Dave: What is autophagy? Why do we care about it?

James: Well, autophagy itself is a mechanism that allowed bacteria to hunker down when times were tough, when nutrients weren't greatly available, and to be able to provide some amino acids to their system from their own cells. So, they would break down proteins and organelles into the amino acids, so that the cell could keep making proteins that allowed it to function.

Announcer: Bulletproof Radio, a state of high performance.

Dave: You're listening to Bulletproof Radio with Dave Asprey. Today's cool fact of the day, is it? Yeah, airplane sewage is actually as bad as you thought. Oh, when I was a kid, I used to always wonder, when they flush the toilet, does it just come out and fall down on someone's house? And I was horrified at the thought. It turns out that they don't really do that, they do have holding tanks and all that, thank goodness. But, the bacteria that's in there is full of bacteria resistant antibiotics along with a smorgasbord of genes that also confer drug resistance. That means that when the airplane that lands in your city from whoever knows where, could be spreading antibiotic resistance. In fact, we may be spreading it all over the planet, according to research by German microbiologists. They looked at five German airports and 90% of 187 E. coli bacteria they isolated and tested were resistant to antibiotics, and some of them were resistant to more than three.

Dave: And scientists found that only 45% to 60% of common gut bacteria collected from inlets to German wastewater treatment were drug resistant. What does that mean for you? Don't sit next to the bathroom on the airplane. Okay, you already knew that, you didn't need any science for that, that's just the worst seat you can possibly get on the airplane. But, what it means is that you might want to just make sure that your overall resistance to infections is where you want it to be, so that you're less likely to get infected. Because, let's face it, there's no really controlling whether you're going to be exposed to bacteria, but you can control whether the ecosystem that is your body, is going to be a place where they can take residents.

Dave: Things like taking your vitamin D, A, K, adequate glutathione levels, and all the things that are a core part of living a healthy life are necessary, avoiding inflammation, not getting drunk on airplanes, all that kind of stuff. But, bottom line, it's interesting to think about how do antibiotic resistant bacteria move around the planet? Airplanes are a rapid vector, but until we get rid of commercial, industrial animal feed lots, we are going to have broad problems with antibiotic bacteria and antibiotic resistant bacteria, and that is what to do. And that one's real easy, don't buy feedlot beef or chicken ever again in your life, and you'll have struck a blow for healthy bacteria around the planet.

Dave: Today's guest just came out with a brand new, very well received book on living way longer than you're supposed to on intermittent fasting, and on turning on a switch in your biology. If you're a longtime listener, you might recognize his name because he was our guest in episode number 608, and his name is James Clement. His book has been very well reviewed as well. It's got endorsements from me, from Dr. David Perlmutter, who's been on the show several times, Dr. David Sinclair, who's just on the show a couple of times, and Dr. Mark Hyman, who's a dear friend, who's also been on the show

quite a few times. And you've might see Dr. Steve Horvath, who is a professor of human genetics at UCLA, and even George Church, who's one of the, I'm going to call him the grandfathers of anti-aging. A professor of genetics at Harvard, wrote the foreword for this book.

Dave: So, it's a book endorsed by some of the finest people looking at anti-aging and all. And James talked about health span last time, but we're going to get really deep on some techniques that actually work from a book that's now becoming very, very successful. And I think you guys are going to love today's episode, because James isn't actually a medical doctor, he's a lawyer and an entrepreneur, turned to research scientist who spent the last 20 years studying life extension. And I met him, geez, it has to be 10-plus years ago, back when I was still a tech guy, and he was just getting really interested in this stuff, and we've stayed in touch ever since. So, James, welcome back to the show.

James: Hi, Dave. Thanks for having me back.

Dave: You identify yourself as a transhumanist, and yet, you wrote a book talking about intermittent fasting. Transhumanists are well known for wanting to upload themselves to the internet and replace their arms with rocket launchers and chainsaws. Why are we talking about intermittent fasting instead of nanotechnology and replacing your brain?

James: Well, those are certainly fun topics and I love reading about them, but the most important way to transcend our biology is going to be through life extension. There're certainly a lot of people who need life extension technologies now, and not 20 or 30 years from now. So, that's why I chose to focus on this with the remainder of my energy and resources till we move past it and we can look at other things.

Dave: So, do you think I can have a rocket launcher or just a chainsaw or a laser for an arm at some point in my life and would I want to?

James: I think you definitely could have some of those now. It would probably be pretty messy.

Dave: That was a very rational and truthful answer. I can't argue with you there. And by the way, if you're listening is going, "Dave, what are you talking about?" I actually believe in making full and efficient use of my existing hardware before I bother replacing any of it, but I'm not above and beyond replacing it when the ROI is the highest thing there. But I don't think I need a rocket launcher, I'd probably want more storage and computer power. But, hey, that's just me. Now, something I love about The Switch, James, and I thank you for the very early copy, people who follow me on Instagram saw me holding it up a while back, you talk about this urgent sense, if you don't get going on this stuff now, and this stuff being intermittent fasting, and something called protein cycling, where you and I are early voices in that idea, and keto, you're saying you're going to miss it.

Dave: And some books, even mine, I'm maybe less urgent, I'm saying, "Look, you can do this, but you don't have to." And you're smacking people in the face saying, "If you don't switch over how your metabolism works, it's going to suck." Why the urgency?

James: I wrote this for a specific audience, and I would say, that's individuals past 40 years old, who are starting to enter the highest cancer and diabetes and heart disease risk portion of their life. And what you know from median age, is that, 50% of the population will be dead by a certain median age. So, for men, it's in the late 70s, for women, in the early 80s. That's half of our population that are going to succumb to cancer and heart disease by that time. So, I think it is urgent, especially in our group of people who are thinking, "I want to do something to live longer," but they haven't really put their house in order yet. So, they may have BMIs that are just way out of proportion to what's considered healthy, they may not be optimizing their supplements, and they may be following some general guidelines, like, "I've cut back on my calories, or I've started a ketogenic diet, or I've gone vegan," without really knowing what it is about those particular lifestyles and diets, that confer a health and lifespan benefit.

James: And so, the purpose of the book is really to go into this molecular biology mechanism inside the cell, which is about as basic as you can get. If you're not working these mechanisms properly, then it doesn't matter what your good intentions are, or the practices that you think you're following, you really need to be activating these proper switches and biohacking as you and I would call it, so that we can get the best effects that we want.

Dave: This switch you're talking about is the switch between autophagy and mTOR. And people who've read The Bulletproof Diet, even back in 2014, there were sections where I talked about these in the context of diet, but since then we've learned so much more about these two states and the things you can do to manipulate them. Can you define autophagy for people who haven't read your book yet or who just haven't checked it on that side of biohacking? What is autophagy? Why do we care about it?

James: Well, autophagy itself is a mechanism that allowed bacteria to hunker down when times were tough, when nutrients weren't greatly available, and to be able to provide some amino acids to their system from their own cells. So, they would break down proteins and organelles into the amino acids, so that the cell could keep making proteins that allowed it to function. This, over billions of years and through lots of evolution to humans, has resulted in a much more refined mechanism that actually selectively takes out misfolded proteins and high ROS-producing mitochondria, dysfunctional mitochondria, and leads the good ones. And so, this has become part of human longevity, is the fact that we need this switch, this autophagy portion of the switch, turned on from time to time, to do repair and to clean out the cell of all these toxic particles.

Dave: Now, what turns on autophagy? For me, in the book, in mind, and this is what, I guess, two, three books ago, I talked about fasting as a way to do it, but there's more than just fasting or calorie restriction. What's the list of ways people can flip that side of the switch, that came about from your research?

James: The primary mechanism is this mTOR complex, made up of mTORC1, 2 and 3. Almost all discussions are about mTORC1 and 2. And for our purposes, most of the longevity benefits have to do with inhibiting this mTORC Complex 1. And that is fed into by numerous other biological switches above it, AMPK being probably one of the better

known ones, which looks at energy levels. So, primarily, the AMP versus ATP ratio, ATP being the energetic currency of the cell. And when you don't have enough energy, the cell basically says, "We need to stop reproducing, stop growing the cell," and as I said before, "Hunker down and actually produce some of the amino acids and things that we need from inside our cell." So, it turns out that there's an increasing number of these sensors, some that are actually in the cell membrane, and are sensing things like insulin and IGF-1 levels in the bloodstream, other sensors that are measuring the amount of oxygen that's available to the cell, others that are measuring specific amino acids, branched-chain amino acid in particular, leucine, isoleucine and valine.

James: So, all of those things are required on a checklist, for the cell to say, "I want to go into growth mode and do a cell division, or just make lots of proteins." And if one of those checkmarks are missing in their checklist, you've gone into a hypoxic state temporarily, or your energy levels have declined, then the cell will stop this cell cycle process, and it will wait until those nutrients become available down the road.

Dave: So, then, if I want to turn on autophagy, you talked about the mTOR autophagy switch, that's, you wrote the book's about. But, okay, I want to eat up more of the cells that need replacing. We've got calorie restriction as a technique, and, in fact, let's go through the list of techniques here, and then let's talk specifically about calorie restriction, because you and I both know a bunch of people who say, "I can live on one-third less calories than I need and I'm stick thin, and I'm like Mr. Smithers," and they're really not happy people, but they think they're going to live longer, and that's not what you're talking about, I don't.

James: No.

Dave: So, we've got calorie restriction, okay, there's intermittent fasting, even if you don't cut calories. There's very low carb diets, i.e. ketosis. There're certain types of exercise and certain types of supplements. So, that's kind of the universe of biohacking we're playing with around engaging autophagy. Did I miss anything there? I'm just going from my notes from the book.

James: Only hypoxia.

Dave: Oh, yeah. Okay.

James: So, the lack of oxygen is also a trigger for inhibiting mTOR.

Dave: Good. I did that lack of oxygen thing just this morning. It was great. I was fasting, I had my coffee and inhibited my oxygen in one of the machines from Upgrade Labs. We call it the atmospheric cell trainer, and it's one that takes you up to basically the height of Everest, and then back down to sea level, then up to Everest. So, it gives you brief bouts of intense hypoxia followed by bouts of sea level. So, it does that sort of thing. I was a little dizzy after that, as I normally am, then you feel really good afterwards. But I actually didn't have intermittent hypoxia on my list of triggers, just in my own notes. So, okay, there're six things then, right? Okay, calorie restriction, how much do you have to

restrict calories in order to regenerate or, at least, to kill off the cells that need killing off in autophagy?

James: Well, when we look at populations that have undergone calorie restriction, whether it's because of war or lifestyle, like the Okinawans, it's somewhere in the 20% to 30% range. And if you dip below that, then you're actually impeding nutrition too much, and, of course, long-term calorie restriction carries its own problems. It's one of the reasons why I tried to emphasize cycling in the book, and the fact that this isn't just one thing you do and you forget it, you go into a ketogenic diet and you never get off of it, or you go into calorie restriction. Yeah, exactly. And I learned some of this the hard way myself. I've seen a number of elderly friends of mine, who have read about metformin and rapamycin and these things, and they've gone on them, thinking, "I'm going to greatly reduce my cancer risk." But what they've also reduced are their immune cells, their stem cells, and their muscle cells.

James: And so, you can't do these things on a continual basis, it's like, as we were saying, "Fasting is good, so, I'm not going to eat for the rest of my life."

Dave: That's the same thing with the vegan diet, "Eating more plants is good, therefore, I'm only going to eat plants for the rest of my life, no matter what happens to me, and the same thing with dirty keto. Oh, sugar's bad, therefore, I'll never eat a carb again." And all of them end up in being miserable, angry, and then dying sooner than you should have. But, at least, that's the nuts of what I've found over my own experience being a vegan, being a keto, for what was dirty keto in the 90s. But, is there anything else around the calorie restriction, other than that point? But, when you restrict the calories, do you care what kind of calories they are?

James: Absolutely. That's one of the key points here, is that, your insulin levels and your branched-chain amino acid, essentially-

Dave: By the way, you said insulin levels.

James: I have no idea what that means.

Dave: I was just waving, I have a continuous glucose monitor on, so, I just [crosstalk 00:16:58] over. But it's in European units. So, I just ate with carbs, and it's around a hundred. Not bad for post-carb meal at a hundred, but I'm just saying, yes, blood glucose and I was visually agreeing. If you're watching on YouTube, you know what talking about. If you're on iTunes, sorry, visual stuff.

James: So, the switches that turn off and on mTOR, for purposes of most people's interventions, are going to be the amount of blood sugar and insulin in their veins, and the level of IGF-1 and proteins that are available to the cell, particularly, leucine. Leucine is found mostly in meats, including fish and chicken, but also in higher concentrations in dairy, and even more so in concentrated areas such as cheese. As an interesting part of what I found out when I was reading about this, human breast milk has four times less leucine than cow's milk. And when you think about children growing up, and you look at

like hunter gatherers, they're carrying their kids on their hips, or keeping them in close proximity for five or six years of their life.

James: And cows, on the other hand, have no way of caring for their young, other than to hope that they can run into the center of the herd and be protected, or to run with the herd, if the herd is running away from a predator. So, it's in the cow's best interest to increase growth as much and quickly as possible, but that hasn't been necessary in human evolution. So, human breast milk is much lower in this particular growth activating a protein.

Dave: And so, what does leucine do for autophagy? It turns off autophagy?

James: Yes.

Dave: Got it.

James: Leucine alone can turn on mTOR to activate it, and to cause cellular growth and protein production, and to stop the beneficial activities of autophagy.

Dave: What do you think about BCAA supplements during fasting?

James: During fasting it's probably counterproductive.

Dave: Exactly. There're still people trying to do that. How about in ketosis?

James: Well, again, it depends. Interesting thing with biohacking is that you can have your cake and eat too. You can literally cake and take rapamycin and your mTOR is going to be down regardless. You can go on a starvation diet, and you can take hydroxymethylbutyrate, and you won't lose muscle. HMB is a particular butyrate that will spare protein catabolism. And it does so by activating mTOR, even in a starvation state. So, you could cycle back and forth between autophagy and mTOR, even while staying on a restricted diet, or do the reverse and stay in autophagy or acquire autophagy, even on a fairly high glucose, carbohydrate-rich diet.

Dave: So, you're saying I should-

James: But for the average person, that's going to be too complex to try and do.

Dave: But you're saying I could make a recipe for the blog or for the rapamycin frosting to go on cake, and then people could have their cake literally, or do I need to put chromium in there too?

James: Oh, they could literally do that. Yes.

Dave: But, guys, don't do that. And please don't do that.

James: I don't think it's recommended, but some very courageous biohacker might try a month of this kind of living.

Dave: And then, with HMB, which is something that's known in weightlifting circles, you would use that because it's activating mTOR. Why would you want to activate mTOR during fasting? You really don't want to. You would use it at the end of a fast? Or how would you use that?

James: Yeah, again, that was simply during the times that you want to turn on mTOR, you can supplement with the branched-chain amino acid leucine, you can get this through dairy in a way, for example, or you could take hydroxymethylbutyrate, which is a metabolite of leucine. All of those would upregulate mTOR and would spare muscle wasting. And I think these are going to be the kind of supplements that in really elderly people, who are not taking in a lot of proteins or their body is no longer making the kind of enzyme levels that would degrade proteins and allow the body to use them very well, that it would be important for them to supplement and to try to increase their mTOR levels and to build and preserve their muscles. Again, all through cycling, they wouldn't want to do this absolutely continuously, nor would they want to turn on autophagy and inhibit mTOR continuously.

Dave: That last part about cycling is the most frustrating thing that I've come across. And it breaks my heart when I sell these keto, keto, keto brands out there, and, guys, you're doing it wrong. My experiences with this is that you have to go into, you have to go out of it, or you can cheat, I use Brain Octane to bump my ketones up, even though I have a moderate to low amount of carbs. So, I'm always able to have ketones present. But, if you don't cycle things, you break. And even with this sort of advanced biohacking stuff, we want to do it, the problem, and this comes from the interview with B.J. Fogg, I just did, who's a Stanford behavioralist author of Tiny Habits, is that we want to make a habit every day, because those are the easy habits to do.

Dave: And if your habit is, "I pop a rapamycin and metformin and HMB or whatever, and I just do it every day," but it doesn't work like that. Or, "I'm going to lift heavy every day." All you're going to do is grow injuries, you're not going to grow muscle after a few months of that. So, this might be something you're doing on Betterhumans on your webpage, is there a calendar for people, saying, "All right, this month, do this, this month, do that, this week, do this"? Because I'm going to have spreadsheets, I track a whole lot of crap and I'm like, I am probably taking my polyphenols at the wrong time of day but there are limits. Have you solved that problem for yourself? Or do you have an AI engine running your lifestyle for you? How do you actually do this as the author of a book?

James: I've been using Google Calendar for probably 10 years, and I have been marking down my blood glucose, my blood chemistry measurements, all this stuff on Google Calendar, because then I can go back and search for a date or I can search for a peak or something like that. It's not perfect by any means, but I can also put notes ahead of time, saying, "One month or two months from now, I want to try something different." Or, I'm cycling on mTOR. So, while the constant banners across my month for everyday might be mTOR, and the other month might say autophagy. So, I do give myself reminders as to what my meal plan is supposed to be for a particular month. And I talk about this at the

end of the book about meal planning and which kind of diet you should choose for yourself, because I think there's a lot of options.

James: Vegans can make it work for themselves, but they need to do some supplementation. Carnivores can make it work for themselves, but they have to be careful too. Because, too much of the wrong proteins in meat and overconsumption, also leads to gluconeogenesis, so, they end up with both their glycogen reserves at a level where mTOR will never be turned on as well. So, I totally agree that this is a complex area. I've tried really hard in this book to make it simple, but I think people really need to understand the basics of what turns this switch off and on, so that, when they read another article or the dairy association, or some other company is advertising how healthy oats are for you, or how healthy eggs or dairy is for you, you'll know where that fits in your place of mTOR and autophagy.

James: You'll say, "Oh, eggs, dairy, meat, those things are high in these branched-chain amino acids to keep mTOR turned on, that's the stage I'm going to be in next week, so, maybe I'll start buying some eggs and dairy for next week. But this week, I'm in autophagy, and I'm going to stick with low-glycemic carbohydrates and make sure that my protein levels are relatively low.

Dave: One of the things that I liked about your approach in The Switch, is you say, "Look, do what I'm talking about for eight months of the year." That means, for one month, you're saying, "All right, I'm going to do low protein." Another month, "I'll do higher protein." You're going back and forth. So, sometimes you're in, get rid of stuff you need to get rid of, sometimes you build stuff you need to build. So, you create these gentle cycles throughout the year. But it's only eight months out of the year. What do you do the other four months? Is this like birthday cake and beer? What do you do if you're not doing anything else?

James: I was actually just thinking earlier of the birthday cake and beer scenario, meaning that, if you wanted carbohydrates, if you wanted proteins, you can feast. It was certainly part of our evolutionary history and I go into a lot of the paleolithic and evolutionary information that's available nowadays, to show that it's very likely that most of our ancestors, I think you and I both are probably Northern European descendants, that they underwent 20,000 years of ice age. They didn't have high energy carbohydrates available at every turn, and they needed to store fat for these long winters, and the body became very good at doing this. It's one of the things that I think is really important for people who are interested in weight loss, is to actually be understanding the mTOR switch, and the fact that when you're in an anabolic state, and your glycogen reserves are full, your body is actually going to go into a fat storing mode, or, if you want to call it a fat sparing, it's sparing it from being burned as energy.

James: As long as the glucose is available, your body's going to use that because it fully expects, based on 90% of human history, that that's going to run out really shortly. And you're going to be stuck with your 150,000 calories worth of fat that you're carrying on your body. Because, believe it or not, 150-pound male is expected to have only about 880 calories of glycogen stored in his body, in his liver, in his muscles, and a little bit in the bloodstream, but 135,000 calories worth of fat. So, imagine how long you can go on

135,000 calories, if you're burning 1,000 to 2,000 calories a day. So, this is what the body has evolved to do. But we're in a period of abundance, where these high energy carbohydrates are not only freely available, but they've, in many cases, been engineered to trigger all the right buttons in your brain and your gut.

James: So, you're actually fighting the gut bacteria as well because they've evolved to give you a dopamine response, when they get their high carbohydrates, and you have to wean them off of carbohydrates, for that process of every time they get hungry, they're going to send you a hunger message and make you eat something, to get that little dopamine release that they produce.

Dave: I've been playing around a lot over the last couple of years with different types of prebiotics soluble fiber, ended up making something called Inner Fuel, which is Bulletproof's version of that with multiple fibers in it, and they don't raise blood sugar. They do get eaten by the bacteria, so, the bacteria are fat, happy, making short chain fatty acids that your body needs anyway, but you don't get that maybe response from bacteria. I have yet to find any data about what soluble fiber does to autophagy or mTOR or prebiotics. Have you seen anything?

James: Well, most of the data has referred to fiber as being something that doesn't count towards the carbohydrate load that turns up insulin. And I've tried this numerous times on myself by taking, Dave and I have chatted about this numerous times, I take between 60 and 100 grams a day of fiber, and I've never seen an insulin increase due to taking fiber.

Dave: Yeah. What I do is I'll put 30 grams of, this is soluble fiber, the kind you digest, not the sawdust, Metamucil kind of stuff. I will put that in my Bulletproof coffee in the morning, and I'll look at my continuous glucose monitor and it doesn't go up. That's a huge amount, that's probably even a hundred calories worth of soluble fiber, if it even counts as calories, which it probably does, because if it gets turned into short chain fat by bacteria and you metabolize the fat, you probably lose some of those calories in the metabolism of it. But, regardless, no change on glucose, same for Brain Octane, and same for butter or in coffee, tiny, tiny increase, but similar to what you get when you wake up in the morning from cortisol, it's not a big deal. If you lay down in bed and get your blood glucose, it's going to be one thing, and then you wait 20 minutes after you got up, it's going to be up a few points, because that's part of the waking up in the morning process.

Dave: So, you don't have any issue with autophagy then with soluble fiber, none that you found?

James: I don't believe so.

Dave: I don't think so either.

James: I don't believe so at all.

Dave: No one's ever studied it that I know of, but all the mechanisms don't point to it. Okay. And you do about what I do, I do between 60 and 80, usually, of soluble fiber, plus vegetables and all that stuff, so, I'm probably getting a hundred. And I think that's an important thing that no one in keto does, even though, Inner Fuel's keto, any sort of soluble fiber that doesn't raise insulin should be keto. That's a question I've been asking a few people who are experts on this show, but talk to me about what, well, there's three kinds of diets that sort of driving as I mentioned to earlier, there's the vegan diet, which is not understanding that plants want to kill you. There's the keto diet, not understanding that your gut bacteria will kill you if you don't feed them. And then there's the paleo diet, which is probably way too much protein is bad for you.

Dave: But, I want to talk with you about what goes wrong when you choose any of those diets. And so, not that any of them are bad, except the vegan diet is the worst, I just have to tell you, having been a raw vegan, that shit will kill you. But, aside from that, what goes wrong with the vegan diet?

James: I have a friend who is a long time vegan, I found out that they were eating like cauliflower pizza with nondairy-

Dave: Aah, highly processed food.

James: And soda. And their justification was, "But I'm on a vegan diet, and you've said that the Loma Linda vegans are really healthy and better off than most Americans." And the thing is that, you can say a candy bar is vegan. You can certainly find lots of processed foods that are vegan. It doesn't make it healthy. So, I'm very much a fan of eating close to the earth, meaning that products that haven't been manipulated very much. Vegetables, I don't really eat much fruit, but I do like berries, and I think that those are important nutrients to provide your body. Nuts, of course. And I prefer fish mostly because I can't afford the low omega-6 versions of meat, and I certainly don't want to buy from a CAFO, concentrated animal feeding operation is... I also supplement with omega-3 and DHA as well. I'm trying to get my membrane percentage of omega-3s up to about 8% to 10%. And for me, that takes about three to four grams a day.

Dave: Yeah. So, the vegan diet, they're not going to get their omega-3s, they can be on, well, actually, plant-based is another pseudonym for cheap.

James: Well, grains are plant-based meat and I eat no grains at all. And I think it's a terrible choice for most humans to consume a lot of grains. But, you could be purely vegan and be a severe Type 2 diabetic as well, if you're having pasta, rice, all potatoes and all kinds of very high energy carbohydrates. So, again, I prefer the low-glycemic vegetables, broccoli, cauliflower, asparagus, spinach, things like that, and you can eat pounds of them and even still be in ketosis.

Dave: Oh, yeah, you can get tons of veggies, but what about oxalates and lectins? I mean, spinach is a huge source of oxalates, which is a big issue. I know a lot of people who go vegan, end up getting plant toxicity from so-called healthy foods. And they build up oxalic acid throughout the body, you get vulvodynia, you get gout, you get joint pain. By

the way, all of this happened to me when I was a raw vegan. So, I'm speaking from experience.

James: I totally agree with that. And nuts also are high as well. And it was actually Joe Mercola who pointed out that there was a woman who specialized in this and had come up with a supplement. It's basically a protein that you take that obviates this problem.

Dave: Oh, a protein, all right. I just saw the interview, I'm actually going to have her on the show. But it's interesting just as we're going through, okay, you want to turn on autophagy, and you end up eating lots of oxalic acid, which also happens if you have toxic molds, and it's going to cause inflammation, which is metabolic dysfunction at its core. So, suddenly, your blood sugar will be not as effective as it could be, because it's shunting energy into inflammation, instead of managing your metabolism properly, and you just go, "Oh, wait, I thought I was doing it right." So, I think people who are going to be unending vegan are going to not like how they'll look when they're old, but it's better than standard industrial diet by a long shot.

James: Oh, yeah. Most of these diets are, in their own way, exclusionary. Right?

Dave: Mm-hmm (affirmative).

James: So, when you go on a paleo diet, a lot of people are pretty pristine for a while, and then they'll maybe get a sweet tooth craving and go to Whole Foods and buy some desserts that are made, claiming to be paleo, but then you'll see that, well, it's got tons of honey in it now instead of raw cane sugar, and that's supposed to be paleo. But, now you're triggering all the bad things that we talked about before. High blood sugar means high insulin, which means mTOR is going to be running at full steam.

Dave: Yeah. They also, though, they sleep better that night because they're eating too much protein that didn't have any carbs. And similar thing for the keto crowd as well, we know they eat bad fats and they eat too much protein as a general rule and not enough fiber. So, is there an approach? I mean, I'll be the first guy to say, "Okay, I was a card-carrying vegan, and I was even angry, like you would expect from doing that after a while." But, I would tell anyone here, "Look, if you know how to do a vegan diet for a month, which means avoiding the inflammatory vegetables that most people, especially the more vocal vegans will tell you are the healthiest ones, like, "I have a kale tattoo or something." And you're like, "Dude, do you know about thallium and oxalic acid? Because that stuff is, it doesn't even taste good and it's not healthy either. Throw it out. See if you can find a pig who'll it, and you might be able to see my pig spit it out. But, whatever, just get rid of that stuff."

Dave: So, you can be a vegan for your month when you want to reduce protein consumption, and there's an argument for doing that. Or, at least, mostly vegan, and that's okay. So, yeah, do a vegan cleanse for a month, you'll probably feel good. But then, so are membranes. Well, what would you do if someone was vegan for a month? What would you do the next month to help rebuild what they took out?

James: Well, definitely you'd want to do those things which turn back mTOR. So, you might suggest that they go to vegetarian and include dairy. They wouldn't necessarily have to eat meat, but, if they were eating cheese, then they'd be getting plenty of leucine. And of course, you can just buy leucine supplements or this hydromethylbutyrate. But, that's probably cheating because that probably comes from cow milk as well.

Dave: Hey, all plants come from dead animals. The soil is made out of animal poop and dead animals. It's really tough to really be a vegan because you have to kill yourself. But, anyway. So, let's assume that they're willing to take HMB because they can't see the animal, they're okay with it, which is how that works. So, then, they could be vegetarian or they could just say, "All right, I'm not a vegan, there isn't an environmental argument for it." By the way, that's a whole different podcast, and the health argument for it is specious at best. But, "Okay, I've done a low protein vegan or quasi-vegan for a month." When you come back, you could go vegetarian and start pounding the cheese and eating some eggs, or you could just say, "I'm going to have some grass fed beef, because I like it when animals poop in my soil, so I can eat my broccoli later. So, I'll support that part of the world."

James: Or, yeah, something more sustainable, whether it's eggs or dairy, as opposed to something that's based solely on slaughterhouses. I think that's an individual choice and where you get the protein is not so much as important as what proteins you're getting. And you need these branched-chain amino acids.

Dave: Say that one more time, because people say, "Oh, I need a high protein diet." And you're saying, "Hold on, what kind of protein was it?" And you're saying what's in it is what matters. So, branched-chain amino acids, leucine, isoleucine and valine, and those are common in muscle meat, they're common in cheese, they're less common in milk but present, right?

James: No, they're higher in milk than in meats.

Dave: Oh, no, but in cheese is more concentrated.

James: Well, cheese is concentrated milk.

Dave: So, it's higher than in milk.

James: Yeah, hard cheeses are the most concentrated. So, that's where you find the highest levels. And it also means that, when you're eating a cheeseburger, so, meat, cheese, and then a white flour bun, you're getting a perfect mTOR of sandwich. Same thing with pizza. So, you have the carbohydrates, the cheese, the meat, if that's what you have on it, those kind of things will definitely activate mTOR. One of the groups I really fell in love with studying were the Mount Athos monks, and I talk about them in one of the chapters. These people reduce their calories 180 days out of the year, but not the other 180. And it's sometimes in stretches of 20 to 40 days of reduced calories. And we're talking about like 900 calories, or 600 calories, as opposed to a normal working amount.

James: But then, they have fees, and they're allowed to have meat and dairy and wine and all this good stuff. And this is all based on their religious Eastern Orthodox calendar, and so, they end up with actually quite a few fee stays as well. And I think this is actually a very rational way of living, where feast and famine that is being your guide for turning on and turning off mTOR. You should have three, four days in a row, three, four weeks in a row, or three or four months in a row, and then, off and then on. I base most of my estimations that you need mTOR suppressed in autophagy on eight months out of 12, mostly because of the cycle that most of the world goes through, where there's a winter on a summer, and summer is the time where plants are productive and you end up with grains and berries and all these good things. And then there's a winter, where you're forced to just eat fat and beet, and much less than in terms of these high energy carbohydrates.

James: And so, I think, we probably, over the course of 900,000 years or more, evolved to that kind of a seasonality. And so, if we followed this in our own life, it's going to be hard to be wrong.

Dave: Now, if we did that seasonally, the circadian nutrition is a big deal. Eating in the middle of the night screws you up, eating sugar in the middle of winter when it's dark outside, screws you up. So, I mean, you're proposing every other month in the book, or as one of the ideas.

James: It's actually one of three type of plans, and that's even described as, you just need to cycle and you need to do probably more autophagy than mTOR. But again, it depends on the person's baseline. So, if they're really overweight, I would recommend people going on into a ketogenic diet, reducing their carbohydrates, turning their fat burning mechanism on, and only occasionally going out of that to turn on mTOR. And when they get down to a reasonable BMI, then they can start stretching out those time periods in which they're activating mTOR, that they're having fees, so to speak, and I think that's going to work out better for them. If you have a 89-year-old individual, who's not digesting proteins very well, and eating like a bird, the last thing you want to say is, "I think you should try a four-day fast."

James: It's going to be devastating for them, and their immune system's going to crash, and their stem cell levels are going to go way down. And so, you have to be appropriate to your existing physiology, your history of what your body has been doing and used to, and then work on how you're going to cycle that, to get to the place where you want to be.

Dave: What would happen to someone who just turned on autophagy without end, and just said, "I don't really need mTOR"? If they do this when they're young, I mean, mTOR is more of a bigger deal as you get sarcopenia over age 60 when you have muscle wasting. Until then, why wouldn't I just be on autophagy all the time?

James: One of the things that's controlled by mTOR is cell proliferation. And in fact, the way that rapamycin protects humans from the rejection of transplants, and is used as a medication for that, is to stop the differentiation of certain stem cells. So, basically, it stops those cells in mid-growth cycle, and puts them in a pause, and they can't

differentiate into the type of T cells that would go on to attempt to reject the transplanted tissue that's been put into you. This is valuable in knowing that mTOR controls all of your cell proliferation. If you put the brake on it all of the time, you're going to lose not only muscle cells, but cardiomyocytes. So, your heart's going to be weaker. You're going to lose your cartilage cells, your immune cells. And I've had a number of friends that have gone on metformin, and they've thought, "I'm going to do 2,000 milligrams a day. I'm going to really reduce my risk of cancer by putting this break mTOR as much as possible."

James: And then, six months to a year later, they're telling me, "I don't know what's wrong, but my white blood cell count is near zero." And it's the fact that they haven't allowed those cells to proliferate either.

Dave: Is this a problem? If people go on a vegan diet, which is very low protein, do people get this problem with too much autophagy and not enough mTOR?

James: It doesn't appear to be the case, but, unfortunately, there haven't been good studies in people like this where you go across different lifestyle, dietary patterns like ketogenesis, vegan, carnivore, et cetera, and you measure all these different levels. Is mTOR turned up or down? Is autophagy turned up or down? And you'd probably want to even take those measurements at different points during the day. Because, if your glycogen stores are being refilled daily but not overfilled, then, you're going to deplete them, and by the morning, you're going to be in a state of autophagy. But, by early breakfast or lunch, you're going to be back out of that state and into the mTOR state. And I think this is, again, how humans evolved. We didn't stay up too late past sundown, we didn't run to the refrigerator for snacks until 10:00, 12:00, 11:00, have one last snack before bedtime. And so, the body fasted overnight for much, much greater periods of time than we do currently.

Dave: Okay. That makes good sense. The reason I'm asking that is not to pick on vegans, it's more when my experience as being, I was a raw vegan, I spent a lot of time on food when I did that. This was back after I lost a little bit of the weight, but this is, geez, early 2000s. And I was very, very dedicated to doing that, and I actually wonder, I did have low white blood cell count at the time, a low neutrophil count actually, and no one could figure out why, but you made me think about that. I wonder what's going on there. You write another one of the chapters in the book, The Switch, is called Walnuts and Corn-Fed Cows, and you talk about these different types of dietary fat. And it's one thing I like about your work, you're saying, "Look, it matters what's in the protein, more than where the protein comes from. And it matters what's in the fat, more than where the fat comes from even." Why did you call it Walnuts in Corn-Fed Cows? What was your point there?

James: Well, I had been doing a deep dive into the omega-6, omega-3 ratio, and I was trying to find out what it was in paleolithic times. And there's not a strong consensus, but there's a general consensus that it was probably somewhere between 1:1 or 2:1. And I think it probably matters a lot where the population was located that they were studying. So, if they were in Spain or the coast, they were eating a lot of shellfish, and so, they may have had much higher omega-3 levels than those who were living in a cave in the middle

of Germany or France. I think that probably matters in why we're picking up small variances. But, if you look at Americans, in 1909, the ratio was about 5.4:1. And in 1999, it was 10.6:1. So, the ratio had even doubled in the last 100 years, even though we were primarily eating livestock and grains, the same that we're doing now, the change I think has primarily been that the livestock was mostly pasture-fed then, and the livestock now isn't.

James: I grew up on a farm, it was actually my grandfather's farm. My parents didn't farm, my dad was an electrician, my mom a nurse, but my grandfather had pigs, cows, chickens, the whole works, and he grew soybeans and corn and hay, again, for a long time to feed his own animals. And they would be pasture-fed 90% of the time. He would bring them into the barn and give them corn, right before bringing them to slaughter. And I'm sure that their omega-6 levels were a whole lot better than what I would find if I went to an inexpensive grocery store in America now.

Dave: I've written a lot about this, I think, three of my last five books I've talked about these things. And in Super Human, I went into great detail about which cell membranes in the body will change in which ways, based on the composition of the fat you eat. Again, regardless of where it's from, it's what's in there. And the life extension foundation years ago and most of the anti-aging people would tell you 4:1 would be the ratio of omega-6 to omega-3, that's ideal for anti-aging. And I got mine down to 1.58:1 one time, this is going back a while. And then, a guy from UC San Diego, the first guy to do a full 3D rendering of his own colon, a computer science professor, Larry Smarr is his name. A really interesting guy.

James: Yeah, I met Larry.

Dave: Yeah, you met Larry at a dinner with him. It was great. He actually took out his 3D printed copy of parts of his colon and put it on the table while we were eating sushi and I took a picture of it for my, it was probably Facebook before Instagram times, and he said, "Can anyone tell me what kind of sushi this is?" And I'm like, "It's a piece of colon, guys." But, it was pretty funny." Anyhow, he is the only guy to ever beat me. He was something like 1.09:1. But, I'm not certain that we want to go that low, that you might actually have excessive fluidity of cell membranes, if you push the ratio too far. And you've studied anti-aging for 20 years, you've talked to the leaders in the field in a similar way and probably even much deeper than I have. What's your gut feel? And that's based on scientific knowledge, but also just based on pattern matching. Where would you want your number to be in your ratio of omega-6 to omega-3?

James: I would want mine, and this is what I strive for, to be somewhere under 5:1, and certainly, better to be under 2:1.

Dave: Really? Under two? You'd go that far down.

James: That's what I'd go, yeah. But my weakness for omega-6s is probably almonds. So, almonds have quite a lot of omega-6. Walnuts, much higher though. And that's why the chapter heading includes walnuts. To my pleasure, macadamia nuts are extremely low

in omega-6. Their ratio of omega-6 to omega-3 isn't tremendously better, but the amount of PUFAs in general, are just tremendously low compared to the monounsaturated fats in macadamia nuts. It's something that you can eat quite a lot of, and not even blink an eye. But if you actually look at how much omega-6 fatty acids there are in walnuts, pecans, and certain other nuts, and you'd think, "I'm eating an ounce of this a day." Well, you're getting like 3,600 grams or some ridiculous amount of omega-6, unless you're having tremendous amounts of fish or fish oil, you're just not going to be able to balance that appropriately.

James: We do know from lots of studies that have been done on inflammation caused by insects or omega-6, it does get counterbalanced by omega-3. So, if you increase your omega-3, so that, not necessarily by cutting back your omega-6, but by increasing the three levels, you can decrease the amount of inflammation. I've actually experimented quite a bit with looking at C-reactive protein in my body, doing things like increasing omega-6 from eating a lot more nuts, or from eating grains from certain types of vegetables, and I find it's a really great biomarker of inflammation. And when I cut out grains entirely, I had a really low C-reactive protein level already was 0.8:0.5. And when I cut out grains, it dropped to 0.25.

Dave: Grains are bad for it.

James: Which basically means I have no inflammation at all in my body. So, it's a way that if you really want to dive deep into this thing, you can determine, I think, on your own, what's the appropriate omega-6 to omega-3 ratio for yourself. You can also take these tests that tell the amount of omega-3 that's incorporated into your cell membranes, and it does seem that, from scientific research that I've read, that somewhere between eight and 10% is an ideal amount. And they find that neuroexcitability and all these good things that you want to happen in your brain, is triggered or optimally expressed at these levels.

Dave: For me, I like my levels between two and four. And walnuts are interesting because a lot of the research that's done on 6:3 ratio, people are getting from refined seed oils, which is already an oxidized omega-6. You're reading a walnut that's not roasted, that's, especially if it's been refrigerated, okay, I'm getting some omega-6 that is present in cell membranes and is necessary as a building block, and you're not getting the lectins and oxalic acid that's pretty darn high in almonds. And people are saying, "Dave, why didn't put almonds in your protein bars?" I use cashews on purpose, because they have less reactivity and way less oxalic acid. So, you see, knock off attempts at bars using almonds, it's cause they don't know the biochemistry. And I found that not eating a ton of almonds is a good idea because I was getting inflammation from the oxalates and the lectins.

Dave: So, I'd rather eat a few walnuts but not too many, and make sure that I take my omega-3 supplements. Fortunately, I formulate them, so, I get my bottles from Bulletproof, I don't have to pay for them, which is nice. So, it's a delicate balance, but I would just say for you listening to this going, "This was too much, Dave. James, what were you talking about?" Here's the deal, don't eat a lot of omega-6 fats, never eat fried and processed omega-6 fats, eat more omega-3s, and you're probably going to feel better. But if you

think you're going to live on just walnuts and omega-6s, your cell membranes, as you read in both of our books, they're not going to look right. And if you look deep in Super Human, the chapter on fats, it turns out that 6:3 ratio is most expressed in your white fatty tissues. Which means that if you eat a lot of corn-fed whatevers, or lots of walnuts or any other omega-6 source, the parts of you that'll change the most will be your white fat, it'll become pro-inflammatory, and the ratio in your brain changes dramatically in that order.

Dave: So, if you want to have really inflammatory white fat, just load up on the sixes. You want to live for a very long time like James and I are working on, you've got to either cut those down, crank up your threes, and not have too much white fat anyway. Is that a good summary?

James: Absolutely. Even on a ketogenic diet, you can load up on macadamia nut oil, on avocado oil, and other healthy oils, and stay away from the high omega-6 oils.

Dave: Exactly. And that's a core part of The Bulletproof Diet recommendations, which is a cyclical keto or avoiding other inflammatory things. But bottom line, there is more to learn than that, and I think The Switch has a very good explanation of this autophagy mTOR, and these are things that are present in the biohacking world. Things that are, even if you go back to The Bulletproof Diet roadmap, one day a week, you can turn on autophagy, just by having less than 15 grams of protein, and I called that protein fasting. And it's on the infographic. It's just something that I didn't put a lot of attention into, we didn't have as much science but you just, you blew the lid off with your book, saying, "All right, here's what we need to do around not just autophagy."

Dave: Because Siim Land has been on talking about metabolic autophagy, that's one side of it. But your idea of a switch and saying, "How would you live to turn the switch on or off?" I think it's a real contribution to the field of anti-aging and to biohacking. And I'm happy you could be on the show again, James. And thanks for writing it and thanks for your incredible focus on research and just on giving back. I appreciate you.

James: Thanks, Dave. I really appreciate being called back and I've talked to Siim a number of times. I think we agree about almost all the key points. And the takeaway I would basically say is that my book is directed at the person who really wants to optimize their lifespan and health span. You can cut corners and you can say, "Well, I just can't fast that often, or I can't do these things." But you have to realize that your health won't be quite as optimal as you might later hope for.

Dave: Very well put. And if you guys, you're listening to this saying, "What should I read?" You should read The Switch. It's a really good book and it's very likely that you're, at least, thinking about living a lot longer. You hopefully by now have listened to one of my dozens of attempts to get you to read Super Human as well. There's great alignment but not a lot of overlap between the two books. There's so much to know about what you can do and what's useful but not necessary, and things that are non-negotiable, if you want to live a lot longer. And we're zeroing in on what those actually are. And going through periods of autophagy and not doing it too much is one of those non-negotiable items that you've got to figure out how to do that and this is a great guide to do it.

Dave: On that note, I would also ask you, if you do decide to read The Switch, or if you read Super Human, or better yet, buy them both, what the heck? Then they'll be paired up on Amazon, everyone's happy. But if you read a book, leave a review. It is one of the simplest and free ways you can express gratitude. And we all know by now, if you've listened to even just a few episodes, that gratitude makes you live longer. So, part of your anti-aging strategy should be leaving a review for The Switch. It's just science, right? Okay. On that note, if you're watching on YouTube, you can probably see right now that James is laughing. And if you're just listening on iTunes, hey, that's cool. But I appreciate you listening today, I hope you learned something useful, and I'll see you on the next episode.