Learning with Lowell 187 - Dr. Matt Kaeberlein on Rapamycin and Longevity

Chunk 1: 00:00–45:00

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Lowell: Welcome everybody to Learn with Lowell. Today we're joining with Dr. Matt Kaeberlein PhD from MIT expert in fundamental mechanisms of aging. Some companies projects he's involved in is just a little list the Dog Aging Project Optispan Ventures and Aura Biomedical. There's also a lab that he's run for about 20 years and on the website right now if you go to it and click the homepage it says live long or die trying. Matt welcome to the show and thank you for taking the time to be here today.

Matt: Thank you it's a pleasure.

[05:00]

Lowell: Jumping into rapamycin and so a lot of people ask questions about this and we're going to layer them in throughout. On a high level for people who are just coming into this very new what is rapamycin and then let's talk about your relationship with it. On a high level what is it and what's interesting?

Matt: Rapamycin is a small molecule. It's actually a natural product that was first discovered on Easter Island or Rapa Nui another name for Easter Island that's actually where the drug rapamycin gets its name from. It's produced by a bacterium that's found in the soil there and it's probably I think most people believe that the reason those bacteria produce rapamycin is as an anti-fungal. So it sort of allows the bacteria to compete with fungal species that are in the soil there. So that's probably the primary biological mechanism of rapamycin is it impairs fungal growth. Now it was discovered 25 30 years ago now maybe more than that in these soil

samples and when people realized it had this anti-fungal anti-proliferative activity people started studying it for that property. So they were thinking it might be a useful antifungal might be a useful anti-cancer. Right so cancer cells are cells that divide uncontrollably if you had a drug that impairs cell division that might be useful as an anti-cancer drug so people started studying it for those purposes. It ultimately ended up being first approved for clinical use as an immunosuppressant. So it's been approved now for more than 20 years by the FDA to prevent organ transplant rejection first I think for kidney transplants and then it's been more broadly used for heart transplants and some other kinds of transplanted organs. So that's how most people in the clinical community will know about rapamycin. It actually also goes under the name sirolimus same molecule I don't know why they decided it needed two names but it's got two names. It's been used for many many years as an organ transplant medication. The reason why I sort of explicitly mentioned that is I think that some of the concepts that we may get into around rapamycin and its potential effects on aging and longevity get complicated by the fact that it was actually first developed as an immunosuppressant. So at high doses there's no question rapamycin can prevent the immune system from rejecting transplanted organs it's always used in combination with other strong immunosuppressants. But in that context there is a side effect profile that is very different from what we see when we use it at lower doses in healthy animals potentially people to have an impact on healthspan and lifespan. So I just think it's useful for people to understand the history here so that you can appreciate that some of what we think we know about rapamycin in the clinical context may not actually apply in a different context right in organ transplant patients versus healthy people so I think that's important.

[10:00]

Matt: The reason why I got interested in rapamycin really stemmed from work that I was doing when I was a postdoctoral fellow at the University of Washington where we were looking for new genes that affected lifespan. So at this time this was the early 2000s 2003 2004 that was really something that a lot of people in the field were interested in because we

didn't know a lot about the genetics of aging back then. So lots and lots of different labs were doing what are called genetic screens to figure out what are the genes that influence lifespan in different animal and organismal models. So that was one of the things I was working on and we found from an unbiased genetic screen meaning we didn't go looking for it we found that a gene called TOR which actually stands for Target of Rapamycin t o r when we turned it down extended lifespan. So I didn't know anything about rapamycin at this point but we found TOR. So I went and looked in the literature and realized there's a drug out there that inhibits TOR. So we found that genetically turning down TOR could extend lifespan there was a drug that pharmacologically could turn down TOR and so it made sense to test whether rapamycin could affect lifespan given that connection and that was my introduction to TOR and rapamycin. It was one of these interesting things that happens in science sometimes where there were four labs actually I was one of the people but then three other labs independently also sort of converged on TOR within this same one or two year period. So in different animal models this was one of those nice situations where through happenstance to some extent multiple groups independently landed at the same spot figured out that TOR was a really important regulator of longevity across many many different organisms. Then we all also got interested in rapamycin about that time and so since then now there's grown to be a massive body of literature showing that either genetically inhibiting TOR or pharmacologically meaning with a drug inhibiting TOR with rapamycin can increase lifespan and improve a whole bunch of healthspan metrics in every model organism where this has been studied all the way from very simple single-celled budding yeast up to mice which are relatively complicated mammals and even some data now in dogs and a little bit of data in people all supporting the idea that when you turn down TOR with rapamycin you can attenuate the biological aging process increase healthspan metrics and potentially increase lifespan certainly in the laboratory models all of that is rock solid. I think where we're at today is we don't know with 100 certainty to what extent will rapamycin positively impact lifespan and healthspan outside of the laboratory and that's kind of the next frontier I would say for the field at least in this area to learn to what extent is that the case.

[15:00]

Lowell: It's interesting to hear that Easter Island bacteria in the soil and then we're able to use that for organ transplant and we're finding these other uses as well. It always makes you wonder what all does the Earth have in store that we don't even know yet. Especially Easter Island where everyone died off I mean it's kind of there's some weird symmetry there especially considering it might have life expansion related properties. For rapamycin when you apply it to the different species is it a normal distribution of benefit relative to the species so 15 to 20 to that species for applied across the board?

Matt: I understand what you're asking yes a couple things I would say there. One is we don't really know what the optimal level of lifespan extension we can achieve is in different organisms okay. So I think it's fair to say that there has not been a comprehensive dose response so to speak for rapamycin in terms of its effects on lifespan certainly not in mice probably not in flies or C elegans or yeast which are the other three major model organisms that are typically used in the field. So I don't know that I can answer your question I think the question you're asking and this is an important one stems from the observation that for things caloric restriction which is much more it's been studied for much longer than rapamycin in this context it seems to be the case that the magnitude of lifespan extension in terms of percent lifespan extension is larger in the simpler shorter lived model organisms. In other words maybe you'd get a 100 effect on lifespan in worms and 30 effect on lifespan in mice and worms live about 10 times shorter than mice do. So the question is I think or one question is as we start to try to extrapolate these interventions to longer and longer lived species humans being sort of at the far end of that distribution would we predict that the magnitude of effect is going to get correspondingly shorter at least in terms of percent lifespan extension. I don't think we know the answer to that question yet I think it's a reasonable expectation and certainly if somebody forced me to say what would you predict Matt given what we know today what would you predict my prediction is that indeed

the relative effect in terms of percent effect compared to average will be smaller in humans compared to mice. So if rapamycin let's say if we could optimize it could have a 40 effect on lifespan in mice maybe we're talking a 10 15 effect in humans but again I think it's important to just say that's really an educated guess and it's no more the answer is we don't know. Even if it's a small percentage I think sometimes people hear 10 they think oh that's not that big but ten percent when people can live to about 100 years old 100 years I mean that's an extra 10 years that's pretty significant actually let me expand on that for just a second because I think this is a really important point. I also think it's important to differentiate between lifespan life expectancy and potential effects on quality of life healthspan healthspan metrics my intuition as well and again admittedly this is a guess my intuition is that in humans in particular it's going to be much easier to move healthspan metrics than it is to move sort of maximal species lifespan. So I actually think it's a relatively easy lift to get most people a decade of extra healthspan I actually think we can do that today with primarily lifestyle interventions. So if we could actually get most people to practice a relatively healthy lifestyle I think they would regain that lost decade that's what I call it a lost decade most people are giving up at least a decade of high quality life by practicing poor lifestyle choices in developed countries. I think there's I don't think too many people would argue with that so I actually think that's important if you said a decade that's actually a pretty long time. I was actually thinking about this just the other day because I'm trying to write something about this but think back so what are we 2023 what was happening in 2013 right and think about that length of time and all the stuff that has gone on since then some of it good some of it maybe not so good right. But if you could get an extra 10 years of really high quality life that's a big deal and I think that's actually not a very heavy lift I think we can do that today. I suspect that we could probably get 15 maybe even 20 years of extra high quality life using some of the interventions that we know about now that target the biology of aging. So I just say all that because I do think it is useful to appreciate that we're not talking about incremental effects right most of what biomedical research and standard what I would call reactive disease care medicine does is incremental we're not talking about incremental effects we're talking about

things that could really have a very large impact on people's productivity their relationships their experiences their overall quality of life and I don't think it's very unrealistic to think that we can do that just given the knowledge that we have today.

[20:00]

Lowell: For the intervention that was 15 to 20 years is that lifestyle changes such as caloric restriction and then therapies adding rapamycin in there or some type of senescent cell strainer lytic?

Matt: Yes yes yes senolytics so I think the answer is conceptually yes I'm talking about those things that people in the field are studying today. So that would include potentially rapamycin would include potentially senolytics might include some of these circulating factors that change with age that seem to impact the biology of aging would include hormones so I would put them all sort of in that bucket. I do think it's important to say right now we don't have the tools to optimize all of those things for everybody at a personal level. So we may get into this because I know people are sort of interested in what's the optimal diet how much protein should I eat all that stuff we can certainly talk about that but again I think it's really important conceptually for people to appreciate that at the individual level we don't really have tools to say what is optimal for you what is optimal for me. So we're sort of left with these population level correlative recommendations okay so I just say that because I think it's important to appreciate. But yeah I'm talking about lifestyle so first of all I would not say caloric restriction I actually am not a big believer in caloric restriction and we can unpack that. I would say not being obese certainly so appropriate nutritional intake but I'm not a huge fan of going below that. So and again personal guess might or might not be right but I do think that certainly nutrition is critical activity is critical right so those kinds of things I think if you were to really not even necessarily optimize but just get within the healthy range for the kind of somewhat obvious lifestyle interventions diet exercise sleep I think most people would get a decade of extra healthy life from that if not more. So yeah and then on top of that and this is where it gets to be a little bit

speculative so again I also think it's important for people to appreciate we're talking about to some extent probabilistic thinking right there are very few certainties when we're trying to predict the future and in particular an individuals future health outcomes it's more about risk reward and probabilities of something happening or not happening. So we have to just appreciate that there's not a ton of certainty here but now we're getting into probabilistic outcomes given what we know today and the biomarkers we have available then I think when you start to put on top of the lifestyle interventions things rapamycin you might be able to get beyond that last decade to something bigger than that maybe 15 years maybe 20 years what those interventions exactly are going to be for individuals now we're talking personalized approaches that's where I'm optimistic and I expect that the diagnostics that are available to help guide us will improve greatly over the next five years. That would include things the sort of currently popular biological aging tests which aren't really biological aging tests in my views but they are telling us something about the biology of aging. So I think as those biomarkers and diagnostics improve will be able to start to get closer to personalized recommendations for some of these interventions which again could include rapamycin NAD precursors autophagy activators senolytics circulating factors related to parabiosis anti-inflammatories right mitochondrial boosters. So there's a whole bunch of potential strategies to target the biology of aging but I think we know enough about today to be thinking about targeted interventions when you pair that with improvements in the biomarkers I think the hope is that we'll be able to get to more personalized recommendations.

[25:00]

Lowell: So working most recent you're saying if biomarkers that the aging related ones that people are talking about aren't tracking aging directly what do you think they are tracking then?

Matt: So I think it's important for people to appreciate that the biology of aging is immensely complicated right and we don't really let me say it this way there's more that we don't understand about the biology of aging then

we do understand I just think people need to appreciate that. Many people who have not been in this field for very long will read some of the popular stuff that's out there and think oh it's all figured out right that's not the case. So one way that is popular to think about the biology of aging is through what are called the hallmarks of aging I think most people who have sort of been around this space will have come across the hallmarks of aging at some point. So depending on who you ask there are between 9 and 12 of these hallmarks of aging and all the hallmarks are is a construct that people have scientists have created to conceptualize what appear to be conserved mechanisms of biological aging that contribute to functional declines and increased mortality risk that go along with aging across all of the different organisms where this has been studied. So those include things mitochondrial dysfunction accumulation of senescent cells dysregulated cellular communication dysregulated nutrient response telomere shortening so there's a collection of these things right. So what is useful hopefully for people to understand is that's a conceptual construct right so it is an imperfect representation of reality underlying that construct is this extremely complicated network of interacting genetic and environmental factors and some of the things in that network we know about mTOR some of the things in that network appear to be useful let's just say nodes in the network to tweak to impact that biology of aging but there's a whole bunch of stuff under there that we don't understand. What the currently existing tests are measuring is just a tiny fraction of the biology of aging so let me give you an example one of the somewhere between 9 and 12 hallmarks of aging is epigenetic changes epigenetic dysregulation. So the currently most popular flavor of biological aging clocks are epigenetic biological aging clocks that's what most of the direct to consumer stuff that you can buy and I don't recommend people do that other than for entertainment purposes only most of the direct to consumer biological aging clocks that you can buy only measure epigenetic changes. So that's one of the hallmarks of aging of which there are somewhere between 9 and 12 of which that's only a fraction of the complexity of the biology of aging. So I would say all of the stuff that we can measure today each of them will measure a different piece of the biology of aging none of them are capturing all of the biology of aging and so I think the unknown at this point is which if any of the existing tests

give us useful information about future health outcomes future disease risk and maybe more importantly about response to interventions that's an unknown. So what we do know is you can take an epigenetic aging test and you can then modify your lifestyle and come back in three months and take the test again and maybe you see a delta on that test right it changes what we don't know is whether that change is meaningful in terms of your future disease risk or future health outcomes. There are people who will argue with me on that there are people who will say but we know that these some of these epigenetic tests can predict future health outcomes from long-term longitudinal studies and epidemiological studies that have already collected samples from people over many many years and that's true. What hasn't been shown is that for a given individual living in a given environment right today which is different than it was 10 years ago or 20 years ago that when you take one of these biological aging tests that at the individual level it's actually predictive for future health outcomes that hasn't been done in people for understandable reasons hasn't been done in mice for not understandable reasons it should have been done by now. So I would say there's a disconnect at this point between what people are claiming these tests actually measure and what we know these tests actually measure and that's an area that the field needs to do better in my opinion.

[30:00]

Lowell: I've been reading a lot about what Bryan Johnson's been doing and he does a lot of these tests and says hey I gained x amount or whatever and I have been wondering what how useful are these types of things in general specifically and then with what he's doing it sounds he's trying to build a case study kind of if Phineas Gage and the railroad spike in terms of understanding different parts of your brain if it's damaged but do you think with Bryan Johnson as an example that he's that he's gaining any benefit from these tests and then developing interventions he's saying I'm 10 years older than I should so I'm doing something that makes it smaller or lower reduces it is he gaining anything from spending two million dollars

on this way or is it just healthy eating is more what he's gained from the things he's doing?

Matt: I'm a little bit hesitant to talk too specifically about what Bryan Johnson is doing I think definitely he's gained attention for himself that's one thing. But beyond that it's hard to know right so again I think there are aspects of what he's doing that I really I the fact that he's sharing data I the fact that he's being honest about the fact that he's experimenting on himself I worry a little bit about the way it gets presented. So as an example I actually just saw a tweet from him today about how he said something about I measured rapamycin in my blood and I'm writing the optimal dose range right and my response is you have no way of knowing if you're in the optimal dose range because nobody knows what the optimal dose range is because science hasn't figured it out yet. So I worry a little bit that he and his team do not understand the biology of aging sufficiently to be able to be commenting with any sort of authority on what the results he's getting actually are telling us and I worry that that's being misinterpreted by the general population or at least the people who are paying attention to what he's doing so that's my big concern there. I do think that many of these biomarkers and he's the panel of biomarkers at least for my understanding that he's looking at makes sense I don't have not saying that he's doing it wrong right. But I think that many of these biomarkers are the best biomarkers that we have currently and it is a reasonable expectation that when you move those biomarkers in what we think is a positive direction that your health has improved and that your risk of developing specific diseases of aging or dying go down there's no certainty there. So again this gets back to what I was saying before this is all probabilistic right and so we can make a probabilistic expectation of future health outcomes based on what we think we know today about these biomarkers but we have to accept first of all there's no certainty he could get run over by a bus tomorrow right if we're talking about mortality that has nothing to do with the biomarker. So there's no certainty there he could just have bad luck get his mutation in a cell that is highly prone to cancer right and suddenly he's got metastatic cancer right so there is a stochastic component that the biomarkers simply don't pick up on. Then secondly the biomarkers that we

know about today are imperfect right we have an imperfect knowledge base is it better than it was 50 years ago sure will it be better than it is today 50 years from now absolutely. So we're making predictions based on what we know today which is limited and so our predictions are only as good as that limited knowledge base and I think what again many people who haven't spent enough time really thinking deeply about this biology don't appreciate is how little we actually know. So I don't know whether or not Bryan is biologically younger or biologically his age is aging more slowly than he was before he started this my guess is he probably is although I worry a little bit that these sort of very very extreme intervention protocols have hidden costs right. So one way to appreciate that that's pretty easy is caloric restriction so we know right if you calorically restrict too much that's going to be detrimental for longevity right there is a there's a sweet spot where you get the optimal benefit for lifespan and if you go past that with caloric restriction you're going to shorten lifespan and that's probably true with almost any intervention that you think about that's going to be true for rapamycin I would guess that you can't just keep taking more and more rapamycin and get more and more benefits right. So I worry a little bit that these very extreme intervention protocols and I would certainly put his protocol in the bucket of extreme have hidden costs or they have they're beyond the sort of point of optimal return now it's my understanding that he's trying to guide the optimal return based on the biomarkers that his team has told him are important. But I worry that there are hidden costs I also think something that's not often talked about by scientists in the field because we don't really most of us are biologists we don't really think about it are the psychological risks associated with these sort of extreme lifestyle interventions. Again I think caloric restriction is a good example here I know many people who have dabbled with flavors of caloric restriction and I'm not a psychiatrist I'm not a psychologist but I can absolutely tell you some of those people had significant psychological consequences from their dabbling with caloric restriction. So I don't think we really pay a lot of attention to some of the potentially adverse events that are more on the psychological mental wellness side of things just because humans are super complicated animals right we're funny animals and we live in this social construct that is very different from studies that are carried out in

mice say in the laboratory and we don't really appreciate some of the consequences of these sort of extreme lifestyle or interventional protocols that people are thinking about and the impact that that can have on psychological health and mental well-being. So I also worry a little bit about things that when you see people start to advocate for these what again what I would call extreme lifestyle interventions.

[35:00]

Lowell: With Bryan in particular I think to some extent it sounds it could be a game of telephone that's the issue yes this scientist translated to him and then he's translating it to the public and there's not someone checking the suites to make sure it's accurate because if the research hasn't been done then how do you know it's optimal. In terms of the psychological effects looking at caloric restriction I have read that there's a link between the gut biome and your psychology how well you're doing is that what you think is causing that psychological harm or?

Matt: It could be part of it I certainly don't think that's all of it. So certainly it could be the case that some of what we would lump under psychological consequences of nutrient deprivation caloric restriction some of that certainly could be related to signals coming from the microbiome again the biology here I and first of all let me say I know much less about the biology of the microbiome and how it interacts with the rest of our physiology than I do about the biology of aging. So now I'm speaking from a non-expert perspective but I know something about it and I certainly know something about biological complexity and so I would I feel confident saying that our understanding of the microbiome and how it talks to the rest of the body for lack of a better way of saying that is even less well characterized than our understanding of the biology of aging. So absolutely do I believe that our food our dietary consumption not just caloric restriction but sort of overall what you eat whether you're restricted or overeating or the composition of the diet that has a huge effect on our physiology and that said a bunch of different levels it could be at the hormonal level it could be at the effect on brain chemistry. So all of those things could go into

impacting your psychological state and so it wouldn't surprise me if that's part of it. But I also think this is sort of what I was more alluding to is human beings live in this really complicated social environment right and so much of our behavior is around our interactions with other people right and diet plays a huge role in that right. So people who practice sort of extreme dietary interventions they change that social interaction and so that can have impacts as well and being hungry impacts your outlook on life right I think anybody who's ever been hungry really really hungry recognizes that impacts all sorts of stuff it impacts your emotional well-being it impacts the way you interact with other people. So that's more what I was alluding to but absolutely I think you can layer on top of that the interaction between the microbiome and the diet and the rest of our physiology and that's going to have an impact as well.

[40:00]

Lowell: Delving in more to caloric restriction before this call I read about you I wouldn't have caloric restriction would have been one of those temples people say yeah do that that's good for a longevity healthspan. What so what are you saying that says the opposite and then I guess we maybe we could steel man why we could be wrong on this but what so that there's a lot of people saying yes that is good you're saying there's concerns and doubts especially if you go too low so if you could just expand on that?

Matt: What I would there are several reasons why I am hesitant to suggest that we should extrapolate from laboratory studies to humans in the specific context of caloric restriction but I also think it's worth simply stating the data. Because again the people who are arguing that caloric restriction always extends lifespan in mice and therefore we should recommend it to people either don't know the data or they're intentionally ignoring the data that suggests otherwise the actual real data in the literature tells us that indeed caloric restriction in rodents mice and rats can increase lifespan quite significantly. I think the largest effect that I've seen is about a 60 percent increase in average lifespan from about a sixty percent

reduction in calories that work was done in the 1980s by Roy Walford and Rick Weinrich and others so absolutely caloric restriction can increase lifespan and along with that caloric restriction can improve a whole bunch of healthspan metrics okay that's rock solid. What's also rock solid is that only is true in certain genetic backgrounds and if you look in other genetic backgrounds you can get the same caloric restriction paradigm you can get no effect on lifespan or you can get shortening of lifespan. So that's true in mice that's true in fruit flies that's true in nematode worms and that's true in budding yeast all of the model organisms that people routinely study in the biology of aging in the laboratory the effect of a given caloric restriction paradigm on lifespan is strongly genetically dependent in all of those systems. It's a little bit we don't know the exact frequency but it's roughly one-third of the genetic backgrounds tested have their lifespan shortened by a given caloric restriction paradigm that will extend lifespan and other genetic backgrounds okay that also is a fact. So it seems to me that it would be irresponsible to recommend to people an intervention that shortens lifespan and about 30 percent of the genetic backgrounds where it's been tested in the laboratory okay that just I mean I don't I don't quite understand the disconnect here where for people who are saying caloric restriction go do it right it just doesn't make sense because we don't really understand what it is about those genetic backgrounds that are harmed by caloric restriction why they're harmed right so we can't really predict in humans. That's again not even considering the psychological consequences of caloric restriction approach in people so that's one reason why I'm not super bullish about caloric restriction the other is that there is a bunch of misinformation out there around intermittent fasting and time restricted feeding. So intermittent and I'm going to define those this way because I know that there's some lack of clarity around what those terms actually even mean so I'm going to say intermittent fasting is a fast of 24 hours or more so at least one full circadian sort of cycle time restricted feeding is limiting the hours within a given 24-hour cycle in which you eat to say 8 or 10 or 12 whatever the flavor of time restricted feeding you're talking about okay. So there is this again misperception I would actually take it as far as to say a misinformation campaign that time-restricted feeding and intermittent fasting clearly have health benefits in people okay I

don't think that's actually been shown I think it's true for some people but on average I don't think that's been shown. What we know in mice is neither of those interventions significantly increase lifespan unless they are paired with caloric restriction in other words if you time restricted feed or intermittent fast but the animals end up eating the same amount over say a month or years the effect on lifespan is essentially zero there might be a very very small three four five percent effect on lifespan from intermittent fasting that's iso caloric that is a little bit unclear in the literature but it's nowhere near the magnitude of effect you get from true caloric restriction. So that often gets unfortunately ignored when this now is talked about in the sort of popular sphere right so intermittent fasting in the absence of caloric restriction even in laboratory animals very little evidence that it targets the biology of aging in any really meaningful way I would say. So I'm I think it's fair to say frustrated by the way that this is misrepresented for the general public in the non-academic sphere even in academic review papers it's misrepresented so that's partly what's leading me to maybe push back on caloric restriction and intermittent fasting a little bit stronger than I than I otherwise would because I feel I'm kind of battling a misinformation campaign that's out there by people who really want to advocate for this kind of a dietary strategy. So here's what I would say and again this is just my opinion right take it for what it's worth my opinion is that intermittent fasting and time restricted feeding can be useful tools for some people not for everybody but for some people to maintain a healthy body weight okay. So there are some people who find it easier to maintain a healthy body weight and not overeat by practicing intermittent fasting or time restricted feeding I don't see much evidence for benefits in people outside of that doesn't mean there aren't any just we don't have a lot of data to support that. The other thing I'd say is I have some real personal concerns around intermittent fasting in particular and the negative effects that that can have on body composition so I said that intermittent fasting and again let's just take a simplistic version of intermittent fasting so two days a week you don't eat anything right some people do this I think that can help those people to maintain a healthy body weight because they then don't feel they have to restrict themselves on the non-fasting days they can eat more in those days than they burn. But I worry about the long-term effects of that sort of a

strategy on body composition for two reasons one is we know that a prolonged fast will preferentially degrade lean mass over fat mass both will come down for sure but you're going to lose lean mass muscle mass which is a bad idea in general. Secondarily this is just my own sort of people that I know who do this and again I know a lot of people who've tried a lot of these different things people who I know who've tried intermittent fasting tend not to focus as much on the quality of their diet on the days they're not fasting now that's not going to be true for everybody but I think unfortunately and this is maybe a psychological thing I think there's a psychological relaxation of your dietary quality because you think well I'm fasting two days a week so on the other days I can eat whatever I want. Again I think from a sort of overall health perspective that's counterproductive you'd be better off in my view eating a nutritious high quality diet most of the time and maybe taking a cheat day once in a while if you want to then fasting two days a week and eating garbage the other five days of the week and unfortunately I think some people fall into that sort of psychological trap of thinking that the two days of fasting is going to make up for the five days of eating a typical western diet and it doesn't in my view. So I know that was sort of a long digression but I think this is unfortunately a really complicated topic that a lot of people are confused about and they want somebody to tell them this is what you should do and so it's very easy for a talking head to get up there and say use my intermittent fasting protocol guaranteed to promote longevity which is you know BS.

[45:00]

Lowell: For the difference can go down it helps reverses hurt and would it be useful to study a genetic test of some kind to differentiate how it would affect different people so then we could say hey if you're looking to increase your lifespan and you fall within this marker with this test this will most be more useful to you to make it more granular I think if we had the information to know what to look for in a genetic test?

Matt: Yeah absolutely I mean that's where we would love to get to I would also say it's probably not even primarily genetic it's partly genetic I would guess in humans. So again this is where you really have to differentiate between what's been done in the laboratory and what the real world is right so in the laboratory we're controlling the environment so the studies where people have looked across genetic backgrounds and say mice though all of those mice were kept in a very controlled homogeneous environment meaning it was the same across all of the different strains people aren't that way.

Chunk 2: 45:00–89:13

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[50:00]

Lowell: I think one if you were to summarize a little bit we were synthesize what we've talked about thus far it's basically on one level it's

humans are really really complex there's so many different things going on and it sounds unbelievably complex and almost stressful to imagine trying to piece out one little aspect. So I'm wondering it's a thought exercise if we gave you a Bell Labs and unlimited funding and just an army of people to research that the fat biomarker or something any of these different things so we could have we could reduce the dark matter in terms of longevity healthspan that currently exists in these fields as we've discussed what would be some of the areas that you'd want to push for I mean that's a really really big thing so I'm trying to limit it as much as I can but it's just it's so complicated it feels there would be some benefit in researching out some really esoteric stuff so they could then build up and have a better sense of how things work and so to some extent it's how do you know if you're building a solid foundation if we don't have the full foundation yet?

Matt: It's a really good question so I'll tell you three areas if I had unlimited resources that I would focus more on than the field yeah okay. One is human clinical trials I think you're right the system is immensely complex but the only way we are really ever going to find out what the impact is in humans of a given intervention is to test the intervention in humans I don't think anybody would disagree with that. We can argue back and forth about rapamycin and metformin and NAD precursors and do they work do they don't work it's just going to be arguing back and forth until we actually get the data so I would invest substantially in well-controlled well-designed human clinical trials not for lifespan because I don't think that's pragmatic and plus I don't want to wait 20 years to get the result but looking at a multitude of functional and molecular measures of function that we believe are important and I think we know enough about functional declines that go along with aging in people right now to do that. So I think it's all doable and so that would be area number one and I think that would be extremely expensive but conceptually it's not that hard to think about what you would actually do you just need the resources to do it and I think we've got a reasonably good list of things we could test rapamycin metformin NAD precursors autophagy activators right senolytics right there's a bunch of things we could test. But the problem is right now people are doing some of that but the clinical trials are crap to be honest with you

right and I mean I guess I shouldn't say that quite so bluntly but none of them are large enough to really answer the question so what we get are 20 person 40 person phase one phase two sort of kind of that's what they're called clinical trials that give a hint but you're kind of left thinking okay maybe maybe it worked maybe it didn't I don't know we need a bigger clinical trial somebody just needs to do the damn bigger trial in my view to answer the question so that'd be one thing. Another thing would be expanding the research in companion dogs so we haven't yet talked about the Dog Aging Project probably won't have time today but I'm happy to come on in the future if you want to talk about the Dog Aging Project in detail but this is something that I've been involved with is this large-scale longitudinal study of aging in companion dogs pet dogs living with their owners and then we also have one clinical trial of rapamycin in pet dogs. The huge advantage right there are several but one huge advantage of doing a clinical trial in pet dogs is we can actually measure whether rapamycin can increase lifespan because dogs age biologically about seven to ten times faster than people do meaning if you design the trial appropriately starting a middle age in a three-year time period you can actually statistically determine whether or not rapamycin or a different intervention increases lifespan and improves healthspan metrics in pet dogs now let's say you're successful at that does that prove the intervention is going to work in people no it doesn't prove it. But I do think it gives you a lot more confidence that is probably going to work in humans plus you've extended the lifespan and healthspan of people's pets that's a big deal in and of itself so I would expand that I and I mean people are starting to do this I would just accelerate it I think that there is huge untapped potential for geroscience discovery and clinical trial interventions validation in companion animals so that'd be area number two that I would put a bunch of resources into. Then area number three is getting back to this idea I talked about before which is that what we understand about the biology of aging pales in comparison to what we don't understand and I worry actually probably more than I should that the field has become very narrow over the last 10 years. What I mean by that is while there are many more people interested in the biology of aging and studying the biology of aging the breadth of research that people are studying is actually quite small

compared to what it was 20 years ago almost everybody and this is a actually you might even attribute this somewhat to the hallmarks of aging paradigm because it's become difficult for people to think outside of that paradigm and think about what don't we know. So almost everybody who's working in the field right now whether it's in basic research or in the biotech community is focusing on something related to the hallmarks of aging and targets that we already know about and yet the what I would call the intervention space right so if you think about all the possible interventions you could test for effects on aging the intervention space is essentially infinite. So we are we've explored a tiny tiny fraction of the intervention space and very few people are thinking creatively about how do we look beyond what we already know so I would put a large amount of resources into trying to encourage people to develop novel sort of innovative approaches to explore the longevity intervention space and there are a couple of reasons for that. One is as I've said a couple times already I believe that there's a lot we don't know about the biology of aging there's a lot that remains to be discovered and the only way we're going to discover it is to look for it I also believe that given what people are studying now it's very unlikely we are going to find new interventions of large effect size okay. We could talk about epigenetic reprogramming that's the only thing that I think has the potential for large effect size and the current crop of things people are studying but I think if you look back over the last 20 years even over the last hundred years so we talked about caloric restriction caloric restriction I said this earlier the most I've seen is a 60 increase in lifespan from caloric restriction and that was a study that was done in the 1980s we've known about caloric restrictions since 1930s why hasn't anybody done better than caloric restriction in terms of magnitude of effect in the last hundred years. Rapamycin 2009 is when rapamycin was first shown to increase lifespan in mice why is rapamycin still the gold standard in terms of effect size and reproducibility for longevity interventions drug small molecule longevity interventions so I think you can make a case that intervention discovery has stagnated in the field and I would argue that's because people have become very narrow in the way they're thinking about the biology of aging. So I would try to blow that up I think we need to blow up the intervention pipeline and be able to screen hundreds of thousands

optimally millions of interventions to find new things that affect longevity and that's kind of the premise behind Aura Biomedical which you mentioned I'm involved in that's a spin out from my lab certainly I'm not going to argue that's the only way to approach this problem but it was my solution or start towards a solution of what I viewed as a problem for the field. So Aura has developed a platform that we are now scaling to measure hundreds of thousands of interventions small molecule could be genetic or effects on lifespan we're actually just just now sort of have gotten the technology to the point where I think we can realistically propose a million intervention studied right five years a million interventions to find out how big can we how big of an effect can we get on longevity just to give people a feel for what that means. If you look in DrugAge which is currently the largest database of small molecule interventions for lifespan across all organisms there are something 1500 drugs that have been tested for effects on lifespan okay so we go from fifteen hundred to a million we're going to find really interesting stuff so those are the kinds of ideas that I think I would to see more people in the field thinking about to try to help us get past what I view as sort of a bottleneck right now that's limiting the potential of where the field can go.

[55:00]

Lowell: To do a million interventions at a time are you looking at something organ or well I guess in addition to this what do you think about organ or organisms on a chip to measure healthspan and aging and then and then slide into how would you do a million if the best so far has been fifteen thousand over several years 1500 oh wow okay I added in a zero I was being generous so okay?

Matt: Good question so first thing I would say is I'm biased towards what are called in vivo whole animals right. So I think if I think if your goal is to find things that affect longevity and healthspan you need to look in a model system where you can actually measure longevity and healthspan okay otherwise you're stuck using what are called surrogate phenotypes or secondary phenotypes that you think somehow correlate with longevity and

healthspan so that's my bias. So what we developed and have spun out at Aura is a high throughput robotic system coupled with artificial intelligence to do whole animal lifespan and healthspan moderate measurements in C elegans at scale okay so and I we could get into the details of all that but it's probably not worth it suffice it to say that we think we can build this pretty reasonably to a scale where you can do a million interventions over a few years it's not going to be simultaneous but we can scale it easily to the point where we can do a million interventions over a few years okay in whole animals. So then the question is could you do something that in cell culture and organoids you could certainly develop screening platforms that screen for something in cell culture and organoids that might be related to lifespan and healthspan you can't measure lifespan and healthspan in those systems so you are making an assumption that you know what to measure that is going to be predictive for lifespan and healthspan and I think that can absolutely work here's the problem your assumption is based on what we already know. So again my whole starting point was there's a bunch of stuff we don't know that we probably shouldn't should find out all of the systems that are that are designed to use in vitro cell based assays or systems that are using artificial intelligence to predict novel longevity interventions today those are all based on the knowledge base that we already have right. So let me give you an example that I think everybody can conceptually appreciate there are people who have taken approaches where they say okay we know that rapamycin is interesting and metformin's interesting and NAD precursors are interesting for their effects on aging right based on studies and laboratory animals. So if we treat cells and culture with those molecules we can see what happens and let's just say we're looking at gene expression we can see how gene expression changes from those molecules in cell culture and then we can take a whole library of small molecules and try to find new molecules that you know look something these molecules that we think are interesting in terms of gene expression and then maybe those will be new drugs that will have an effect on longevity right and that's perfectly reasonable. The problem is the only thing you're going to find are things that act the things you've started from rapamycin metformin NAD precursors are they going to be better maybe probably not so my view is what we really need to do is find new things

maybe combinations of things and again I really am biased to the idea that the only way you're going to be successful at doing that is to do it in a system where you can actually measure what you're interested in which is lifespan and healthspan. Now is C elegans the best system I don't know we thought it was simply because we knew we could develop the technology could if you could do it in mice that would be great do you know how much it would cost to do a million molecule longevity study in mice we actually did the math it's I think just for the animals it's one and a half billion dollars when you put all personnel and facilities cost and all that on top of it it gets to be pretty expensive. So let's just say it's two billion dollars to do that million molecule screen in mice we can do it in worms for probably five million right so you know I think there is a pragmatic component here as well maybe maybe you could do it in flies maybe killifish you know maybe planaria I don't know there are options we figured we could build it in worms and we built it now and so we're pretty confident we can execute I'm not going to argue worms are the only place to do it. But I do believe strongly that you're going to be much more likely to get the answer you want at the end of the day if you're actually measuring the phenotype that you're interested in and from my perspective lifespan and healthspan are the phenotypes that we're interested in.

[60:00]

Lowell: We touch on the subject with your dog project but I want to expand on it because I think it's something that people don't talk about which is the quality of love and how it affects people's just healthspan and in your life in general there's many stories of people who their loved one passes and it's six months later and they're gone as well and I don't I don't know clinically I don't think they die from heartbreak but I feel there's something there to effective you know I think sometimes people say get three hugs a day or whatever but what what are your thoughts on that correlation between love healthspan and having a good long life?

Matt: Well so I one thing I would say is first of all I'll dive into the actual connections to health in a minute but I'm a pretty pragmatic guy and my

view is if you're miserable what's the point of living longer right. So I think joy happiness love however you want to kind of frame that if you're missing that piece I would say you don't have certainly don't have optimal healthspan and I would say it's probably hard to have good healthspan if you're not happy right if you're miserable so that's kind of the first thing I would say about that but you're absolutely right. So what different people have a different number of pillars of health right but I kind of I kind of the idea of of four pillars right so I would say nutrition activity which would encompass exercise sleep and then I don't know what the right word is I've been actually trying to think about what's the right word for the fourth pillar is it you know wellness is it happiness is it joy maybe love I don't know but it sort of encapsulates for me all of that and I and absolutely that's very real and I think also we have to recognize these pillars are interconnected right. So that's easy to see if you look at the connection between nutrition and exercise we already talked about that right the optimal nutrition is going to be different depending on what sort of exercise people are doing it's also easy to see with sleep there's no question that sleep impacts the biology of aging the biology of aging impacts sleep no question it's a little bit less characterized I think when we start to get into wellness anxiety stress fear those are sort of you know anxiety stress fear sort of the negative side of it joy happiness love the positive side of it. But I would say those are all sort of touching on the same biological component I'm guessing at least overlapping and it's really it's clearly important there's been some work done on the interactions between chronic stress and the biology of aging and longevity so we can point to you know molecular connections at that level certainly some work done on brain chemistry changes with aging which are going to be impacted by anxiety fear stress and also impact the perception of anxiety fear stress so there's some connections there. But I think what you were getting at which is something that is less studied but maybe equally if not more important is how our interactions with other humans and potentially companion animals can also impact our biology and that's real no question about it I mean there is some work showing for example that humans interacting with their pets that can actually show a reduction in stress markers in the human interestingly it also shows a reduction in the stress marker in the pet right so there's clearly biological

connections there which are really important and I think but I think also pretty poorly understood. So at this point what I would again I would go back to sort of my pragmatic answer to begin with which is I think people need to think about and try to figure out what can they do in their own lives to sort of increase their joy their happiness right their wellness reduce stress reduce anxiety I know that's easier said than done but I think you have to start by thinking about it and there are lots of people who have spent much more time thinking about this than I have who have recommendations on how to approach that but paying attention to it is where you have to start. But absolutely I would put that up there you know again if I had to say from a purely pragmatic perspective if you're not happy the rest of the other stuff doesn't it matters a lot less right so that's got to be maybe that's where you start I don't know but it should be a part of everybody's equation here when they're trying to think about their overall healthspan.

[65:00]

Lowell: I was reading recently and I have some friends relatives that are in high school and stuff and that COVID has really shattered how people socialize now and so how people form bonds or relationships that happy component of a balanced life is for people who grew up under it apparently it's much harder now so is there a person in particular that you point at those people who are trying to I guess everyone needs more love and more happiness and they're enjoying their life is there a researcher out there that you'd recommend people check out?

Matt: That's a good question I don't have an answer for you I should I will I will do some homework I wish I did I don't I mean again I think I think the specific case of COVID right there are certainly people who are thinking along the lines of what are the impacts of COVID on social development particularly for younger people who went through COVID say when they were in high school or college important social forming years that's way outside my area of expertise. What I would say though is while I think it's important certainly to pay attention to that human beings are pretty resilient

right so I think we went through this period of sort of extremes all sorts of extremes the political spectrum the social spectrum right we went and maybe we're still in it I don't want to say I don't want to suggest that we're out of the woods yeah. But having said that I think that there will be long lasting impacts from the pandemic but I also think people are pretty resilient so I think a lot of the a lot of the impacts psychological impacts social impacts will you know come down with time and so I yes I guess where I would land again without having thought a lot about this is for most of us we're hoping that we've got multiple decades of healthspan ahead of us right. So I would really think about psychological well-being emotional well-being from that perspective right you've got decades to go and so what can you do in that context to optimize your emotional psychological well-being and I think one thing for sure that that this seems to me that the data clearly backs up is forming strong community social family connections now is important for the future. So I don't I mean again this can be for different for everybody I can say for my own personal perspective I've spent more time thinking about this in the last year and I can say I'm pretty probably pretty typical for a male in his early 50s where I didn't spend as much time as I probably should have thinking about friends and those those kinds of social connections and so I'm making a dedicated effort to do better going forward and I think probably most people can do that right. So forming real bonds with other human beings I think is a place to start it's going to solve all your problems no but it's going to you can think of it exercise for your body this is exercise for your community right if you don't exercise your community that may be one of that may be the pillar that crashes down first when you're older right so paying attention to that now I think makes a ton of sense.

[70:00]

Lowell: I have a bunch of I have some fan questions and then some just rapid fire you can just as quickly as you feel appropriate but this one this one's for me when you close your eyes before you when you wake up in the morning and before you look in the mirror how old do you feel mentally is there an age associated with your internal feeling of age?

Matt: Oh that's a good question I don't know that I've ever thought about it young I guess I would say. But I mean look my wife will tell you I'm a little kid at home I'm a 13 year old mentally so yeah that's probably about where I start.

Lowell: Last call 2021 says there's a weird dichotomy of IGF-1's role in biology of aging some super super super centurion populations have a down regulated IGF-1 receptors and knocking out IGF-1 receptors and mice causes them to be smaller but live longer but there seems to be some measurable effect on the ability to maintain muscle mass is some sort of therapeutic boost life I'm trying to scan this as a giant paragraph the basically they would love to hear your thoughts on the connection between IGF-1 mTOR through the PI 3K forward slash can you give a short answer to this question?

Matt: I will not do it justice but let me first of all just try to summarize what I think the question is asking which is in the in the mouse models in particular but also in nematodes and fruit flies turning down insulin IGF-1 signaling increases lifespan that was one of the first things that was discovered Cynthia Kenyon Tom Johnson with daf2 and age one that's in that pathway so these are connected to mTOR and the common theme is these are growth promoting pathways during development. So what we know is that all the way up through mice mutants that have reduced growth signaling through these pathways during development live longer and they appear to age more slowly in the laboratory there are humans that have mutations in these pathways some are probably moderate reduction in function that you can find enriched in centenarians but there's no evidence yet that that's causal or their ability to up to 100 or more and then there are extreme versions the Laron population so dwarfism right where we have severe down regulation of growth hormone signaling and IGF-1 signaling in people they don't live longer but they do seem to be protected against certain age-related diseases some forms of cancer things that so I think it is absolutely the case in humans that there is a similar relationship meaning if you substantially reduce growth hormone IGF-1 particularly during

development your risk for many age-related diseases decreases and you may be aging biologically more slowly. However as we've already talked about in this conversation humans are funny animals there are complicated social consequences and probably environmental interaction consequences to being very very small right and in some cases maybe frail so I don't think it's I think it's unlikely that significant reductions in growth hormone and IGF-1 signaling say in middle age would be net beneficial at least to a large extent in humans and this gets complicated really fast because there's this weird dichotomy that we don't completely understand which is that reducing mTOR seems to be beneficial right at least transiently reducing mTOR with rapamycin seems to be beneficial for a whole bunch of healthspan metrics and potentially lifespan in people and dogs and certainly in mice and yet maintaining muscle mass maintaining strength which is promoting mTOR at least in muscle also is clearly beneficial in people and so how do we how do we resolve that and I think a lot of it comes down to context but the real answer is we we don't completely understand it I think a lot of it comes down to tissue and some of it comes down to when and how much so I think chronic inhibition of mTOR growth hormone IGF-1 in middle-aged people from my perspective is probably a bad idea. But I don't know for sure I can only say that my guess is that will increase your risk of frailty loss of muscle mass might slightly reduce the risk of cancer but I don't think it's going to lead to very large increases in longevity so it's just super complicated question that there probably isn't a simple answer for right now.

[75:00]

Lowell: Techno future eight these everyone has great usernames ask them about mesenchymal stem cells stem cells from exosomes and even if just are you aware of them and just that's that would be sufficient for this person but they're wondering your thoughts on it?

Matt: I'm aware of them yes so they've linked a bunch of research questions around exosomes from mesenchymal stem cells so yes let me take a step back in general there is a lot of interest in various types of stem

cell therapies for regenerative purposes right. So you can go to clinics around the world that will inject you with stem cells and you may or may not get some regenerative benefit from that there is emerging interest in factors that are secreted from stem cells and exosomes are lipid-bound particles that are secreted from cells from cells that may contain the rejuvenating properties that or some of the rejuvenating properties that you can get from stem cells I think this is a super interesting and important area of research there is certainly some evidence in animal models that you can get regenerative properties from stem cell exosomes people are starting to try to study what the factors are that are maybe mediating those properties microRNAs things that would I go out and inject myself with mesenchymal exosomes today no I probably wouldn't. In part I would say part of my the reason why I'm hesitant to really you know think too much about going even for stem cell therapies is there's no regulation as far as I can tell at this point which means you don't really know what is in these preparations of stem cells that people that you're going and getting at these stem cell clinics so that makes me nervous and so I personally wouldn't recommend doing that but I do think it's a super important area of research and there's a lot of potential there so I would actually to see I know people are gonna hate me for this and honestly I'm not a big fan of FDA if people have followed me but I would actually to see FDA take a little stronger role or somebody take a little stronger role in regulating these stem cell therapies that are mostly offshore right now maybe bring them onshore and regulate them so that we have some knowledge about purity and quality and outcomes because right now it just kind of feels the wild west and I personally would be nervous about going somewhere and getting stem cell injections and I'm not saying there aren't reputable places that do that I'm certainly not trying to suggest that but how do you know how do you know which are the reputable places and and so that would be my concern I'd to see more regulation so that we can have some more confidence in these sorts of offerings.

[80:00]

Lowell: I think this might be the last fan question given our time so stoic Optum one issue in a rapamycin RCTs is the risk of unblinding due to characteristics of AES mouth ulcers have you thought about this aspect in future human trials this might mitigate this might be mitigated by careful consideration of endpoints being measured I think they have a PhD in biology so that this is yeah?

Matt: Yeah so a couple things I'll say about this so let me rephrase just to make sure everybody's on the same page I think the first part of that was so you do a clinical trial if it's a randomized double-blind clinical trial the provider the doctor doesn't know who's getting the placebo or the treatment and the person the participant doesn't know that's the double-blind part so the unblinding comment there I think is around the idea that one of the known side effects of rapamycin is mouth sores mouth ulcers and so if somebody's in a clinical trial they don't know if they're getting the placebo or they're getting rapamycin they develop a mouth ulcer they might conclude that they're getting the rapamycin that's absolutely a possibility. There's not a lot you can really do about that I will say people who aren't taking rapamycin get canker sores all the time so it's not that's a definitive you're getting rapamycin just because you've got a canker sore and in fact there's a study that is now accepted should be out in general science soon where we collected data from people who've been using rapamycin off label and it's something four or five percent of the non-users had mouth sores in the past three months and 15 of the rapamycin users don't quote me on that that's my recollection something that so it's not a definitive all or nothing I would say regardless but it is a concern that people then might conclude they're getting rapamycin and that would affect the rest of their perception of what the drug's doing a couple things to say about that I think again in a well-designed clinical trial you would also want to look at a variety of in addition to patient reported outcomes a variety of more biochemical measures functional measures that you would expect to be less susceptible to whether the participant thinks they're getting the medication or not not to say that there's no effect because placebo effect is real but you would expect them to be less sensitive blood-based parameters grip strength walking speed depending on what the clinical trial

is for echocardiographic parameters for heart function cognitive assessment so things that are I think the things you would want to measure but also I would say you won't if the trial is sufficiently designed so large enough long enough I think the concerns about potentially potential bias from people believing they're getting the placebo or not are minimized you can't ever completely rule that out but I think you can reduce it.

[85:00]

Lowell: A quick bonus one is do you recommend any books people check out it doesn't have to be in your field it could just be a book that you've enjoyed?

Matt: I mean one that's pretty recent is Peter Attia's book Outlive I think that's a primer that anybody who's interested in this space should absolutely read I think Peter nailed it.

Lowell: I just want to thank you Matt for coming out today everyone listening for the fan questions sorry that we couldn't get to all of them and if there's one one place I would guess is the best place to stay up to date with what you're working on it's your Twitter you seem very active but is that the best place and then thank you for coming?

Matt: The best place for now I will say I have a love-hate relationship with Twitter so I have periods of activity and then periods where I don't look at it although I will say I'm sure everybody else knew this already but I only realized in the last six months or so that if I just mute the people who annoy me it's great because I don't see their nonsense so that's been my solution to Twitter frustration is I just mute the people who annoy me yeah you're training the algorithm for what you're looking for but it's you know what it's better than getting frustrated no I think that's a good thing it's a good thing to do.

[89:13]