of more wide understanding and maybe use of rapid mice. And I think we need to be honest, right. We still don't know Inhumans whether or not Rapid mission is going to have the same effect on lifespan and health spa that it does in mice. I think we could talk, we could probably spend an hour talking about the data around that but we don't know for sure right. There haven't been double blind placebo controlled clinical trials or at least very many of them to try to answer those questions. So there are really two things I think that have been barriers.

One of them is that wrapped in the clinical world. It goes by the name Sarah llamas or Rapamune has sort of a bad reputation because of the way that it was developed and approved by the FDA. So wrap a mission against Sarah llamas Is an FADA approved drug. It's been approved I think since 1997, something like that 20 plus years and it was approved as an organ transplant drug. So at high doses daily doses, rapid mission will help patients who have had an organ transplant in combination with immunosuppressants, not reject that transplanted organ. So that's how it's been used. And in that context there are a long list of side effects that go along with taking rapid mission. So it has sort of a bad reputation among clinicians and it has a bad

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reputation at FDA as a drug that has lots of side effects. So I think that's been that's been one of the one of the real barriers to people, even psychologically thinking about rap a mission as a is a drug that healthy people are healthier people, people who are aging normally, maybe, let's say not organ transplant patients might take to modify their biology of aging in a positive way. There's a lot of pushback against that because the gut reaction is that's a dangerous drug. Right? So I think that's one thing, the other thing is that it's really, you know, in the timeline of scientific discovery fairly recent that we've learned about these effects of rapamycin on health span and lifespan, even in laboratory animals, like mice.

Right? The first study for lifespan was 2009, I think the first study showing that you could increase lifespan with a short term transient treatment with rapamycin Came from my lab and that was in like 2000, I should remember this 2,016 maybe when that was published. So, you know, in the timeline of science, this is all happening really, really recently. So it's only started to become appreciated. You know, how widespread the effects are in different tissues and organs and that you don't necessarily have to start taking the drug as a teenager if you are a person and we extrapolate from mice to get some of these effects.

So we're learning a lot in the last few years and there are probably now you know somewhere between 1000 and 10,000 people around the world I would guess who are taking rapamycin off label for potential effects on health span and lifespan. And I know you've been involved in trying to collect information from some of these people. I've been involved in that as well. To start to try to learn you know anecdotally. It's going to be imperfect data but start to try to learn what are the real side effects look like? What may be the real benefits look like for people who are taking rapid missin. You know with the idea that it might have a positive impact on their health span.

Robert Lufkin, MD
Several other of our interviewees have mentioned biological clocks sort of D. N. A. Epigenetic methylation clocks. It's always hard to get longevity data on human beings. What's your what have these been used with rapper mice and what's your take on that? Are they valuable?

Matt Kaeberlein, PhD
Yeah so I would say I mean I think it depends on the, so this word clock is sort of a catch all for biomarkers of longevity or biomarkers health and that's really what we're talking about. Can we use different phenotype to assess whether or not somebody is aging at a different rate. That's the ultimate goal and a variety of different types of data have been proposed as useful biomarkers or clocks. So epagenetics is one, there's blood biochemistry. You can do that that correlates with future health outcomes. Is another I really like functional measures of aging. I

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think what's really important. So I would put those in the category as well. How well are you functioning? And there's a variety of different organ functional measures that you can do. There's physical functional measures. So I think the answer to your question though is conceptually, yeah, these things can be really useful. What we don't know yet is what are the best set of biomarkers to put into? You know what I think we all would really like, which is an integrative clock. That is telling us overall how well is somebody aging at the moment and maybe more importantly, how well are they going to age in the future? So it's pretty early days with these clocks. I don't I'm not convinced yet that we have biological aging clocks that are actionable.

And by that, what I mean is what I would really like is a test that I could take on myself or give to someone else and say if you take rapamycin and it moves the needle on this test up or down. That's a good sign and you should keep taking rapid mission if it doesn't do that, that's a bad sign. And you should stop taking rapid, that's what we really want, right? We want actionable tests that will allow us to make personalized recommendations for people to get them on the, you know, something closer to their optimal aging trajectory? I don't think we have that yet.

And I think, you know in some ways the marketing has gotten ahead of the science where you can there's a bunch of these direct to consumer biological aging tests that people can go by. I don't have a lot of faith in any of them right now that they're actually telling you information that's useful. I think we'll get there but I think it's a little. I think it was still a little bit early to know which of these tests are going to be most informative. That's something I'm working on right now and I'll probably be working on for the next couple of years is trying out some of these different biological aging and trying to get closer to some sort of you know, integrated signal that I feel confident about.

Robert Lufkin, MD
It seems like one function of em ter as a sort of a master survival switches to turn from growth when nutrients are present and then when nutrients are not sensed turn to sort of protection mode, turn down inflammation. Khafaji goes up all those things. Thinking about the mind and stress. One model for stress is that chronic stress I guess acute stress can be good for longevity but chronic stress shifts our bodies from growth to protection and that seems like that's opposite of what we want to do with them tour. Does that ring any bells for you or it's a little bit off topic. But

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Matt Kaeberlein, PhD
Well, so I think I mean I think you're right again conceptually from a general general sense that that's all true. I think this this word Strat this is a catch. All right. So that can mean a lot of different. I mean a lot of different things. So when when we talk about rap emission and turning down enter inducing a stress resistant state, what we really mean is that at least for certain types of acute stress, it makes cells organs, tissues less likely to be damaged by the stress. Right? So stress itself isn't a bad thing. It's the consequences of stress and the damage that it does to organs and tissues and cells that lead to the functional declines and diseases that we associated with with chronic stress. And so I think that we have to appreciate that turning up protective mechanisms that make cells more resistant to stress is part of the chronic stress response.

But it's not the only thing that's happening, right? So when you have, for example, you know, you're constantly exposed to radiation, let's just say you get exposed to radiation, your body, your cells are immediately going to turn on a protective response that helps keep those cells to the best of the cell's ability from being damaged that radiation. But if you keep being exposed to more and more radiation eventually you're gonna overload those protective responses and then you're going to accumulate damage. So the stress itself ultimately is what's going to drive the damage. But it's only when you overload the protective responses, wrap a mission in some ways, turns up the protective responses, but you don't necessarily have the stress itself driving that response.

So one way to think about it is your preconditioning maybe the cell and the tissue to be more resistant if it gets hit by the damage before the damage gets there. That's sort of hand. But I think that's part of what's going on. But again, I think the there are a variety of different types of stress response mechanisms and I certainly wouldn't want to suggest that wrap a mission is turning up all of them. Right. So I think we have a lot to learn about, you know, which protective mechanisms are being affected by enter and which are independent and how does that integrate with, you know, longevity and aging.

There's again, this goes back to what I was saying before. There's a lot we don't understand a lot to still be figured out. And even this idea of inflammation I think is complicated. Right? So, you know, we know that with aging there is an increase in increased amount of what we call sterile inflammation, which I think the easiest way to think about that is your immune system reacting to stuff that it shouldn't be reacting to. So we need our immune system, we need inflammation to respond to infections and things like that. But with age we get this dramatic increase in sterile inflammation which is your immune system, responding to things that it shouldn't be responding to. And wrap a mission is quite potent, knocking that down. So that's a good aspect

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of what rap a mission does. If you have too much suppression of inflammation though, that's where you get into the realm of immuno suppression, which is what rapid mission is used as an organ transplant patients. So there is this balance and this dose response with stress resistance and anti inflammatory effects where you know, there's a sweet spot where we would want to be that gives you the benefit without so much of the detriment. But we don't know exactly where that is. And if you push it too far, you may get into the point where you're actually having negative effects in addition to the positive effects? I think that's true with inflammation and immune function. I think that's also more generally true with stress resistance.

Robert Lufkin, MD
Is there any evidence for interactions between psychological stress and enter or rappa mice in any interactions there in the psychology space.

Matt Kaeberlein, PhD
So I don't know the specific answer to the question about psychological stress. So I'll say a couple things that I do know. One is that there's absolutely clear mechanistic connections between chronic psychological stress and the biology of aging. I think a lot of there's been several studies that have looked at chronic psychological stress and telomere shortening. Telomere shortening is one of the hallmarks of aging. Clear evidence that people who are under high levels of psychological stress tend to have shorter telomeres.

You can find many other connections where it seems clear that psychological stress can accelerate to some extent, the hallmarks of aging which is consistent with the idea that they're biologically aging more quickly. And when you think about it, that's not shocking. Right? Again, we know that people who are exposed or experience high levels of chronic stress throughout their lives tend to have a variety of poor health outcomes later in life consistent with the idea that they're aging more rapidly. So they're absolutely those connections.

And then there are these connections between wrap a mission and brain fun that I honestly don't understand but have fascinated me. So let me just put a little bit more meat on that. So we know that changes in brain function with aging right happened. There are declines in cognitive function, changes in cognitive function that happened during aging in some people that manifests itself as dementia or things like Alzheimer's disease, which is a subtype of dementia in animal studies. Rap emission is very potent at reversing or preventing some of those age related changes in brain function. That makes sense in the context of aging biology. But then there's this whole other body of literature on rapa Missin that's kind of evolved in parallel to the studies in the biology of aging, where rapid mission has potent effects on autism, for example, or on

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seizure related diseases. And I don't understand that. So let me say this, let me be careful how you say this. I speculate that there are mechanistic similarities to what rapid mission is doing in the context of dementia and normative brain aging and why rapid mission has these effects in autism and seizure disorders. But I don't know what those mechanisms are, but I speculate that they're important and probably tell us something really fundamental about how am torre's act in the brain that we don't currently understand.

And then there's this emerging sort of literature that I'm peripherally aware of on rapa mice in combination with some psychedelic drugs or things like ketamine where you get these really interesting interactions. For example, there's some evidence that ketamine that that rap emission potentially eight's the effects of ketamine on things like depression or pain. And again, I think that's going to be related to these observations that rapid mission has effects on autism spectrum disorders and seizure disorders, but I don't know what the mechanisms are yet. So I think there's a bunch to be learned there that we don't really understand right now. We're kind of at the observation stage where we see that there are these effects and interactions but we don't mechanistic lee really understand how it how they're working. At least I don't

Robert Lufkin, MD
Yeah, it's so many unanswered questions. I am reminded of Chris Palmer's work from Boston. He's a psychiatrist who's taking some of his Schizo effective disorder patients and on serious medications and he's putting them on a ketogenic diet, putting them into ketosis, not all of them, but some of them will respond to the point that their medicines are already dropped. And if you met, I mean you think turning into our down, just remove the glucose from the diet and switch to ketosis, you'll effectively turn into our down maybe that's a common mechanism. But who knows? Like you say we don't even we're just scratching the surface.

Matt Kaeberlein, PhD
I think there is something there though. So I'm glad you brought up the ketogenic diet because that also is quite potent and seizure related disorders. At least some patients. Right. So again, I think you're right, I think that enter is a common denominator there, that probably is important. But it's again, ketogenic diets kinda like caloric restriction in the sense that it's going to hit enter, but it's going to do a bunch of other stuff as well. And so you have to be careful not to say that all of the effects of the ketogenic diet or through some of them probably are. Yeah, I think the interactions with ketamine in particular are fascinating area that it will be interesting to see how this evolves. So you know, I have a colleague here in Seattle who's a psychiatrist who has been treating some of his patients with ketamine plus rapper mission and he's told me some really profound stories about improvements in his patients, particularly things like chronic pain. And

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it's reminiscent of what you were saying with the ketogenic diet where sometimes people come off of medications that they've been taking for decades, right? When they go on this combination, they don't have to take the chronic pain medication anymore. They have a strong antidepressants. So yeah, there's clear interactions there that are going to turn out to be really important. And it's fascinating to see how that evolves. And also whether or not to what extent are those related to the way that wrap a mission is impacting the biology of aging.

Robert Lufkin, MD
Yeah, there's so many projects to talk about. But one project that you're working on I wanted to mention because our audience can actually participate in it or at least their companions can, could you talk about the dog aging project. It's so interesting.

Matt Kaeberlein, PhD
Sure. So the dog aging project is a large scale what we call longitudinal stuff of aging in pet dogs, companion dogs. So what we are doing is really trying to understand the biology of aging in companion dogs with the goal of being able to help our pets live longer healthier lives. And so I can say, I think generally maybe the way to think about it, there are really two pieces to the dog aging project. This is an oversimplification, but it's an easy way to think about it. There's an observational study which is very, very large. We have about 40,000 dogs in the observational study right now. Any dog is eligible for the observational study, any age, any breed, any size. And the goal there is to understand what are the most important genetic and environmental factors that influence healthy aging in our pets. So if any of you have dogs, I'd encourage you to go to dog aging project dot org. There's a little button nominate my dog up in the upper right hand corner of the website, join the dog aging project pack.

And you will be part of what is one of the largest, if not the largest community science open science projects in the world with the goal of helping our pets live longer. The other piece of the dog aging project is to do something about the biology of aging. So we have a smaller double blind placebo controlled clinical trial of rapamycin in dogs to really try to answer the question, does rap emission increase health span and lifespan in And pet dogs. So to be eligible for the wrap of mice and trial dogs have to be at least seven years old between 40 and £120. And can't have any significant pre existing health conditions because it's a study of healthy aging. So if and we are recruiting for both the longitudinal study and the clinical trial. So again, if anybody's interested, please consider going and nominating your dog for the study. I'm obviously particularly excited and interested to find out, you know, to what extent does rappa mice and have an impact on healthy aging and our pets.

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Robert Lufkin, MD
Yeah. And you're, I know you're already mining that data. The dog, the dog trial data. I know 11 interesting observation you make was that dogs who were fed once a day versus dogs that were fed twice or three times a day had a different rate of chronic disease complications. Maybe I'm not summarizing that correctly. So that's safe for humans.

Matt Kaeberlein, PhD
Yeah, I mean, so, so first of all, let me let me just be a little bit precise. So, you were close. But again, I think it's really important to appreciate because this is an observational stuff. We were very careful about correlation versus causation that study that you're alluding to though the way that that the way that analysis was done, These are owner reported pre existing diagnoses of disease or conditions. And the question we asked was very simple. We thought dogs might be an interesting natural model of time restricted feeding because some owners feed their dog once a day, some twice a day, some three times a day.

Some actually feed their dog was called ad litem. The dog has free access to food. So the simple question was, are dogs that were the owners only fed them once a day? Are there any differences in the likelihood that those dogs were diagnosed with one of 10 different age related categories of disorders that included cognitive function, kidney disease? You go down the list and I didn't think this was going to work because I'm not a big believer in time restricted feeding, but as it turns out I was wrong. So, what we found was that That in all 10 cases, the Arrow direction of the effect was going towards dogs that were Fed once a day were less likely to have been diagnosed with any of these 10 conditions. And I think in six or seven of them, it was statistically significant in a couple of cases.

The effects were pretty big. So what that tells us is that, you know, this is now looking backwards and times had the dog been previously diagnosed with these disorders if the dog was fed once a day, the likelihood of a previous diagnosis was lower. Does that mean that being fed once a day caused them to not be diagnosed? We can't answer that. And here's where I think you do have to be careful because there are obvious potential explanations for this correlation. One being the dogs fed once a day compared to two or three times a day might be less likely to be obese. And we know that obesity is a predisposition for multiple age related comorbidity. So, we have to do more work to figure that out. But it is intriguing and it certainly may suggest that feeding your dog once a day means that it's less like your dog's gonna get any of these 10 Diseases or one of these 10 diseases. It may also suggest that this is a useful strategy in humans or at least in some people, but I think we have to be really careful not to jump the gun. It's a hypothesis generating

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observation that requires additional study to really get to definitive. I know that frustrates people, it frustrates me, but that's the reality of the situation. We can't say that there's causality there

Robert Lufkin, MD
So many questions, but not enough answers, but it is an exciting time Matt. Maybe you could tell people how they can reach you on social media, how they can sign up for the dog aging project if they like and how they can find your website.

Matt Kaeberlein, PhD
Sure. So my website is kaeberlein.org and I'm on twitter @MKaeberlein, So first initial last name. And then the dog aging project website is dogagingproject.org. I'm pretty easy to find online, so I'm sure if anybody really wants to find me, you can find me online. I certainly again will make the plug that if you have a dog and you love your dog and you believe in science, please consider participating in the dog aging project.

Robert Lufkin, MD
Yeah, very worthwhile and and and a very creative approach to adding knowledge to this space. So thanks again Matt for spending an hour with us today and sharing your knowledge and thanks also for all the great work that you do and in your lab and we're expecting great things from you in the future.

Matt Kaeberlein, PhD
Thank you. Thanks for having me. This is a great service that you're doing.

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