CUTTING EDGE Health

Welcome to the *Cutting Edge Health podcast* with Jane Rogers, where we discuss science to help prevent cognitive decline.

Jane Rogers: I am a dog lover and several years ago, I learned of the Dog Aging Project at the University of Washington. Using a drug called rapamycin, these dogs are living longer and healthier. Rapamycin targets the molecular causes of Alzheimer's. If it's helping dogs, could it work with humans? Dr. Matt Kaeberlein is the director of the Dog Aging Project, and he joins us to share what he's learned. Welcome, Matt, to the podcast. Thanks for your time.

Dr. Kaeberlein: Thank you. Yes, it's a pleasure to be here.

Jane Rogers: I have been a fan of yours for some time. Ever since I heard of the Dog Aging Project and I had a dog that now I know was too big, a Bernese Mountain Dog. You only take dogs who are more medium size, but at the time, I was so excited about what you were doing in your lab at the University of Washington. You've been on NPR, you've talked about this a lot, but can you, for people who don't know about the Dog Aging Project, can you tell them about it?

Dr. Kaeberlein: Sure. The Dog Aging Project is really what we call a large-scale longitudinal study of aging in companion dogs, in pet dogs. What that really means is we want to follow pet dogs over many years to really try to understand what are the most important genetic and environmental factors that influence aging and age-related health outcomes in companion dogs.

That's really the primary goal of the Dog Aging Project. One component of the Dog Aging Project, though, goes beyond just trying to understand aging in dogs and actually do something about it. That's the clinical trial, which we call TRIAD, which stands for Test of Rapamycin in Aging Dogs. The goal of TRIAD is really to determine whether or not the drug rapamycin can slow aging in dogs, increase lifespan, and increase healthspan.

What I mean by increasing healthspan is to really delay or push back many, maybe all of the declines in function that go along with aging and also the diseases of aging, which is, I think, what most people think about when they think about aging, they think about cancer, heart disease, dementia, kidney disease. Our goal is really to really try to push all of those diseases of aging back as far as possible in companion dogs in the Dog Aging Project, but then in the larger field of aging biology or geroscience in people as well. We're testing whether rapamycin can have that effect in dogs.

Jane Rogers: I can't wait to unpack this on what you're finding with dogs, but before we do that, rapamycin was a bacteria found on Easter Island, right? And it affects the mTOR protein.

Dr. Kaeberlein: Yes. Rapamycin is a small molecule produced by bacteria on Easter Island. The way this was actually discovered was that there were some scientists who were looking for novel antibiotics or natural products, and they were collecting soil samples from around the world. One of the places they collected samples from was Easter Island, which also goes by the name Rapa Nui, that's where rapamycin gets its name from.

What they found was that the bacteria on Easter Island that they had collected produced this effect, this molecule that could inhibit cell division, first in mammalian cells and culture, and then also in budding yeast, which are a type of fungi. They started studying this because they noticed that it had this effect. It was originally studied as an antifungal, and then as an anti-cancer, then, eventually, approved by the FDA for human use to prevent organ transplant rejection.

It's got an absolutely fascinating backstory to it, how this drug was discovered and brought off of Easter Island and developed, and then ended up in a freezer for several years, and then came out of the freezer and got studied some more. People are interested, it's really a cool story. Someday there will be a really, I think, interesting documentary on how rapamycin was discovered and developed, and, hopefully, how it was found to have the effect of slowing biological aging and increasing lifespan.

Jane Rogers: What originally got you into this? Why were you, all of us, into rapamycin? What keeps you going-- [crosstalk]?

Dr. Kaeberlein: I've been studying the biology of aging since I was a graduate student. I got interested in this idea that we could understand at a genetic, biochemical, molecular level what aging was and potentially do something about it. Then as a post-doctoral researcher-- A postdoctoral scientist is somebody who's just gotten their PhD and it's sort of an additional period of training that most people go through before they start their independent academic career if they stay in academia.

I was a postdoc, and we were doing what we call an unbiased genetic screen for genes that affected lifespan. One of the genes that we found was mTOR, and so I didn't know a lot about rapamycin before that. What we did was we found, really by luck and accident and being in the right place at the right time, that if we knocked down mTOR itself, we could extend lifespan.

What did I do? I went to the version of Google that was around at that time said, "What do we know about mTOR?" It turns out there's this drug, rapamycin, that's a specific inhibitor of mTOR, and so that led me to think, well, maybe rapamycin would have the same effect, would increase lifespan, and it turned out it did.

It sometimes happens in science, it turned out that three or four other labs right around the same time had also converged on mTOR. There were three or four of us that published papers between 2004 and 2006 in different animals, showing that if you inhibit mTOR, you could increase lifespan and slow aging. That really is what set the stage for where we are today, where now we know that rapamycin is pretty much the gold standard for a longevity drug.

What I mean by that is it's the most reproducible and most effective way to increase lifespan and increase healthspan across many different laboratory animals. We still don't know for sure that it will have the same effect in people or in companion dogs, but that's what the field is figuring out right now.

Jane Rogers: Now, mTOR, it's exciting because it's like the powerhouse of the cell. It's the general contractor of a cell, right?

Dr. Kaeberlein: Yes. You've got to be careful what you--

Jane Rogers: If you could rejuvenate mTOR, you've got-- that's a positive for aging.

Dr. Kaeberlein: Yes. You have to be careful with calling it the powerhouse of the cell. That's the mitochondria. We don't want to usurp the mitochondria. I'm joking, [crosstalk] but that's the colloquial way that people refer to mitochondria, which are important in aging, by the way. The way you could think about mTOR, it's a really important regulator of cell growth and organismal development.

One of the ways I think about mTOR is-- and it's conserved in every, what we call eukaryote. Basically, every animal on the face of the earth, every organism that's not a bacteria has mTOR. It's very highly conserved throughout evolution. The way I think about mTOR is if you think about fundamental decisions that every organism or animal has ever had to make, one of those fundamental decisions is, is it a good time to reproduce? An important factor in making that decision is whether there's food around.

It's not a good idea to have a bunch of babies, no matter what kind of organism you are, if there's no food around. An mTOR is really the central decision-maker that helps the cell or the organism evaluate the environment, especially the nutrient levels in the environment, and determine whether or not it's a good time to grow and reproduce.

If there's lots of nutrients around, mTOR's turned on, it gets activated, and that sends a signal that it's a good time to develop quickly, have lots of babies, pass your genes on to the next generation. mTOR really makes a lot of sense if you think about it from the perspective of natural selection and evolution, because that decision has to be made well, or your genes aren't going to get passed onto the next generation. You're not going to be evolutionarily successful.

Why is this important for aging? Well, it turns out that one of the things that happens in the context of biological aging is, post reproductively, those same signals grow and reproduce. Once you've already reproduced, continuing to have those signals on at a high level leads to many, maybe all of the functional declines in diseases that go along with aging.

There's this idea that, to some extent, aging is the continued activation of mTOR at a suboptimal level post reproductively that drives all of these different diseases and declines in function. So, consistent with that, if we inhibit mTOR in adults, again, at least in laboratory animals, we can delay those diseases of aging, increase lifespan, and actually, in some cases, actually restore function that's already been lost, which is pretty exciting from a therapeutic perspective. It's not only about slowing down the decline. In some cases, we might actually be able to reverse some of the decline.

Jane Rogers: The community that listens to this podcast were concerned about preventing Alzheimer's. I know with the Dog Aging Project, you've done a lot of work with dogs. Can we really jump that bridge and say, okay, this is something that's got potential for humans because we haven't had a good clinical trial on this yet for humans?

Dr. Kaeberlein: Yes, absolutely. No, that's absolutely true. I think there's reason to be optimistic that rapamycin can be a very powerful preventative for not just Alzheimer's disease, but other types of dementia as well. We know a lot about the biological mechanisms that at least precede dementia and Alzheimer's disease, and we know that rapamycin can have an impact on those mechanisms. We could talk more about that if you'd like to in a few minutes.

The other thing we know is that in mice, there's a lot of debate about whether mice can be used as a good model for Alzheimer's disease because, mice, during normal aging, don't get true Alzheimer's disease, but they do show cognitive decline with age during normal aging. The cool thing about rapamycin is that in the mouse models it's been shown in basically all of the major mouse models of Alzheimer's disease to be beneficial. It's also been shown to delay or prevent normal age-related cognitive decline in mice.

This is why I think it's a better bet than things that just affect the Alzheimer's disease models in mice because those Alzheimer's disease models are missing the normal aging component, the changes that go along with normal aging. If you think of all of the different diseases of aging, Alzheimer's disease is one of the strongest in terms of risk as a function of age.

Your risk of getting Alzheimer's disease goes up dramatically exponentially as you get older. There's clearly an underlying normal aging component that creates a permissive

state for dementia and for Alzheimer's disease. I think there's lots of reason to believe that rapamycin can be beneficial as a preventative for Alzheimer's disease and other dementias. I'm a little bit less sure whether rapamycin will be beneficial once a diagnosis of Alzheimer's disease has been made. That's a much heavier lift as you can imagine to have a benefit once the pathology's gotten to the point where it's been diagnosed.

Jane Rogers: I made a decision in December to try rapamycin, in large part, because of the research you've been doing, and I have seen good benefits personally. I only take it once a week. I take 6 milligrams once a week, and that's part of this theory, isn't it? That you want to have a peak in the levels of your body and then let it drop down into a trough and you don't want to take it every day, right?

Dr. Kaeberlein: I think it depends. You're right. That is the current thinking for age preventative effects of rapamycin. That once weekly is a good strategy as opposed to daily. Partly this is driven by, like you said, the idea that you want to get very high levels of rapamycin early on, which will be strong. Remember, rapamycin is an inhibitor of mTOR, and actually, for the aficionados out there, it's an inhibitor of mTOR Complex 1 or mTORC1.

You want to get high inhibition of mTORC1 right after you take it, but then you don't take the next dose until the rapamycin has been cleared from the blood, which allows mTORC1 activity to come back up to normal level.

This gets back to what I was saying earlier about the idea that aging may be partly driven by too much expression of mTORC1 chronically. What you're doing by once-weekly rapamycin dosing, is you're inhibiting it. Transiently, there are all sorts of effects associated with inhibiting mTOR Complex 1, many of which are beneficial, but some of which, in the long run, probably aren't beneficial, but by allowing mTORC1 to come back up, you can allow the system to reset itself before you do that next dose.

The other thing that this is driven by is actual clinical data in people where we know that in organ transplant patients who would take maybe a few mgs of rapamycin, but that would be every day that in that daily dosing of rapamycin, you actually get some off-target effects on mTOR Complex 2. By doing the once-weekly dosing, you avoid some of those off-target effects.

There's a model that those off-target effects are what lead to the side effects that are seen in organ transplant patients. I think the data-- Again, it's early. There are probably a few thousand people around the world right now ike you, maybe more, but at least a few thousand who are doing this once-weekly rapamycin dosing around 6 mgs.

We're starting to get data from those people. It seems to be consistent with the idea that that sort of a protocol the side effects are minimal. Very, very few people have any real side effects at that dose. A lot of people report anecdotal benefits like it sounds like you feel like you've experienced. So far so good, I would say.

One of the projects I'm involved in is actually trying to collect data by survey from people who've been taking rapamycin to really try to get more information on both what are the real side effects that might be being experienced and what are some of the effects that people feel like they are experiencing from this dosing with rapamycin? I think we're going to learn a lot in the next couple of years.

Jane Rogers: I guess I jumped on this because my family has a history of Alzheimer's. My dad passed with it, my mom's in memory care now, and I started showing signs of cognitive decline myself at the same age as my dad in my mid-50s, and it scared me. I went out, trying to find research like yours to say, what can we do? It's cutting-edge, and it's maybe a little out there to be taking rapamycin now before all the clinical trial results come in before you've done your study and experienced what's happening with other people. I think it's worth it based on what you're seeing with dogs.

Dr. Kaeberlein: And with people. There are, actually, two relatively large clinical trials that were done by a company called resTORbio with a derivative of rapamycin. These are called rapalogs, but they work exactly like rapamycin. They were testing a derivative of rapamycin in healthy older people for effects on immune function. What they found in both clinical trials was that the people who got the mTOR inhibitor actually showed a better response to a flu vaccine, which is based on exactly the same data in mice.

At least for immune aging, it really looks like rapamycin probably has similar benefits in people as what's been seen in mice. There's a bunch of different lines of evidence, I think, that all, again, consistent with the idea that at least some of these effects of rapamycin on aging that have been seen in all the laboratory animals will also be seen in companion dogs and in people.

The unknowns at this point in my view at least are, what are the right doses to get those effects? Will it be as broad in terms of the effects on aging as what's been seen in mice, or will it be more specific to certain age-related declines or diseases in people and dogs? Again, I think we'll learn a lot more about that in the next few years.

I also want to comment on something you said, which I think a lot of people, especially people who maybe haven't heard much about rapamycin will have exactly the opinion you had, it's edgy, it's a little bit risky to be taking rapamycin, and it is. I think we have to recognize, it is an unknown, it hasn't gone through double-blind placebo-controlled trials for this purpose, so we don't really know what the efficacy is. How well is it going to work?

In terms of the side effects, again, everything has a risk, but I think people don't really weigh risk-reward in a rational way when we think about things like rapamycin. What I mean by that is we've been trained by the culture and the way our government regulates medications to be very concerned about side effects. I'm not saying that's a good thing or a bad thing, but it's the truth. We are trained to really worry about if it's a prescription medication, what are the side effects?

Yet we pay absolutely no attention to the risks associated with supplements, which haven't been tested, in many cases. Haven't gone through any FDA process. We pay no attention to the risks of dietary interventions. I always try to make this point, if you think about the effects of something like a Ketogenic diet, and actually, I like Ketogenic diets, I'm not picking on Ketogenic diets, but if you think about the effects, the biological consequences of a dramatic change in what you're eating are far more widespread and far more profound than the biological consequences of something like rapamycin, and the risk of side effects is much higher.

Probably not side effects that are going to kill you. Although, it could, certainly, if you took nutritional changes to the extreme. I'm just trying to make the point that I think many people, and even the way we think about and regulate medications could benefit from a little bit more rational thinking about what are the real risks associated with the different interventions that we might employ to improve our health? Then don't even get started with the stuff that people do that aren't good for ourselves like alcohol consumption, or too much alcohol consumption, or smoking.

As a society, we really don't take a very rational approach to risk-reward analysis. All of this is just to say, in my personal view, the risk associated with the kind of rapamycin regimen that you're practicing is really pretty low, lower than a substantial dietary change, way lower than smoking or overconsumption of alcohol.

Jane Rogers: Thank you. That makes me feel better. [chuckles] I appreciate it. If someone is listening and saying, "Whoa, I've got the Alzheimer's gene, I have this in my family, rapamycin is something I might want to consider." It's, A, hard to get, and, B, it's expensive. It's a real investment. What do you recommend?

Dr. Kaeberlein: Number one, I'm not an MD, I don't recommend anything.

Jane Rogers: That's right.

Dr. Kaeberlein: I do recommend that people who are interested, potentially, in learning more about rapamycin or taking rapamycin, if at all possible, find a medical doctor who will prescribe it for you. I know there are people who get rapamycin from offshore pharmacies without any medical supervision. My advice would be to do it under medical supervision. There are a growing number of MDs who are comfortable with evaluating

people and determining whether something like rapamycin is the right choice for those people.

There is a website, rapamycin news, you can Google that. They have a list of MDs who are prescribing rapamycin. It's not as difficult as it used to be to find a doctor who is knowledgeable about rapamycin and who is willing to prescribe it.

I think, unfortunately, it is expensive, and it's more expensive in the United States than in other parts of the world. That's a reflection of a lot of stuff that's above my pay grade, honestly. Unfortunately, the way that we handle healthcare in this country is a mess, and prescription drug prices reflect some of that. There are all sorts of lower-priced options that are out there once you've got a prescription, and so shop around, I would say.

I think as long as the rapamycin that you're getting is coming from an international, multinational pharmaceutical company who's producing it, it's probably going to be just fine in terms of quality. I know there's a lot of concerns about the quality of drugs from different parts of the world. It's my impression that most of the drugs are made in the same places, and then they're just packaged differently, so I'm not personally so concerned about that.

One thing I will say, don't buy the powder and try to take it. I know people who've done that, and it's not a good idea. Get a real pharmaceutical formulation of rapamycin. Rapamune is the gold standard, but anything that says sirolimus on it and it comes in a triangular tablet, is going to make good manufacturing practice.

Jane Rogers: We could go a lot of different directions from here. I want to ask you so many questions. We haven't really dug deeply though into what you are seeing in dogs and hopefully people too, but dogs, especially, what are the areas that rapamycin is helping? I made a list that I have seen, and one of them was exciting. What happens with a dog who might have some heart problems, and you're seeing that rapamycin really helps a dog with heart problems to improve?

Dr. Kaeberlein: The one thing I would say is, yes, we have seen that, and I'll tell you about that data in a minute. I think it's important to make a disclaimer that the studies we've done so far, we've done two clinical trials. They've both been very small. The clinical trial to really answer the question how effective rapamycin is at extending lifespan and improving health is happening now.

I view the data that we've gotten so far as, in some ways, preliminary data. You might think of it like a phase two clinical trial for human drug development. It's intriguing, suggestive, not definitive. In terms of heart function, what we saw-- First of all, just to take a step back, what we knew from the mouse studies, multiple labs have now seen this.

If you take a mouse and you just allow it to age normally, and you give it an echocardiogram, which is like an ultrasound for the heart, what you will see are very characteristic changes in the function of the heart that are part of the normal aging process. Declines in function in different chambers of the heart that can be seen by ultrasound.

In our first trial, we gave the dogs echocardiograms before and after rapamycin treatment, and what we saw was-- if you looked across all the dogs that got rapamycin and you compared them to the placebo dogs, so all of our studies are double-blind placebo-controlled randomized clinical trials. The dogs, on average, who had gotten rapamycin, had an improvement in heart function by these echocardiographic parameters compared to the dogs that didn't get rapamycin.

The interesting thing there is that on average, if you look at the individual dogs, what it really looked like was the dogs that came in with lower heart function were the ones that got the benefit. The dogs whose hearts were still functioning fine showed no change with rapamycin treatment. The dogs who had low function were the ones who got the benefit. That's suggestive that rapamycin was having similar effects in dogs as to what had been previously seen in mice. We're looking at heart function in the ongoing clinical trial.

The other thing that I think I feel pretty confident was probably a real effect, because we saw this in both of the trials that we've done so far, was that the owners whose dogs got rapamycin, without us prompting them really, said that their dogs were more active compared to the owners whose dogs had gotten placebo. Again, the owners didn't know whether their dog was getting rapamycin or placebo until the study was done.

I think it's probably a real effect of rapamycin. What that actually means I don't think we know yet. It might mean that the dogs had less arthritis. It might mean that they were in less pain. Could have had an effect on something in the brain. We don't really know the mechanism, but I think that was a real effect, that the dogs who got rapamycin showed an increase in activity over the course of the study that the owners picked up on.

Jane Rogers: That's encouraging. One of the things that I thought was encouraging, especially with the gut-brain connection, was how you're finding that rapamycin changes can change the microbiome in a dog's gut.

Dr. Kaeberlein: We haven't done it in dogs yet. I think you're thinking of the mouse study that we did, that was really interesting. What we found there was that 12 weeks of rapamycin treatment in mice-- 8 to 12 weeks, we've done a couple of different experiments, was enough to remodel the gut microbiome. Interestingly, that also remodels the oral microbiome. A lot of people don't realize this because most of the time when you hear about microbiome, you think about the gut, the microbes in the gut.

We have a different microbiome in our mouth, and we have a different microbiome on our skin, and there are other communities of microbes.

We haven't looked at skin yet. I bet rapamycin would affect the microbiome on the skin as well. In the gut and even, in a more pronounced way, in the mouth, the oral microbiome, we actually saw that there's a change that goes along with aging in the composition of the microbiome. At least in the mouth, rapamycin actually reverts the composition of the microbiome back to something more like a young microbiome.

The gut microbiome was more complicated, so I can't make a definitive statement about a reversion back to a youthful microbiome, but in the mouth, that's really what it looked like. At the same time-- This is all in mice, at the same time, it reversed clinical signs of periodontal disease in the mice. It regroups bone around the teeth, and it reduces the inflammation in the gums.

We're really intrigued and excited about the idea that aging of the oral cavity might be a particularly good endpoint to look at in people for effects of rapamycin, because it's pretty noninvasive, and dentists are very good at measuring inflammation of the gums, that's gingivitis, and bone around the teeth by x-ray or by pocket depth that's periodontitis.

We can actually do a clinical trial and see whether rapamycin is having an effect. My colleague here at the University of Washington, his name is John Hon, actually got a grant to do this clinical trial. I'm really, really excited to see how that comes out. He's in the dental school here, he's a dental PhD. He has a PhD. He was one of my graduate students. He got it in my lab, and he has a DDS, so he is a dentist. He's really well-positioned to actually answer this question.

Jane Rogers: How about stem cells? Have you seen any kind of effect on stem cells in mice or dogs?

Dr. Kaeberlein: Again, we haven't really looked at it in dogs, so one thing that we always have to keep in mind in our studies of dogs, they're all in companion dogs. These are people's pets. The kinds of things that we look at need to be relatively non-invasive and need to be something that can be queried in a typical veterinary office or a veterinary teaching hospital.

Some of the more specialized stuff, it's just much more difficult to do in companion dogs. In mice, both in my lab and several other labs have seen that if you treat old mice-- First of all, again, you always have to think about this in the context of normal aging. If you look at an old mouse compared to a young mouse, and most, maybe all, but certainly most tissues, you will see a decline in stem cell function with normal aging.

In multiple tissues now, people have seen that if you treat mice with rapamycin for between 6 to 12 weeks, you see improvements in stem cell function in many different tissues. The one that excites me the most are hematopoietic stem cells. These are the stem cells that see the immune system. We know that immune dysfunction is a real problem during aging in people. Just look at where we've been for the last two years. If we had a way to rejuvenate immune function in older people, that's really, really important.

Jane Rogers: That's big.

Dr. Kaeberlein: Yes. It's important, not only for the obvious reason, like COVID-19 or influenza but one of the most potent anti-cancer mechanisms we have is our immune system. That's probably one of the big drivers of why we see a big spike in many cancers as people get older, it's because their immune system isn't doing as good of a job at clearing out those cancers early.

If we can boost the immune system, we can have an indirect effect on age-related cancers, and that's what's seen in mice with rapamycin. It's pretty exciting. We know something about the mechanisms for how rapamycin is probably affecting stem cell function in many different tissues, and so it makes biological sense that it would have that effect.

Jane Rogers: Look to the future. You're young, this is an exciting time for research in your area. You are young. Where do you think it's going to go? Where do you think you're going to see?

Dr. Kaeberlein: I expect that we will see the first true clinical applications of what I call geroscience. Stuff that's been learned about the basic biology of aging in the laboratory making its way into the clinic, and that'll be the veterinary clinic and the human clinic. That, for me, is really exciting because that's been something the field has been working towards for decades.

We're finally at the point now where we have interventions like rapamycin that are being tested, and some of them, I think, will show efficacy in clinical trials, and then you'll really see uptake by the clinical community.

The other thing that's super exciting is that there is a growing recognition among many different stakeholders, including funders and philanthropists, that science has gotten to the point where big investments are needed. We're starting to see influxes of resources into the field that will drive the research and drive clinical development. I think things will start to accelerate.

In terms of rapamycin, again, it's speculative how these clinical trials are going to come out. I would be very surprised if we don't see evidence for at least some age-related endpoints that rapamycin is beneficial in both dogs and people.

Again, I don't know if it's going to broadly affect aging. I don't know if it's going to dramatically increase lifespan, but I think we will see endpoints where rapamycin is quite effective, and, in particular, disorders that are driven by chronic age-related inflammation. In the context of dementia and Alzheimer's disease, there's a growing recognition that inflammation of the brain is a contributing factor to dementia and Alzheimer's disease. I think rapamycin will be quite effective at knocking that down.

I think we will see that over the next couple of years, and we'll start to get a better feel for what the right dosing strategies are. Again, this goes back to your comment that it's a little bit early, it's a little bit edgy. That's true. We don't know yet, is the once-weekly 6 mgs once a week. Is that the right dose? Is that the optimal dose? Certainly, it's going to be personalized at some point, optimal dosing in different people is going to be different. I think we'll learn more about that over the next few years, but my expectation is we'll see benefits from rapamycin.

I think that it will become a household word in the next five years if I'm right. If we really do start to see these benefits. I also would say rapamycin it's the first best shot on goal right now. There's going to be better things coming down the pipeline. I don't want to make people think rapamycin is a miracle drug. It's not. In the sense, it's not a fountain of youth. I think better things will come along as the research continues to progress.

Jane Rogers: I have to ask you about your own personal regimen to slow aging. What are you doing?

Dr. Kaeberlein: I try to do the stuff that we all know we should do. I'm not perfect by any sense of the imagination. I try to eat a relatively healthy diet. Honestly, I think for most people, you can get 75%, 80% of the way there if you can eat a relatively healthy diet, exercise regularly, sleep well, and this is a harder thing, sleeping well is hard. That's a hard thing. On top of that, which is even harder, be emotionally and mentally balanced.

I think if you can do that, you're most of the way there, and then things like rapamycin will get you that other 20%. With the exception being, if you have a genetic predisposition to an age-related disease that will predispose you to Alzheimer's disease and dementia. You can do a lot even if you have that genetic predisposition though, by diet and exercise and lifestyle and sleep.

That's what I try to do. I try to focus on those, some people call them pillars. Most of my attention is there. I try to eat a relatively healthy diet. It's been a journey, but I have learned that for me a relatively low carbohydrate diet works really well in terms of how I

feel, how much energy I have, and how much mental clarity I have. That's the other thing, one size does not fit everybody. I think we should be honest about that, but for me, that works pretty well.

I try to eat a healthy diet. I exercise regularly. Again, this works really well for me, and I think it's probably true for most people. I would say resistance exercise, weightlifting, is more important than cardiovascular exercise, or it's at least equally important in the context of aging. Loss of muscle mass drives many, many problems in the elderly. The best way to stop that from happening is to do resistance training.

I try to get lots of sleep. I'm one of these people, I'm lucky. So far, my sleep quality hasn't declined with age. I'm just naturally an optimist, so, again, I feel like I'm pretty balanced in terms of the way that I deal with stress. I don't get stressed out, but whatever you can do to help yourself there. Those are the things I focus on, and then I take rapamycin, and I do it in a cyclic manner, so I usually do 10 weeks of rapamycin and then I'll stop for a few months and then I'll do another 10 weeks. Again, it's guesswork. That seems to work for me, and I feel pretty good with that regimen.

The other thing that I try to do is I try to evaluate data as it comes in, and I'm open to the idea that what I'm doing now may not be optimal, and as I learn more, I'm totally willing to change the things that I'm doing. I think that's another-- I see people, especially in the health and wellness space who get married to a particular idea, and even when data comes along that clearly shows that idea should be reevaluated, they have a really hard time doing that.

I think you want to be open to new information as it comes along because science is a progression, and a lot of stuff that we thought 20 years ago about nutrition, we now know was incomplete at best and outright wrong in some cases. You have to be willing to change what you're doing if the data says that that's what needs to happen.

Jane Rogers: This has been fabulous. Thank you for your time. Thank you for sharing all of this.