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

Speakers: Lowell (Host), Matt (Guest)
Duration: 89:13
Note: This transcript follows the generalized formatting rules. Fillers ("um," "uh," etc.) are removed. No mistranslations of "senolytic" were found; the term is correctly used (e.g., at 20:00, 50:00). No speaker mis-identifications detected; Lowell is the host, Matt is the guest. Timestamps are included every ~5 minutes, speaker names are bolded using double asterisks, and double spacing is applied after each response (two line breaks). Commas are inserted for grammatical clarity and readability. The transcript is split into two chunks: Chunk 1 (00:00-45:00) and Chunk 2 (45:00-89:13). Formatted in Markdown for PDF conversion with a target of 16-point Arial font via Pandoc or Google Docs.

Chunk 1: 00:00-45:00

[00:00]
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 company projects he's involved in include 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, 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, a natural product first discovered on Easter Island, or Rapa Nui, another name for Easter Island, which is actually where the drug rapamycin gets its name from. It's produced by a bacterium found in the soil there, and most people believe that the reason those bacteria produce rapamycin is as an anti-fungal, allowing the bacteria to compete with fungal species in the soil. That's probably the primary biological mechanism of rapamycin: it impairs fungal growth. It was discovered 25 to 30 years ago, maybe more, in these soil samples.

[10:00]
Matt: When people realized it had this anti-fungal, anti-proliferative activity, they started studying it for those properties, thinking it might be a useful antifungal or anti-cancer drug, since cancer cells divide uncontrollably, and a drug that impairs cell division might be useful. It ultimately ended up being first approved for clinical use as an immunosuppressant, approved for over 20 years by the FDA to prevent organ transplant rejection, first for kidney transplants, then more broadly for heart transplants and other kinds of transplanted organs. That's how most people in the clinical community know rapamycin, also called sirolimus, the same molecule with two names. It's been used for many years as an organ transplant medication. I mention this because some concepts around rapamycin's potential effects on aging and longevity get complicated by its initial development as an immunosuppressant. At high doses, rapamycin prevents the immune system from rejecting transplanted organs, always used with other strong immunosuppressants, but its side effect profile at high doses is very different from what we see at lower doses in healthy animals, potentially people, to impact healthspan and lifespan. It's useful to understand this history to appreciate that some clinical knowledge about rapamycin may not apply in the context of healthy people versus organ transplant patients.

Matt: My interest in rapamycin stemmed from work as a postdoctoral fellow at the University of Washington, where we were looking for new genes affecting lifespan. In the early 2000s, 2003-2004, many labs were interested in this because we didn't know much about the genetics of aging. We were doing genetic screens to figure out what genes influence lifespan in different animal models. From an unbiased genetic screen, we found a gene called TOR, which stands for Target of Rapamycin, and when we turned it down, it extended lifespan. I didn't know anything about rapamycin at that point, but I looked in the literature and realized there's a drug that inhibits TOR. Genetically turning down TOR extended lifespan, and a drug could pharmacologically turn down TOR, so it made sense to test whether rapamycin could affect lifespan. That was my introduction to TOR and rapamycin. Interestingly, four labs, including mine, independently converged on TOR within a one- or two-year period in different animal models, a nice situation where multiple groups landed at the same spot, figuring out TOR was a key regulator of longevity across many organisms. We all got interested in rapamycin, and since then, a massive body of literature shows that genetically or pharmacologically inhibiting TOR with rapamycin increases lifespan and improves healthspan metrics in every model organism studied, from single-celled budding yeast to mice, with some data in dogs and a little in people, supporting the idea that turning down TOR with rapamycin attenuates biological aging, increases healthspan, and potentially lifespan in laboratory models. Today, we don't know with 100% certainty how rapamycin will impact lifespan and healthspan outside the lab, and that's the next frontier for the field.

[15:00]
Lowell: It's interesting to hear about that Easter Island bacteria in the soil, then using it for organ transplants, and finding these other uses. It makes you wonder what else the Earth has in store that we don't know yet, especially on Easter Island, where everyone died off. There's some weird symmetry, considering it might have life-expansion-related properties. For

rapamycin, when you apply it to different species, is it a normal distribution of benefit relative to the species, like 15% to 20% for that species, applied across the board?

Matt: I understand what you're asking. We don't really know the optimal level of lifespan extension achievable in different organisms. There hasn't been a comprehensive dose-response study for rapamycin's effects on lifespan, certainly not in mice, probably not in flies, *C. elegans*, or yeast, the major model organisms used in the field. Your question stems from the observation that for caloric restriction, studied much longer than rapamycin, the magnitude of lifespan extension, in terms of percent, is larger in simpler, shorter-lived organisms. For example, you might get a 100% effect in worms and a 30% effect in mice, and worms live about 10 times shorter than mice. The question is, as we extrapolate to longer-lived species like humans, would the magnitude of effect get correspondingly smaller in terms of percent lifespan extension? We don't know the answer yet. It's a reasonable expectation, and if forced to predict, I'd say the relative effect in humans, compared to mice, will be smaller. If rapamycin could achieve a 40% effect in mice, maybe we're talking 10% to 15% in humans, but that's an educated guess, and we don't know.

[20:00]
Matt: Even if it's a small percentage, people sometimes hear 10% and think it's not big, but when people can live to about 100 years, an extra 10 years is significant. I think it's important to differentiate between lifespan, life expectancy, and effects on quality of life or healthspan metrics. My intuition is that in humans, it's easier to move healthspan metrics than maximal species lifespan. I think it's a relatively easy lift to get most people a decade of extra healthspan with lifestyle interventions. If most people practiced a relatively healthy lifestyle, they would regain a lost decade of high-quality life that most are giving up due to poor lifestyle choices in developed countries. There's not much argument against that. A decade is a long time. Thinking back to 2013, consider all that's happened since then, good and bad. An extra 10 years of high-quality life is a big deal, and it's not a heavy lift. We could probably get 15, maybe 20 years of extra high-quality life using interventions targeting the biology of aging that we know about now. These aren't incremental effects; they're large impacts on productivity, relationships, experiences, and overall quality of life, and it's not unrealistic given current knowledge.

Lowell: For the intervention adding 15 to 20 years, is that lifestyle changes like caloric restriction, therapies adding rapamycin, or some type of senolytic?

Matt: Conceptually, yes, I'm talking about things studied in the field today, including rapamycin, senolytics, circulating factors that change with age impacting aging biology, and hormones. We don't have tools to optimize these for everybody at a personal level yet. People are interested in optimal diets or protein intake, but we lack tools to say what's optimal for you or me individually. We're left with population-level correlative recommendations. I'm not a big believer in caloric restriction, but appropriate nutritional intake, not being obese, is critical, as is activity. If most people got within the healthy range for obvious lifestyle interventions—diet, exercise,

sleep—they'd get a decade or more of extra healthy life. On top of that, with interventions like rapamycin, you might go beyond that decade to 15 or 20 years with personalized approaches.

[25:00]
Lowell: You're saying the aging-related biomarkers people talk about aren't tracking aging directly. What do you think they are tracking then?

Matt: The biology of aging is immensely complicated, and we understand less about it than we don't. People new to the field might read popular material and think it's all figured out, but that's not the case. One popular way to think about aging biology is through the hallmarks of aging, a construct of 9 to 12 conserved mechanisms contributing to functional declines and increased mortality risk across organisms. These include mitochondrial dysfunction, senescent cell accumulation, dysregulated cellular communication, nutrient response, and telomere shortening. This is an imperfect conceptual representation of an extremely complicated network of genetic and environmental factors. We know some nodes in this network, like mTOR, are useful to tweak to impact aging biology, but there's much we don't understand. Current tests, like epigenetic biological aging clocks, measure only a tiny fraction of aging biology. Most direct-to-consumer aging clocks measure epigenetic changes, one hallmark among 9 to 12, which is a fraction of the complexity. These tests don't capture all of aging biology, and we don't know which, if any, provide useful information about future health outcomes, disease risk, or response to interventions.

[30:00]
Lowell: I've been reading about what Bryan Johnson is doing, taking these tests and saying he gained a certain amount. I've wondered how useful these tests are, specifically with what he's doing, building a case study like Phineas Gage with the railroad spike to understand brain damage. Do you think Bryan Johnson is gaining any benefit from these tests and developing interventions, saying he's 10 years older than he should be, then doing something to reduce it? Is he gaining anything from spending two million dollars, or is it just healthy eating driving his benefits?

Matt: I'm hesitant to talk too specifically about what Bryan Johnson is doing, but he's definitely gained attention for himself. Beyond that, it's hard to know. There are aspects I appreciate: he's sharing data and being honest about experimenting on himself. I worry about how it gets presented. For example, I saw a tweet from him today saying he measured rapamycin in his blood and is within the optimal dose range, but nobody knows the optimal dose range because science hasn't figured it out. I worry that he and his team don't understand the biology of aging sufficiently to comment with authority on what his results mean, and that this is misinterpreted by the public. Many of these biomarkers make sense, and they're the best we have currently. It's reasonable to expect that moving biomarkers in a positive direction improves health and reduces disease risk, but there's no certainty. This is probabilistic. We can make probabilistic expectations of future health outcomes based on current knowledge, but there's no certainty. He could get run over by a bus tomorrow, or a random mutation could cause cancer, which

biomarkers don't predict. The biomarkers we know today are imperfect, and our knowledge base is limited. I don't know if Bryan is biologically younger or aging more slowly than before he started. My guess is he probably is, but I worry that extreme intervention protocols, like his, have hidden costs.

[35:00]
Matt: For example, with caloric restriction, we know that restricting too much is detrimental to longevity. There's a sweet spot for optimal lifespan benefit, and going past that shortens lifespan. That's probably true for most interventions, including rapamycin. You can't keep taking more and get more benefits. I worry that extreme protocols are beyond the point of optimal return. He's trying to guide optimal return based on biomarkers his team deems important, but there may be hidden costs. Another concern, not often discussed by scientists, is the psychological risks of extreme lifestyle interventions. I'm not a psychiatrist or psychologist, but I've seen people dabble with caloric restriction and face significant psychological consequences. We don't pay enough attention to adverse events on the psychological or mental wellness side. Humans are complicated animals in a social construct, unlike lab mice, and we don't fully appreciate the psychological impacts of extreme interventions.

Lowell: With Bryan in particular, it sounds like a game of telephone could be the issue. A scientist translates to him, he translates to the public, and there's no one checking to ensure accuracy. If the research hasn't been done, how do you know it's optimal? Regarding psychological effects of caloric restriction, I've read there's a link between the gut microbiome and psychology. Is that what you think causes psychological harm?

Matt: It could be part of it, but not all of it. Some psychological consequences of nutrient deprivation or caloric restriction could be related to signals from the microbiome. I know less about microbiome biology than aging biology, but our understanding of how the microbiome interacts with physiology is even less characterized than aging. Our dietary consumption—whether restricted, overeating, or the diet's composition—has a huge effect on physiology at hormonal levels or brain chemistry, impacting psychological state. Humans live in a complicated social environment, and much of our behavior revolves around interactions with others. Diet plays a huge role in that. People practicing extreme dietary interventions change those social interactions, which can have impacts. Being hungry affects your outlook, emotional well-being, and interactions with others. That's what I was alluding to, but the microbiome-diet-physiology interaction could also play a role.

[40:00]
Lowell: Delving more into caloric restriction, before this call, I read that caloric restriction would have been a go-to recommendation for longevity and healthspan. You're saying there are concerns and doubts, especially if you go too low. Can you expand on that?

Matt: There are several reasons I'm hesitant to extrapolate from lab studies to humans for caloric restriction, but let's state the data. People arguing that caloric restriction always extends

lifespan in mice and should be recommended to people either don't know or ignore the data. In rodents, caloric restriction can increase lifespan significantly—up to a 60% increase from a 60% calorie reduction, as shown by Roy Walford and Rick Weinrich in the 1980s. It also improves healthspan metrics. That's rock solid. But it's only true in certain genetic backgrounds. In other genetic backgrounds, the same caloric restriction paradigm can have no effect or shorten lifespan. This is true in mice, fruit flies, nematode worms, and budding yeast—all model organisms used in aging research. The effect of a caloric restriction paradigm on lifespan is strongly genetically dependent, with roughly one-third of genetic backgrounds tested having their lifespan shortened by a paradigm that extends lifespan in others. That's a fact. It seems irresponsible to recommend an intervention that shortens lifespan in about 30% of tested genetic backgrounds without understanding why or predicting its effects in humans, not even considering psychological consequences.

[45:00]
Matt: There's also misinformation about intermittent fasting and time-restricted feeding. Intermittent fasting, defined as a fast of 24 hours or more, and time-restricted feeding, limiting eating hours within a 24-hour cycle to 8 or 10 hours, are often misrepresented as clearly beneficial in people. I don't think that's been shown on average. In mice, neither significantly increases lifespan unless paired with caloric restriction. If animals eat the same amount over a month or year, the lifespan effect is essentially zero, maybe a 3-5% effect from isocaloric intermittent fasting, but nowhere near true caloric restriction. This gets ignored in popular discussions, even in academic reviews, which frustrates me. Intermittent fasting and time-restricted feeding can help some people maintain a healthy body weight, but there's little evidence for benefits beyond that. I worry about intermittent fasting's negative effects on body composition, as prolonged fasting degrades lean mass over fat mass, and some people relax dietary quality on non-fasting days, which is counterproductive.

Chunk 2: 45:00-89:13

[45:00]
Lowell: For the difference, it helps reverse hurt. Would it be useful to study a genetic test to differentiate how it would affect different people, so we could say, if you're looking to increase your lifespan and fall within this marker, this will be more useful to you, to make it more granular, if we had the information to know what to look for in a genetic test?

Matt: Absolutely, that's where we'd love to get to. It's probably not primarily genetic, but partly genetic in humans. In the lab, we control the environment, so studies across genetic backgrounds in mice are in a homogeneous environment. People aren't that way.

[50:00]
Lowell: If we synthesize what we've talked about, humans are incredibly complex, with so many things going on, and it feels stressful to piece out one aspect. As a thought exercise, if we gave you a Bell Labs with unlimited funding and an army of researchers to study a biomarker or any

of these things to reduce the dark matter in longevity and healthspan, what areas would you push for? It's so complicated, how do you know you're building a solid foundation if we don't have the full foundation yet?

Matt: That's a great question. I'd focus on three areas with unlimited resources. First, human clinical trials. The system is complex, but the only way to find out an intervention's impact in humans is to test it in humans. We can argue about rapamycin, metformin, or NAD precursors, but we need data. I'd invest in well-controlled, well-designed human clinical trials, not for lifespan, which isn't pragmatic, but for functional and molecular measures of aging we know enough about now. It's doable but expensive. Second, I'd expand research in companion dogs through the Dog Aging Project. Dogs age 7 to 10 times faster than people, so in three years, you can determine if rapamycin or another intervention increases lifespan and healthspan in pet dogs. Success doesn't prove it works in humans, but it gives confidence and extends pets' lives. Third, we understand far less about aging biology than we don't, and the field has become narrow, focusing on known targets like the hallmarks of aging. The intervention space is infinite, but we're exploring a tiny fraction. I'd encourage innovative approaches to explore the longevity intervention space, as we're unlikely to find new large-effect interventions otherwise.

[55:00]
Lowell: To do a million interventions at a time, are you looking at organisms on a chip to measure healthspan and aging, and how would you do a million if the best so far has been 1500?

Matt: I'm biased toward in vivo whole animals. To find things affecting longevity and healthspan, you need a model system where you can measure them, not surrogate phenotypes. At Aura Biomedical, we developed a high-throughput robotic system with AI to measure lifespan and healthspan in *C. elegans* at scale. We can scale to a million interventions over a few years in whole animals. In cell culture or organoids, you can screen for something related to lifespan, but you assume what you're measuring predicts longevity, based on current knowledge. That limits you to finding things similar to known interventions like rapamycin or metformin, which may not be better. We need to find new things in systems measuring lifespan and healthspan directly. *C. elegans* is practical; a million-molecule study in mice would cost about two billion dollars, versus five million in worms.

[60:00]
Lowell: We touched on your Dog Aging Project, but I want to expand on the quality of love and how it affects healthspan and life. There are stories of people whose loved one passes, and six months later, they're gone too. I don't think they die from heartbreak clinically, but there's something there. What are your thoughts on the correlation between love, healthspan, and a good long life?

Matt: I'm pragmatic: if you're miserable, what's the point of living longer? Joy, happiness, or love is essential for optimal healthspan. If you're missing that, it's hard to have good healthspan. I

think of four pillars of health: nutrition, activity, sleep, and a fourth pillar—maybe wellness, happiness, or love. These are interconnected. Nutrition and exercise are linked, sleep impacts aging biology, and wellness, stress, or joy touch overlapping biological components. Chronic stress affects aging biology, and brain chemistry changes with aging impact stress perception. Human and pet interactions reduce stress markers in both, showing biological connections. These are poorly understood but important. People need to think about increasing joy and reducing stress in their lives, starting with awareness.

[65:00]
Lowell: I read that COVID shattered how people socialize, especially for high schoolers, making it harder to form bonds or relationships. Is there a researcher you'd recommend for people trying to increase happiness and enjoy life?

Matt: I don't have a specific researcher to recommend, but I'll do some homework. COVID impacted social development for younger people, but that's outside my expertise. Humans are resilient, and while the pandemic had lasting impacts, many psychological and social effects will diminish with time. For long-term healthspan, forming strong community, social, or family connections now is critical. I've been thinking about this myself recently, making an effort to improve social connections, and most people can do that. It's like exercise for your community; neglecting it may cause that pillar to crash later.

[70:00]
Lowell: I have some fan questions and rapid-fire ones. When you wake up in the morning, before you look in the mirror, how old do you feel mentally? Is there an age associated with your internal feeling?

Matt: That's a good question. I feel young. My wife says I'm a 13-year-old at home, so that's probably about right.

Lowell: LastCall2021 mentions a dichotomy in IGF-1's role in aging. Some supercentenarian populations have downregulated IGF-1 receptors, and knocking out IGF-1 receptors in mice makes them smaller but longer-lived, yet it affects muscle mass maintenance. Can you give a short answer on the connection between IGF-1, mTOR, and PI3K?

Matt: In mice, nematodes, and fruit flies, reducing insulin/IGF-1 signaling increases lifespan, discovered early by Cynthia Kenyon and others. These growth-promoting pathways, connected to mTOR, show that reduced signaling during development leads to longer life and slower aging in lab models. In humans, moderate reductions in these pathways are enriched in centenarians, but causality isn't proven. Extreme reductions, like in Laron dwarfism, don't extend lifespan but protect against some age-related diseases. Reducing growth signaling likely lowers disease risk and may slow aging, but humans' social and environmental interactions complicate this. Reducing mTOR with rapamycin benefits healthspan and lifespan, but maintaining muscle mass, which promotes mTOR, is also beneficial. Chronic inhibition of mTOR or IGF-1 in middle

age might increase frailty and isn't likely to yield large longevity gains. It's complex, with no simple answer.

[75:00]
Lowell: TechnoFuture8 asks about mesenchymal stem cells and exosomes. Are you aware of them, and what are your thoughts?

Matt: I'm aware of them. There's interest in stem cell therapies for regeneration, and exosomes, lipid-bound particles secreted from cells, may carry rejuvenating properties. It's a promising research area with evidence in animal models, but I wouldn't inject mesenchymal exosomes myself today. There's no regulation, so you don't know what's in these preparations at clinics, which makes me nervous. I'd like to see stronger regulation, perhaps by the FDA, to ensure purity, quality, and outcomes, bringing these therapies onshore for more confidence.

[80:00]
Lowell: This might be the last fan question due to time. StoicOptum notes that in rapamycin RCTs, there's a risk of unblinding due to side effects like mouth ulcers. Have you thought about this in future human trials, and could it be mitigated by careful endpoint selection?

Matt: In a randomized double-blind clinical trial, neither the provider nor participant knows who's getting the placebo or treatment. Mouth ulcers, a known rapamycin side effect, could lead participants to conclude they're getting rapamycin, potentially unblinding them. However, canker sores occur in non-users too. A study soon to be published shows 4-5% of non-users and 15% of rapamycin users reported mouth sores in the past three months, so it's not definitive. In a well-designed trial, you'd measure biochemical and functional outcomes—blood parameters, grip strength, walking speed, echocardiographic parameters, cognitive assessments—less susceptible to bias from perceived treatment. With a large, long enough trial, concerns about bias from unblinding are minimized, though not eliminated.

[85:00]
Lowell: A quick bonus question: do you recommend any books people check out, not necessarily in your field, just ones you've enjoyed?

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

Lowell: Thank you, Matt, for coming out today, and thanks to everyone listening for the fan questions. Sorry we couldn't get to all of them. The best place to stay up to date with what you're working on is your Twitter, where you seem very active. Is that correct, and thank you for coming?

Matt: For now, Twitter is the best place. I have a love-hate relationship with it, with periods of activity and periods where I don't look at it. I realized recently that muting people who annoy me

works great, as I don't see their nonsense. It trains the algorithm, and it's better than getting frustrated.

[89:13]