The Switch: Ignite Your Metabolism With Intermittent Fasting, Protein Cycling, and Keto: A Special Interview With James Clement

Dr. Joseph Mercola

JM: Dr. Joseph Mercola
JC: James Clement

JM: Welcome, everyone. This is Dr. Mercola, helping you take control of your health. Today, I have got a real treat for you if you're interested in living healthy. I've got one of the sharpest scientists in the United States in the aging field. His name is James Clement. He has written a book, "The Switch: Ignite Your Metabolism With Intermittent Fasting, Protein Cycling, and Keto," which is going to tell you how to live healthy to be 100. We're having a really engaging discussion later in the interview about how to go beyond that, if you're interested, and do it in a healthy way.

But anyway, let me give you a brief history of James. He has no formal scientific or medical training. He's a lawyer by trade, but he loves to solve puzzles. I met him early last year when I contacted a person named Reason who has a blog called "Fight Aging!" I was really curious about finding – I was diving deep into the senolytics and I just needed someone to answer some questions. Reason suggests that I contacted James.

I invited James over to my house. He lives not too far. He lives in Gainesville. He came down and we literally didn't stop talking for about six hours straight. I don't think we ever even stopped for food. But it was the most engaging conversation I've had for a long, long time. He's read 20,000 scientific papers, which is just beyond extraordinary. He gets his information from the research. He's a researcher himself. We'll talk more about that. But I think that's probably enough of an intro, James, without me messing things up along the way. Welcome and thank you for joining us today.

JC: Thanks, Joe. I'm really pleased to be talking with you. I'll say that I was incredibly impressed with how much effort you take to stay up with the scientific literature and how vast your area of knowledge is.

JM: Well, thank you. That's why we resonated so well, because we both share similar passions. That is to live as long as you can. You really are one of the leaders in this field from my view. I think anyone who doesn't know of your work is missing the boat. You actually told me – At the time we met, I didn't realize there was actually a transporter of the nicotinamide adenine dinucleotide (NAD) molecule, which is used therapeutically clinically, and hold, not a precursor, the actual NAD itself. A superficial review of the literature would suggest it shouldn't work because there's no transporter. But you pointed out where the transporter was. That was really the game changer for me.

But there are so many other things and so much to talk about. But you wrote this book because there was a need for people to understand the basics. You put together a manual that essentially tells people how to – The switch is the switch between activating mTOR and not activating it, which we'll got into deep. But most people are not going to live to 100. That's just the facts. There's no way you're going to live to be 150 if you don't live to be 100 first. That's sort of like the kindergarten groundwork that you've got. You review the primary basics on how to do that. But not just the things that people have been talking about for decades and centuries. But the new information that we need to know how to upregulate mitochondrial function and activate all these other important pathways to set the stage for the future.

JC: That's right.

JM: Yeah. Why don't you talk about your journey? I don't want to spend a lot of time there. But I think for people, it's important to know how you got to this state. I know the problem, the challenge with you is to not go on a tangent. I want to go straight to the meat.

JC: We did a lot of that in conversations. For the time that I can remember, I've always been interested in longevity. I think it was probably because of the stories my great grandmother told me when she was alive. I was like 25 or so. She saw the Wright brothers and travelled across the country in a Conestoga wagon and saw Indians in the South Dakota et cetera. This is the same woman who also saw the Gemini, Mercury and Apollo space flights and watched men walk on the moon. I thought, "Man, in her youth she never would have imagined these things. What are we going to be able to witness 100 years from now? We would never have imagined the technologies and things people would be doing."

I just didn't know that there was any sort of field that dealt with this until Durk Pearson and Sandy Shaw's book came out in 1982. I happened to be a third-year law student at the time, married to another law student. As soon as I read the book, which I did in like two days, I said, "I'm going to be a molecular biologist." She said, "No. You aren't." But in a funny mood. But I did start reading molecular biology. I became very passionate about keeping up with anti-aging science.

I was lucky enough in 2009 to go on the board of the first direct-to-consumer genome company called Knome that George Church had co-founded. I had my own whole genome sequence in 2009. George was the scientist who read me my interpretation of my genome. We started talking about aging. I found out that he had this similar passion. We came up with a project called the Supercentenarian Research Study. That sort of launched my becoming a full-time scientist as opposed to a lawyer and entrepreneur that I've done previously.

JM: Yeah. Thank you for mentioning George Church. For those who may not know who he is, you might have seen the 60 Minutes interview that they did with him at the beginning of December. That was last month. It was all about reversing aging. He is a professor of genetics at Harvard Medical School. Really, in my view, he's probably one of the premier scientists in the world at actually reversing aging. We'll go into more details on that. But actually, George wrote the foreword for James' book. They're really close collaborators. I believe you stated in the book that at the time you were considering doing a Ph.D. program. Why don't you say it yourself? Because I'm just going to paraphrase what you already know.

JC: Well, I first approached him with the idea. I've been going to a lot of medical conferences and scientific conferences on aging. What I thought was going to be the most powerful tool for reversing aging that I could tell that would be in a path that if I spend the next five or ten years working on would be useful, it was to take otologists themselves, those are ones from our cells, and to genetically alter them so that we would get rid of our genetic predisposition to various diseases and improve our odds of not being diabetic, of not having Alzheimer's, of lowering our cholesterol and all the things that are land mines in our lives to help shorten our life. Eventually, through this Supercentenarian study, they figured out how those people make it to 110, still riding bicycles, taking world cruises, often working and driving their own cars, etc.

JM: Yeah. It might be a good tangent – I guess what I wanted to say to that before we go into with the supercentenarians is that you ask George if you should just do a Ph.D. program. He said, "Are you crazy?" Because he mentors a lot of Ph.D. students. Tell them what he told you. Tell us what he told you.

JC: We were a couple of years into the supercentenarian project. I was starting to open my own lab. I started a vivarium and eventually added 1,200 mice that I raised by myself in a small lab with a couple of interns. At that time, I approached George and asked him, "Do you think it would be beneficial to my credibility and career and knowledge to enroll in a Ph.D. program?" George kind of looked at me and said, "You're doing projects that grad students would give their right arm for. You're already reading 10 to 20

scientific papers a day. You're involved in writing up research papers. This is what a scientist is. This is what they do. You don't need to go work for someone else to learn this processes." I stuck with what I was doing.

[-----10:00-----]

JM: Yeah. That's a really strong testimony to the fact that you don't need to have formal accreditation. I mean it's a nice process. It certainly provides many people who aren't as gifted and disciplined as you to do this process, to get some of those skills. Even if they do that, there's no assurance that they're going to achieve the level that you have. Congratulations. You're a rare bird and an inspiration to others to know that this path is possible. Why don't you expand a bit on the supercentenarian project? Because I think it's intriguing. First, describe what a supercentenarian is.

JC: I came across papers in my early research from Dr. Nir Barzilai's lab at Albert Einstein Medical School, and Tom Perls, particularly, at Boston University, where they had looked at the health of centenarians and those individuals called supercentenarians. Those were the individuals who have made it to and past their first decade. They have to be 110 years old to be called a supercentenarian.

At any given time, there are somewhere between 50 to 80 supercentenarians in the entire world. In the United States, about 20 validated supercentenarians at any given time. I think it's about 120,000 people in the U.S. who make it to 100, but only 20, at any given time, get to 110. I thought by just reading these papers, that they were an incredibly interesting group of people. But it wasn't until I started meeting them in person to do these blood collections, talked to them and found out what their lives were like, what they ate, smoking habits, all kinds of things like that, that I discovered how really incredible they were, how they had essentially been what you would consider 70- or 80-year-old health up until maybe 105 to 108, and then slowly aging started creeping up on them. They had no age-related disease of any kind and usually died from an immune failure just a month before their death; or they came to an immune failure and got pneumonia and would die in a very short period of time.

JM: Yeah. That is an important point. But you've got to get to 100 first. If you do reach that level, then somehow, improving the functioning of your immune system is going to be an absolute essential criteria if you have any hope of making it longer than that.

JC: Absolutely.

JM: Yeah. Actually, it's not even over 100. There are many elderly people, 70s, 80s and 90s, where it's an immune insult that gets them. It's not heart disease or stroke or dementia.

JC: I would argue that in many respects, supercentenarians are merely leading normal aging, and that all the rest of us are experiencing accelerated aging.

JM: That is a very good point. It really sort of capsulizes what your book is all about – to help us lead normal aging as a consequence. This is the key, because a lot of people get distressed. "I don't want to be 90 years old, crippled and in a care facility." But this is free of any diseases or impairments or disabilities or frailties. We don't want to spend the whole time talking about supercentenarians, but you did publish this study. What were the most dramatic findings? We hear a lot of these stories, a person of 105, and what their tips and successes for living that long. But you've interviewed most of these people. So what did you come up with?

JC: Well we know from work that's been by the two researchers I mentioned, Dr. Barzilai and Dr. Perls, that the siblings of supercentenarians have a 17 times greater chance of reaching 100 years old as "normals."

In genetic terms, 17 times is an amazingly strong gene relationship. We know that this protection, whatever it is, is in the genes. It is carried to the offspring and brothers and sisters. In most of the families that I talked to, there were aunts and uncles or mothers or fathers who'd also lived well past 100, often 105 or 108, et cetera. Again, this reinforces the idea that there is a very strong genetic component. Nir Barzilai determined a number of years ago that in women supercentenarians, but not in men, there was a mutation in IGF-1. I don't believe it was the receptor, but it was IGF-1 pathway. It makes them short in stature, small women, so 5 feet is about the size of the normal supercentenarian woman.

JM: Really? I did not know that.

JC: Yeah. They're very, very petite women in general.

JM: Like Laron syndrome in some ways.

JC: Well, not quite that severe. But definitely along the same lines. In men, it tends to be a growth hormone mutation that similarly makes supercentenarian men somewhat smaller than other men. In both ways, this a tie-in, of course, to the switch. It limits mammalian target of rapamycin (mTOR) and turns on autophagy. One of the things that we did find in studying supercentenarians was that they very much carry the same characteristics that you would find in like miniature or teacup animals. For example, pigs and dogs. We have lots and lots of examples of the miniature version, like the pinscher, for example, where the full-grown version of this dog lives 7 to 9 years, but the miniature version lives 15 years. At 7 or 9 years, they're still young and frisky and doing all the dog things. Whereas the full-size dogs are on their last leg, so to speak.

JM: Interesting. Why don't – I guess it's a good time to really go into the switch and allow you the opportunity to discuss what mTOR is, the benefits of turning it on and off. And then I think we can dive deeply. Because I think understanding that switch and optimally integrating that understanding into your lifestyle can have enormous – And actually let me even exaggerate it even more – beyond enormous benefits for improving your health and longevity.

JC: I totally agree. I like to start off with sort of the 30,000-foot view. To do that, the discussion really has to take into account evolution. TOR, from which mTOR also derives and from which we evolved that mechanism, started with bacteria. The things that all organisms need are nutrients, the ability to make proteins and to reproduce. When resources are abundant, they do these things. When resources are scarce, which is what nature generally provides, you consume all the resources in the spot you're in, and then you have to go out and seek new resources. The organisms that developed ways to hunker down and to protect themselves during these times of scarcity are the ones that survived and we evolved from. We evolved and carried with us those genes that protected bacteria, yeast cells, C. elegans worms, drosophylla, mice, primates, et cetera. They all have a version of mTOR. They all go through this metabolic switch called mTOR and have an anabolistic state, anabolism, and a catabolic state, or catabolism.

JM: Some people may not know those terms. Anabolism is improving in growth, essentially improving muscle mass, where catabolism is breaking down, repairing and regenerating. Actually not regenerating, just repairing and removing.

JC: That's right. Catabolism is really the phase that the cell goes into when resources are scarce. The cell is essentially looking to quit making proteins or slow down protein production and not to do cell division. But instead, to try and find poor resources which we can do even internally through this process called autophagy.

[-----20:00-----]

We should probably talk about what autophagy is. I like to use a metaphor because we're talking about what goes on inside a single human cell, again, evolved all the way from bacteria. Basically when these genes get turned on, it creates the little garbage truck light into these, inside the cell that find, surround and encapsulate misfolded proteins and dysfunctional organelles and then bring those to a recycling center, called the lysosome, which is basically a big bag full of acid that breaks down these proteins and organelles into their component parts and then releases it back into the cell. So you end up with these dysfunctional, unusable, misfolded proteins, which the cell can make being turned back into amino acids that can be rebuilt into new proteins that are better, and replacing organelles, like mitochondria, that are dysfunctional.

For example, they produce too many free radicals, reactive oxygen species (ROS), then specifically autophagy will be directed to and take these high producing, highly dysfunctional mitochondria to the lysosome to be broken down and to be gotten rid of. This is very beneficial for the cell. It's beneficial for the organism. It's something that obviously sounds like, "We would want this thing turned on on a regular basis."

Now, the problem is that like all other organisms, humans, for most our evolutionary history, encountered this feast-or-famine state. And only until really recently, like literally the last 150 years, has food production, industrialization of farming and livestock management and refrigeration, all these wonderful technological achievements have made it possible so that people in the West, in particular, have a never ending abundance, mostly of foods that we didn't evolve to eat in the first place.

JM: Yes, indeed. So that process of breaking down of mitochondria is called mitophagy. The key is to cycle back and forth between the two. You learned about mTOR long before I did. My mentor who initially introduced me to that concept was Ron Rosedale. He actually introduced onto me a fear of mTOR that got me into serious trouble because I just thought that you should be actively inhibiting mTOR continuously. I was down to like 60 grams of protein. I was very cachectic and getting frail. I kind of learned through life that that was not a good approach. It's not the approach that you advise in your book, because you've got to cycle back and forth between the two.

JC: That's right.

JM: Why don't you go and take it from there?

JC: Well, you have this state in nature where humans evolved with seasons mostly. During the summer months, you have vegetation: fruits, nuts and grains. All these things occur in abundance. Life is good. Everyone's fed and happy. And then the body puts on more weight. It gets more muscle and then you enter, for most European descendants, a very long, cold winter. Of course 10,000 to 20,000 years of human evolution in Europe also involved these monstrous glaciers and incredibly cold weather that prevented us from having this sort of abundance that we have or think about having as even Paleolithic people.

So of these two states, the anabolism, as you rightly pointed out, is for the cell growth. That includes stem cells. The stem cells replace your muscle cells with satellite precursors. You have cardio myocytes, which replace heart tissue. You have chondrocytes that replace cartilage in your body, on and on and on. All of those require that mTOR is turned on. If you learn about mTOR and you say, "Well, I don't want cancer, and turning on mTOR full-time and really keeping autophagy off and mTOR on leads to cancer, then I'm going to do the reverse." What you end up doing is not having a strong populating of stem cells, not replacing damaged tissue or muscle wasting and you end up losing muscle mass through sarcopenia.

I experienced this myself. I think we talked about this when we met, that I was on a vegan version of the ketogenic diet for five years. I was doing this as self-experimentation in a way of doing autophagy. I ended up losing a lot of muscle mass. But as soon as I recognized what was going on and really thought about the

literature and what this meant, I realized that I was foregoing the thing that nature had previously required, which is that you go through this feast. One of the things that I concentrated in this book in doing is not only discussing the molecular mechanisms of MTOR and autophagy. But also, showing these large populations that we have in the world, from not only hunter-gatherers who are still alive and living that kind of lifestyle, but more importantly for us in the West, people in Japan, in California, in Greece and Italy who are currently living lifestyles that are modern, except for their food intake and are in fact living much longer, much healthier, not getting exposed to these diseases of civilization, as it used to be called. I don't know if you've come across this, but in the mid-1800s, European and American countries that doctors all over the world, to colonies, then to explore things. They came across populations that were not consuming sugar and flour and lots of meat. They were following more of the traditional hunter-gatherer lifestyles. These people didn't have diabetes. They didn't have Alzheimer's. They weren't getting hypertension and cancers.

They started referring to this difference as our having these diseases of civilization and the native hunter-gatherer populations that they were meeting not having them. As soon as they saw those populations, whether it was Okinawans from the big island on Japan, coming to places like Hawaii and the mainland of Japan, and all of a sudden being exposed to different ways of eating, grocery stores and fast foods and things like that, or people up in New Guinea going to New Zealand and all of a sudden being in the middle of an urban center where there are all these food possibilities, they saw those people immediately gaining weight, becoming obese, getting diabetes and later dying from all of our diseases, like cardiovascular disease, atherosclerosis.

JM: Yeah.

JC: Cancer, et cetera.

JM: Yeah. Let me just summarize that because I think most people on our site already know this, because we've talked a lot about it previously about the work of Dr. Weston Price, who was a dentist in the early 20th century who went around the world and documented those things. We actually have a 21st century version of Dr. Price, who is Dr. Chris Knobbe, who's an ophthalmologist. Price was a dentist, Knobbe's an ophthalmologist.

He plans to go around the world and document age-related macular degeneration. He proved very conclusively. He wrote an extensive book on this. It had never existed before in the 1900s or 1920s. He concluded that it was just the result of processed foods. That's all it was: processed foods, primarily processed oils. And it's extending that to heart disease and cancer, which didn't exist in the same timeframe. I mean it was there but it was a very, very rare disease.

[-----30:00-----]

I think we're all in agreement that that's not the issue. We know. We kind of beat on it on our site too. We've been writing about that for many years. But I want to focus on are the things that haven't been done, 21st century tweaks that we can do to improve this. So yes, stay away from processed foods if you want any hope of living long and healthy, you've got to avoid them like the plague.

JC: I think for a lot of people, they really do need to learn the molecular mechanism, this evolutionary mechanism that we have, how it works. And then two weeks from now or months from now, when they see a television commercial about dairy, a cheeseburger, a pizza or something like that, they'll know what those ingredients are going to do to them and how those ingredients are going to affect that switch and ruining their chance of keeping this balanced, the cycling of mTOR and autophagy in the right direction.

JM: Yeah. I couldn't agree more. That sounds like a very frightening approach for many people who might be listening to this or watching it. That's because pizza is the favorite food of America. There's no question. It used to be my favorite food too. But the really good news here is once you apply these principles and you develop metabolic flexibility, the ability to easily switch back and forth between burning fat and sugar as your primary fuel, then you don't have these cravings. They simply disappear and you have this knowledge and understanding. It's so easy. It's not like you have to have iron-willed discipline or willpower to do this. It's just easy. It's just easy as can be. It's not something that you have to be afraid of. It's just that you love life and you enjoy what you eat and you just eat healthy foods. It's not a burden or a challenge.

JC: We have a whole chapter describing the different ways that you can implement this in your own life. There's no one plan. There are basically guidelines. We certainly allow – Because this is how these groups that I've discussed – the Okinawans, the Loma Linda Seventh Day Adventist vegans, the Mount Athos monks who fast 180 days a year – these people still are allowed feast days. You can still have your pizza, your cheese, cake, ice cream, et cetera, but you can't do this day in and day out. You can't leave mTOR essentially on and the brakes on autophagy full-time.

JM: Yeah. That's the key. That's what I want to talk about now. I think that's where the gold nuggets are. It's understanding how do you – What's the best way to get this switch going on and off and what's the frequency and the timing. The devil's in the details. I think there are even more details that you discussed in your book that I really want to expand on here. I think no one who is rational, if they've carefully examined the evidence, is going to disagree with the fact that time-restricted eating, which is restricting the amount of time that you're eating your food is absolutely essential to stay healthy. Now the question becomes "What the window is," and "How does that window change?" Would you agree?

JC: I totally agree with that. I'm a huge fan of both intermittent fasting, which is really better described as time-restricted dieting. I personally have gone now to a four-hour window. I never was really a big breakfast eater. I have a couple cups of coffee in the morning. But historically, breakfast didn't exist until the middle ages. We didn't evolve as cave men eating at 6 a.m. or 7 a.m. breakfast of eggs, toast, jam and milk. It's literally in the English version of the name, "break-fast." It's the period in which you're breaking your overnight fast. This is essential to keeping mTOR down and autophagy on as long as possible.

I would argue that this is what people evolved to have autophagy turned on every single night of their life, not just on occasions when they would like once a year would go on a fast or try a ketogenic diet for a month and then go back to the normal lifestyle.

JM: Yeah. So the key then is to get this time-restricted eating window. You and I were both doing – Well, I was doing four-hour window for many months, and you're doing it now. But I'm evolving. I'm thinking that that window needs to change. That four hours is okay, but maybe not continuously because I think it's running down the same mistake that you and I both did because we're zealots at this, with "A little bit is good but more is better," so we do prolonged fasts. We're activating autophagy too much. The key, the absolute key is seeking to identify what the optimum is for each individual.

What I wanted and hoped to accomplish for this conversation is to give people principles and philosophies on what they can use to determine what that is, with some starting guidelines. First of all, according to Dr. Satchin Panda, who I think you know well, out of Salk Institute, he's done surveys and found that 90% of people eat over 12 hours. I think both of us agree that is not a good idea. That is a prescription for metabolic disaster, right?

JC: Yeah. I totally agree.

JM: Somewhere between four and 12. I think you probably – four to eight is probably your sweet spot. Maybe you can do 10 hours occasionally or maybe even more than 12, but four to 10. So I've actually just recently come to the conclusion that maybe it's only four hours a few times a week. That's it. And then because – I want to go on another tangent. I really would love your feedback on it because they're clearly – I mean even if you're fasting for 20 hours a day with a four-hour window, you're going to activate autophagy and you'll get some of the benefits of a multiple-day fast. Not as many, you won't.

But my understanding or belief is from the literature I reviewed – I'd just love to get your opinion on it – is that when you're in that long fast, that 20-hour fast before you're eating, in that hour or two hours before you eat your food, if you are aggressively exercising, meaning really nailing the hammer and doing an aggressive workout, pushing it, you are going to activate autophagy even further, increase metabolic markers like 5' AMP-activated protein kinase (AMPK) and decrease insulin-like growth factor (IGF) or might increase at least IGF in the muscle. But anyway, you're going to suppress mTOR even more. Would it be reasonable to assume that if you integrated a long time-restricted eating window and you integrated that with the exercise that you may be able to achieve the benefits of two to three day fasts?

JC: I totally agree. One of the problems in discussing autophagy is that the general public has it turned off all the time. Most of the –

JM: Our audience is a little smarter than that. They're not the general public.

JC: I agree with your audience. But by and large, the average person, who is in fact obese and on seven medications by the time they're 70 years old and has hypertension and all these problems, those people got there because they weren't paying attention to this switch. These discussions that people like you and I are having about autophagy tell people essentially what to do to turn it on but hasn't really focused in the past so much on the balance.

The fact that we need both sides of this. I've also concentrated on – You and I have talked about this before as well. "What are the triggers that turn on mTOR?" Because if we want it on, then we want to make sure that we aren't taking supplements or doing something else in our lifestyle that tends to inhibit it, when actually it's a period of time when we want it turned on.

It turns out, and I think you've read the literature of David Sabatini, the mTOR guru, that basically one amino acid, a branched-chain amino acid named leucine, which is four times higher in dairy than it is in human breast milk, that this one amino acid essentially locks on mTOR. Generally speaking, if you are consuming dairy or animal meat, you will likely have sufficient levels of leucine. Now, the cell also needs, for mTOR to be working fully, it needs the insulin levels to exist, which means you need certain levels of blood sugar that will essentially trigger insulin to be relatively high, and causation – Sorry?

JM: Doesn't insulin appear to be a stronger activator of mTOR than leucine?

JC: My understanding is that leucine is almost like a key that alone, without any help from anything else, in sufficient quantities, will trigger mTOR activation and turn of autophagy.

JM: But relative to the insulin, does insulin do it stronger? Or you're suggesting that you can't, even with high insulin levels, activate mTOR unless you have leucine?

[-----40:00-----]

JC: Without leucine or sufficient amino acids, mTOR is going to essentially wait. That's what autophagy would actually be meant to do. It's to create more amino acids by breaking down organelles and misfolded proteins and things like that to supply the cell. It's got the sugar. It's got the energy. The insulin receptor is turned on but it lacks the amino acids. So through a short bout of autophagy, the cell would most likely have enough to go through with cell division or protein production.

JM: Okay. Makes sense. So the recommendation, I think, for the general public is spot on. If you're having large amounts of dairy or animal proteins more than 12 hours a day, that is just a prescription for disaster. But the contrary is that's not what we're recommending. Anyone who's wise or rational or who's read the literature is not recommending it. We're recommending a relatively restricted eating window. If you're only eating for four hours, six hours or even eight hours and you're fasting the rest of the time, I think that it would appear that the amino acids from an animal protein or dairy, even though they may be relatively high in leucine, become less problematic, especially if you're integrating aggressive exercise in the fasting period, because they're going to drive those levels down, so you're still essentially switching mTOR off in that period.

JC: That's right. And if you look at the diets of these people who don't have the diseases of civilization, which include, as I said, the centenarians in Okinawa, these monks in Greece, these vegans in Loma Linda, California, you see that what's really happening is that they're running through their glycogen stores, in their liver and their muscles overnight. Because we only carry about 800 calories worth of energy in our glycogen stores. It doesn't really take that much. Even metabolically resting, like through sleep, burns up calories that your system becomes in a deficit state and insulin drops, glucagon goes up, and you enter this catabolic state.

That can happen every day. I think it's probably how humans evolved and probably we want to have happen most of the year. And you don't see that they have early sarcopenia or other problems. They're still having their feast days. Even the monks that fast and break their fast – It's not a water fast, they're having, I think, 700 to 900 calories a day on their fast days. But no. They're not allowed dairy. They're not allowed wine or meat on their 180 fast days a year. But that still means that they have 180 days in which they are having dairy, wine, bread and sort of more normal foods.

This balance is what people have to find. I personally think that it's going to be somewhere along the ratio of 8 to 4. And whether you make that eight days in a row of a sort of turning down mTOR and two days of turning it up consecutively or four months on of autophagy and then two months off in a repeated – there are lots of different ways to do this. In the long run, I don't think we know what's absolutely optimal. We just know that cycling back and forth is the way to do it. Probably if we keep those periods relatively shorter, especially as we get older, the chance that you're inhibiting mTOR too long goes down.

JM: Yeah. I just had a conversation with a medical consultant prior to our interview. I'm really excited about this. I want to share this with you because I think I've developed a new strategy, which is called cyclical time-restricted eating. It looks like this: Two days a week, I eat in four hours. One day a week, I eat in eight hours. And the other five days is somewhere in between.

JC: Okay.

JM: Yeah. And then making very sure that on the tail end of all of those – and I want to talk about this next, it's the exercise, because I think this is the part of the equation that most people who talk about autophagy really miss. That is fasting exercise. Right before I eat, as close as I can before I eat, I will do a really hard fasting workout. I do that pretty much every day. Well, not really intense resistance training with regular conventional weights. I only do that twice a week because you need about three days to recover. But I do something called blood flow restriction training.

When this interview comes out, we're going to be, this month in January, we're going to be discussing that extensively. It's something I introduced you to. There are a lot of different varieties, but the form that I think is the best out there is KAATSU. You've got an older unit and we just got upgraded to the newer one. First of all, if you can comment on my cyclical time-restricted eating and then we'll go into the integration with the exercise and the fasting state.

JC: Well, I certainly think that that's a regimen that's going to work, whether it's right for everyone more out of lifestyle, then whether or not it's the perfect regimen or whatever, I don't really know.

JM: How can you? Right.

JC: Yeah. But I do think that the idea that we cycle back and forth between turning mTOR on and turning it off. It probably, on the whole, we want it off more than we want it on, because that's where all the long-lived people have. They all have mTOR more suppressed than the normal people.

JM: Yeah. That's the key. I'm really excited about this. I think it's a strategy you could have because most people, I think you and I both, we get a target for a window and say, "That's it. It's going to be four hours every day." Just totally ignoring the possibility that you can have a hybrid system. It just never occurred to me before I talked to this consultant that that is an option. Just knowing how the body loves the variability, it makes perfect sense.

JC: Yup. That sort of goes against my personal nature. I'm one of these guys who has a very limited wardrobe.

JM: You and I both.

JC: I tend to not want to think about food or clothing and things like that, and focus on whatever I'm interested in at the time, like in this case, solving these aging questions. For me, just knowing like, "Okay. Between 11:00 and 3:00, I eat." I don't really have to worry about how much I eat because it's sort of self-regulating anyway. But under a four-hour window. I have a food type. I eat very low-glycemic vegetables. But I'll have 2 pounds of vegetables a day. I vary back and forth between straight vegan and pescetarian, meaning that I eat fish, primarily wild-caught salmon.

[-----50:00-----]

I focus on keeping my diet clean and healthy, as you said. I have no grains. I dropped grains from my diet several years ago. I noticed that, as a self-quantifier who does a lot of blood tests and even more so that I have my own laboratory, I've noticed that my inflammation markers, which were relatively low, had just completely plummeted once I stopped consuming grains.

JM: Yeah. That was a good move. I think it's wise for most people to consider that option. My first book, the first book I ever wrote – I've written 14 now – was the "The No-Grain Diet," so I couldn't agree with you more. What are your comments on integrating the exercise, specifically the KAATSU? I know you've got the new unit now. Have you started using it in the blood flow restriction cycling mode when you're walking.

JC: Yes. As you know, I'm a big fan of walking. It's also really good for my mind that I go out on literally 4- to 8-mile walks about once a day. It's really hard to get a power workout in a walk. I keep my endurance up and my ability to absorb oxygen and things like that. But with the KAATSU, it has an amazing ability

to actually stress my muscles in a way that makes them grow and get stronger and larger without really having to do weight presses and those kinds of exercises.

JM: Yeah. Or at least heavy weight presses. You can do weight training, resistance training with it with very light weights, literally one-fifth of what your maximum lift would be.

JC: Yup. I do deep-knee bends and that sort of thing.

JM: You could do it with body weight too.

JC: Yup.

JM: So then you like the concept and agree with it, at least in theory, that it could pretty significantly activate the benefits of autophagy if you do it fasting? Because there's a lot of debate in the sports world, especially if you're a competitive athlete. Do you think you need more glycogen, sugar and glucose? So they'll integrate that. You can't work out as hard if you're fasting. That's for sure. You're not going to get as big a lift certainly. But it may not be necessary. The goal isn't to get bigger. It's to improve your metabolic health.

JC: Right. And not all sports, like sprinting, for example, require a burst of energy. Again, when you think about the energy that we carry in our bodies, a 150-pound person carries about 880 calories in blood sugar, glucose.

JM: Glycogen. And that's split between the liver and the –

JC: And about 130,000 calories with the fat. If you train your body to be metabolically adapted so that it could switch back between fat-burning and glucose-burning, and over a five-year period of fasting fairly frequently and going on a ketogenic diet, I think I can metabolically adapt to the lack of glucose very, very quickly now. I don't even notice when I don't eat. It's just my body basically says, "Okay. We're not getting carbs right now. We're not getting the energy input that we expected. We're just going to quietly switch over to burning fat." I don't even feel it.

JM: Yeah. Actually, you had mentioned before or previously that you chose a vegan diet. That could be problematic, but you're very wise. You really addressed the supplementation issue. Even one of the most important ones, that's not really well-appreciated in most people who choose that path. Most people get the B12 right and the DHA, but they miss important nutrients that they're only in animal foods. There are four of them. There's carnitine, carnosine, choline and creatine.

The one that intrigues me is the one that you were taking large amounts of, basically from a longevity perspective, because of its purported association with improving telomeres, which was carnosine. I think that maybe one of the most important nutrients in meat aside from B12 is carnosine, and you're not getting hardly any of it because it really is only in muscle meats for the most part. And seafood too, but you were getting a lot of it so that was good.

But I want to switch to a different topic now. That is really what kind of attracted me to you. It's this NAD. Maybe just give us a brief description from your perspective of what NAD is. Walk us through what you're doing now. You have one of the – It's a very, very difficult biomolecule to measure. I want you to describe that process. You've been going through the last six months to a year to set up your lab to measure this. Tell us what the process is and tell us how many other people in the world can measure this thing accurately.

JC: Sure. I'm friends not only with George Church in Harvard Medical School but also David Sinclair, who you've spoken with a couple of months ago. I was meeting with David in the early summer of 2016. Most of our conversations were about sirtuins, resveratrol and reprogramming of cells. He said, "James, what do you know about NAD?" I said, "Well, I think the only time that I've ever come across it is that it's a coenzyme needed by the sirtuin enzymes." He said, "That's right. I think you should start paying really special attention to NAD. It's going to turn out to be one of the most important longevity molecules that we know of, above resveratrol. It's sort of the underlying factor under a lot of longevity genes, including the sirtuins."

I looked around in the literature and I wanted to look specifically right away at clinical trials, and then I couldn't find anything. I found a paper from a scientist in Seattle from 1961, in which he was giving intravenous NAD to alcoholics and drug addicts and having remarkable success, but that was it. There wasn't another paper from him about this. I called up all the doctors that I know and asked them, "What do you know about NAD? Any kind of treatment, any clinical trials, what do you know?" They put me in touch with someone who was doing, currently in 2016, alcohol and drug withdrawal treatments in the Los Angeles area using intravenous (IV) NAD.

I got in touch with that person and talked to them. They said, "You know, the doctor who brought it to America, right after the paper was published in the '60s, the company Avet Labs, who was making the IV NAD, stopped making it. It basically disappeared from research in America. It was picked up in South Africa. A Mexican doctor picked it up from South Africa and started offering NAD treatments in Tijuana, and then this doctor in Louisiana experienced the treatments and started using it in their practice."

This person in L.A. told me the doctor in Louisiana who's been doing this for 15 or 20 years is going to have a conference in a couple of weeks. She said, "I'll get you invited." I went to this conference. There were maybe 20 or 30 people there. Half of them were doctors.

JM: What year was this? 2016 or 2017?

JC: This was Halloween weekend in New Orleans in 2016.

JM: Okay.

JC: It ended up that I sat next to a doctor from Idaho, from a beautiful little joyous town called Coeur d'Alene, who was there because he was treating patients with IV NAD not only for alcohol and drug problems, but also for geriatric-type problems. He had given it to people with Parkinson's and Alzheimer's. There was in fact a Parkinson's patient who came to the conference to talk about how it had just completely turned his life around.

I was talking to this doctor about, "This all sounds great. But as a scientist, I'm looking for data. I'm looking for human clinical trial data in particular, not just mice studies." I said, "You know, maybe I'm going to look at doing something like this myself." He said, "Well, if you decide to do that, I'm interested in helping, because I also agree that there's a lack of data." So I went to an IRV committee. I got approval for clinical trial testing intravenous NAD in elderly people for a two-week period. This doctor in Coeur d'Alene, Dr. John Sturges, and I conducted this clinical trial in December of 2016. The results from that were really remarkable and also remarkable for me personally. I had never taken a precursor supplement for NAD.

JM: But this wasn't a precursor. You were taking an actual molecule.

[-----1:00:00-----]

JC: This was the actual molecule. Of course, being a good scientist, I wanted to tell the patients that I was asking to essentially undertake this experiment in the name of science. I wanted to tell them that, "Look. I've done it too." The doctor and I both underwent the IV infusions. I'm somebody who's had essential tremors since I was 20 years old. My hands would shake like this. It was just some neurological problem. It wasn't the onset of Parkinson's at 20 years old or anything else that anyone could point to. But surprisingly, within an hour or two of starting the IV infusion, my tremors went away completely, which I had had for the previous 40 years.

I noticed later that evening that I fell asleep. I didn't wake up during the middle of the night to go to the bathroom or just wake up. I woke up way earlier than I normally would, just completely refreshed and ready to get back to work. This was the same kind of experiences all of our elderly patients were telling us as well. We had several people who had tremors that went away. We had individuals who –

JM: What was the dose you were using? A gram IV?

JC: We used the same dose for this study that was being used for alcohol and drug withdrawal, which is 1,000 milligrams a day for six straight days.

JM: Okay.

JC: I think this is too much for people who don't have issues that would cause incredibly severe NAD depletion, and certainly alcohol is something that uses copious amounts of – Your body uses copious amounts of NAD to detoxify alcohol. In and of itself, drinking every single night of your life will drastically deplete your NAD levels. There are other things that people do that can deplete their NAD levels. We've seen that even teenagers who get an infection, influenza or something, and then start all of a sudden getting migraines, that NAD will totally prevent the onset of migraines for periods of two or three months at a time. People who have had multiple migraines a month get on the NAD patches, these iontophoresis patches. They can go years without having migraines.

JM: Yeah.

JC: There are many, many symptoms of NAD depletion that we're just now learning. We're finding that restoring the NAD to healthy levels gets rid of these symptoms almost immediately.

JM: Thank you for sharing that. That was a great frame for what we're going to talk about next. Because it's obvious that there's great potential there. There's a lot that you didn't share about all the other benefits of NAD. But the cause for those infusions, because you can get them available today. I don't even know that you need a doctor's order to do them, but they're expensive. I think they're over 1,000 dollars for an IV, if I'm not mistaken.

JC: They definitely are.

JM: Yeah. That is just not a starter for most people. That's way off their budget. That is what striving the push to find alternative solutions to raise your NAD levels. The problem here is that this is not an easy biomolecule to measure, as I mentioned. I want you to go into how it's measured and how your association with Nady Braidy, who you perceive as the top NAD researcher in the world, how he's developed this protocol to measure it and how many labs in the world can measure this thing accurately. For me, the key is, if you're going to have an intervention to use precursors or some other strategy, you've got to measure it accurately. Why don't you tell us about that?

JC: Sure. One of the participants at the conference in 2016 was a professor from the University of New South Wales named Ross Grant. His lab at University of New South Wales has been studying NAD for quite a number of years. They pioneered – One of his post-docs and a chemistry technician at the university pioneered a mass spectrometry protocol for measuring NAD. It can be measured in blood plasma, in whole blood and from the peripheral blood mononuclear cells, the white blood cells that you collect in blood or any tissue.

So this mass spectrometry, which is incredibly precise at measuring microgram levels of proteins, molecules in samples, it's able to measure these particular metabolites of NAD, because there are about 13 steps of going from basic protein, like tryptophan to the end molecule, NAD. And then that NAD, when it's used by other coenzymes, breaks down into nicotinamide and other metabolites.

All in all they were looking at about 13 different molecular compounds that were all related to NAD and measuring them. He put me in touch with this post-doc named Nady Braidy. I told him about this clinical trial that I wanted to do. I said, "If we send you blood samples, would you be able to measure NAD?" I told him that we were going to have like a dozen or so participants. What I didn't tell him was that we were going to take multiple samples per hour for the first five or six hours, and then we were doing this every day for ten days.

JM: Oh, Jesus Christ.

JC: We ended up sending this poor guy 1, 500 samples. Of course I didn't know how a mass spectrometer ran in those days. I wasn't really familiar with – I was familiar with the results of what they do, but not the methodology that it takes to run them. It turns out that it takes about one hour to run two samples. I've given him like half a year's worth of work, and he had to share that machine with other researchers.

He got us back – To his credit, he worked night and day and got us back some data within about a month. It was really important for us to know. We obtained blood samples from a blood bank, of samples from 20-year-olds all the way up to these mid-80-year-olds who were in our studies. We ran those through the mass spectrometer, not just for NAD, but all 13 of the metabolites. We created a graph showing for each metabolite, how it changes over age. It was really incredibly enlightening and I don't think anyone has ever done this kind of study to show in humans, normal, healthy humans, how NAD actually plummets by the time you're 60 years old, down to almost undetectable levels by the time you reach 80.

What you and I know and we want your audience to know is that NAD is absolutely essential to repairing broken DNA. Broken DNA is not something that occurs once in a while. It's something that occurs 125 times an hour a day in every cell of your body, in single-stranded breaks and about 25 times per day in every cell of your body in double-stranded breaks.

JM: And more if you have EMF exposures.

[-----1:10:00-----]

JC: Absolutely. There are lots of lifestyle practices and exposures that will increase this dramatically. You need NAD in order to turn on gene repair. If this is naturally going down by the time you're 60, it's maybe 50% of what it was when you were in your 20s and 30s, and then by the time you're 70, it's at like 10%, and then at 80, it's just almost off. You can see how this huge build-up of damaged DNA in every cell of your body is potentially one of the driving forces of these morbidities that you see with aging, heart disease, cancer, Alzheimer's and all these things in depth.

JM: Yeah. Congratulations on the study. I believe you were the senior author on it. It was never done before. I mean it was so crucial to this work that you establish the parameters of what the aging curve for NAD looks like. It was never done before. But I still want to know how many other labs in the world or the U.S. can measure NAD to this precision?

JC: Well, I think there may be a couple of other labs other than the University of New South Wales. I went back – I run a nonprofit medical research organization called Betterhumans. It's the one that was doing the supercentenarian study. It's the one that I had my mouse lab under. It's now the one under which I do all these clinical trials and analytical lab research.

We went back to our funders and said, "We're not going to be able to give proper feedback in our clinical trials so that we can essentially, on the fly, determine, 'Okay, this is working to increase NAD levels, or they fall off very rapidly after we do something,' if we're getting them to a lab where it's going to take six months to a year to get the results back because they just don't have full-time accessibility to run just our clinical trial data." These machines run from like 400,000 to 500,000 dollars up to 1 million and a half.

I was lucky enough to have funders that saw the opportunity that if we had our own mass spectrometer, we can turn around this data. We could publish papers and let the work know what we find out much more rapidly. So we now have our own mass spectrometer. It has been, unfortunately for me, a long and kind of slow process getting this installed and set up. They're very complicated machines. They take enormous amounts of time to get exactly right, calibrated and then fine-tuned to do the particular metabolites that we need to look at.

Now, we're going to be in the position where we can do collaboration with lots of labs. I've offered this to David Sinclair and to others as well who are also focused on NAD, because we want to accelerate this kind of information and to make rapid progress in determining, "How do elderly people maintain high youthful levels of NAD and keep all of these pro-healthy, anti-aging genes turned on in the long-term?" This is going to require optimizing or, as you and I and others call it, hacking our biology.

JM: That's what I want to get into now, just as an aside that you didn't mention that you, first of all, had to hire a post-doctor to run this machine. That was like a two or three month process to find the post-doc. And then you had to send the post-doc for like six weeks to Australia to train with Nady Braidy and then you had to come back and get the machine. It was just one catastrophe after another – not catastrophe, but challenge that had to be surmounted. But finally it's up and running, or if it's not, it's really close to it.

You've got the machine. Now we can examine the precursors, like nicotinamide riboside (NR), nicotinamide mononucleotide (NMN) and NAD itself in different forms, like the patch that you put on, which works. You actually have this metabolic parameter that you referred to earlier with the essential tremors that show – and I think with restless leg syndrome too – that seems to be moderated when you get the right dose of NAD. You don't need to measure levels. You know clinically when you're getting that. Most of us don't have that, that canary symptom.

So the interesting thing is we are in the process. You and I are going to evaluate this very soon, probably shortly after this interview comes out, maybe even now. Actually taking NAD itself, the molecule and rather than injecting it putting it into a suppository and using it transmucosally and into the blood – because you can't swallow this thing. It's an unbelievably fragile and perishable molecule. It is just the most delicate thing. You've got to be incredible cautious with it. But the precursors, you can, the problem is that they get methylated in the liver when you swallow them, so you don't want to inject them at all. I mean, you could, but it's less easy. So we're looking at liposomes.

You actually have – You can test those. You've got a dozen or half a dozen people lined up to test that. We've got 40 nanometer liposomes. These are not like any liposomes. These are nano-liposomes that should get in there and should have some good results. I'm so excited. And then we can test them on other things too, like transrectal NR, transrectal NMN and see if they make a difference and what the actual levels are.

JC: I'm really excited about this possibility. As you alluded to earlier, you can raise NAD levels through this really expensive process of taking the IV. But then you would have to, even at these high levels, you can restore like a youthful level of NAD very quickly doing that with just a single afternoon. But it doesn't last very long. It's metabolized and then you need to do it again.

Honestly, no one yet knows how long these high levels of NAD last in individuals or whether over a period of time you'll build up higher and higher levels as you essentially quench all of the deferred maintenance in your cells, so to speak. If you didn't have NAD levels and you have the buildup of DNA that needs repairing, then NAD is going to be used up as soon as it's available with these genes that do DNA repair. It's going to be used up whenever you get an infection with CD-38. It's going to be used up by these sirtuins.

At some point, we think that the cell will catch up and become healthy and it won't have such a draw down on NAD levels. But right now, the trouble for elderly people is that you can take 1,000 milligrams of nicotinamide riboside and it will double your NAD levels. That sounds really terrific, but if you – and we've talked about this – if you think about a person who should have levels between, plasma levels, which we talked about, between 30 and 60 milligrams per milliliter of blood –

JM: Is it that high? It's actually milligrams? It's not micrograms?

JC: This is of just NAD itself. It's micrograms of other metabolites.

JM: Okay. I did not know it was that high. I knew, but I forgot that it's milligrams. That's a lot.

JC: No. That's very true. For nicotinamide, it's milligrams. For NAD, it's micrograms.

JM: Okay. I thought it was micrograms.

JC: It varies between micrograms and milligrams. That's what they are. So it is a relatively miniscule amount that we're measuring. But this range of youthful versus elderly, where the elderly is almost undetectable, they need to increase their levels by 10 or 20 times.

JM: Maybe even 100.

JC: Yeah. If you take this precursor for six months, it will double your levels. They're still tremendously depleted.

JM: Yeah. It's a joke. It's an absolute joke.

JC: Yeah.

JM: We wouldn't know that if it wasn't for you landmark study.

JC: Well, thank you. It really opened our eyes to the fact that to take a sufficient dosage so that you would get physiological effects from it, a lot of these people would have to take 4 or 5 grams a day, at least for some period of time. The way they're priced right now would be exorbitantly expensive for most people to add a supplement that would be like 50 dollars a week.

[-----1:20:00-----]

JM: But it's not even a price issue. It doesn't work because at those levels, it's not going to get into the blood. The liver is going to methylate it and you won't get those increases.

JC: You and I have talked a little bit about this. I haven't done plasma level measurements or whole blood and intracellular measurements. But I know that when my restless leg syndrome or tremors start reappearing because I haven't been keeping up with taking the patches or IV, then it takes me about 2 to 3 grams of NR for the symptoms to go back away.

JM: That's interesting.

JC: But I'm also somebody who had completely restored their levels and kept it high, so I'm not severely depleted the way maybe a normal 64-year-old, 70-year-old or 80-year old would be.

JM: Yeah. Have you tried the liposomal NMN yet? In that scenario?

JC: I'm off everything. I'm not taking any B vitamins of any kind or niacin, which is a precursor of nicotinamide, anything that would raise my levels, so that when our post-doctor is ready and our machine is finally tuned, I can take this liposomal NMN of yours and measure before and after levels. Because I want to try it with myself as well.

JM: Okay. Alright. Good. It's exciting news. I thank you for sharing that backstory. It's so important. Hardly anyone knows it, but I think you're really the key because – Let me just give you the sequencing here. You've got to eat right. You've got to avoid processed foods. You've got to exercise ideally, integrating exercise in the fasted state, so that you can do a few things. Obviously we've talked about increasing autophagy. But what you may not understand – now that we had the NAD discussion, you can appreciate this – is that the exercise and the time-restricted eating will both increase by about 30% nicotinamide phosphoribosyl transferase (NAMPT). What is NAMPT? It is the rate-limiting enzyme for the recovery of NAD from its metabolic breakdown product, which nicotinamide.

You're going to increase your NAD levels significantly without any precursors, without any NAD supplements, just by doing those things. It doesn't cost anything. In fact, for most people, it's cheaper than nothing. Because you're eating less food. It's great. But once you reach that level, that's the first step. You've got to do those things. Then you can go to NADs. And then if you want to go – So you've got everything done. You've got the exercise, the diet. You've got the NAD, which I think is the next step. That's step number two. Get NAD right, get your NAD levels right. And we don't know what it is. You're going to help us figure it out within the next year, maybe sooner.

But then what I'd like to – Before we sign off, I really want your comments, because you, David Sinclair and George Church are, in my view, the guys who are going to help us understand how to reprogram the cells. I want you to explain to people that that technology exists today. If for some reason you're especially motivated and you want to do it yourself, you could do it. It is not illegal. You can cellularly reprogram your cells. I would not recommend it until they do the research, but the technology is this. It's called the clustered regularly interspaced short palindromic repeats (CRISPR). It's relatively easy and straightforward and not really expensive.

Why don't you talk about that whole strategy and what you perceive is going to happen in the near future, whether it's five years, 10 years, 20 years? It's somewhere down that range. What's going to happen after

we've got the diet optimized, the exercise exercised and the NAD optimized? What's the approach with cellular reprogramming?

JC: You know that as researchers really started thinking about aging and they started understanding the Hayflick limit, for example, and that cells, normal somatic cells, do not have infinite lifespans – There seem to be clocks that regulated them and had very particular preprogrammed time, these cells would go through apoptosis and die, or they would stop replicating – they scratch their heads and basically said, "But wait, the egg cells from females and sperm from males are as old as the parents. When they unite, they make a baby that has a whole, new, fresh lifespan ahead of them. The baby is not born as a 40-year-old parent with those genes and that burden. They're born with a clean slate."

Various researchers started looking at, "What was it in embryos that was triggering this, turning this egg cell from a 40-year-old egg into essentially a brand new, fresh baby?" The person for whom that discovery is named, Dr. Shinya Yamanaka in Japan, discovered that four particular genes producing proteins were responsible in the egg. And that if you turned those genes on in any cell, if you took skin cells from you and you turned those four genes on in that cell for a period of time, that it would revert to a pluripotent stem cell.

That's the cell that makes the entire human, other than the placenta and the umbilical cord, which then you have to come back to the pluripotent stem cells to have that encompass. But it makes the whole baby. It makes them with relinked telomeres and with epigenetic age, meaning that the expression that's allowed on their genes controlled by methylation sites on the backbone of the DNA, that those are also young. And as we age, our telomeres shorten and our methylation patterns change. Some become more methylated and some less. As a result, genes that should be turned on or we would like turned on for our health and longevity get turned off as we age.

Well, it turns out that not only can you do this, which is now kind of referred to as total reprogramming where you use these Yamanaka factors to create induced pluripotent stem cells, but if you do it with fewer than the four Yamanaka factors or you do it with less time, so you expose them to these genes, proteins for only five or fewer days rather than five to eight days, which is required for pluripotency, then what you end up is something called partial reprogramming. In that case, the fibroblast doesn't turn back into a stem cell. It stays a fibroblast, but it does reset the methylation clock. If you've heard of Dr. Steve Horvath, the researcher at University of California Los Angeles (UCLA) –

JM: Have you published papers with him? Have you published papers with Horvath?

JC: We're doing research with him right now. We have the paper that's being submitted to journals right now regarding the methylation patterns of supercentenarians.

JM: You've got to send me a draft of that one.

JC: He's looking at the methylation patterns that result from the kinds of anti-aging clinical trials we've been engaged in for the last couple of years. Because there's evidence from sort of mock methylation profiles like Dr. Morgan Levine's phenotypic age calculations that use biomarkers from blood tests rather than methylation profiles that we are turning back the epigenetic clock in some of these even short-term anti-aging therapies that we've been testing. Now, Steve is running methylation profiles for us and will tell us truly whether we are reducing the risk of morbidity and mortality with these interventions.

JM: What are some of these interventions? Are these the NAD trials or are there other ones?

JC: We're going to be looking at what happens to methylation profiles when we returned the NAD levels to a youthful amount. I ran a one-year senolytic study in which we gave compounds that kill so-called senescent cells. These are cells that have lost their ability to replicate. They go into this state called senescence, in which they basically send out these pro-inflammatory cytokines and they try and get rid of whatever might have environmentally affected them to have essentially DNA mutations that caused them to fail to go through this replication cycles.

[-----1:30:00-----]

As we age and these senescent cells build up, they produce large amounts of pro-inflammatory cytokines. And because fat tissue is one of the main tissue types that go into this senescent state and give off these pro-inflammatory cytokines and lots of people have vascular adipose tissue, VAT, which are fat cells that are surrounding their essential organs, that means you're essentially sending off inflammatory signals to all your organs. You're causing them to malfunction and to think that something's wrong. It puts you into a chronic state of inflammation and causes dysfunction in all of your body's organs. Researchers –

JM: A good reason to be lean.

JC: Absolutely. You definitely – One preventative factor here is keeping your body mass index (BMI) down and specifically going and getting something like a DEXA scan that will tell you how much vascular adipose tissue, VAT, you have in your central cavity, around your organs, and specifically lose weight until you drop those pounds. Because just dropping 5 or 10 pounds of fat, if it's not coming off your belly fat area, which is where this VAT is located, that's not going to protect you from these senescent cells damaging your organs.

So the Mayo Clinic did some experiments on a combination of a particular nutraceutical flavonoid called quercetin and a chemotherapy adjunct drug called dasatinib, that those worked together to kill of senescent cells very well. They did experiments in mice. They found that they could kill off a very large percentage of the senescent cells and that the mice would recover from the problems caused by both cognitive and other health problems caused by this chronic inflammation and senescent cells.

JM: I think James Kirkland was the senior author on that. I think he's also published this year two clinical trials in humans and individuals with pulmonary fibrosis, I believe, and they got significant improvements.

JC: That's right. This doctor and I in Coeur d'Alene, Idaho, Dr. John Sturges, when we got Institutional Review Board (IRB) approval to gather together 30 patients who had osteoarthritis and two of whom had pulmonary fibrosis and to give them, over the course of a one-year period, three doses of this dasatinib and quercetin, the effects were really remarkable. We had people who were literally having to walk upstairs sideways because their joints hurt so badly or their joints would just give out in the middle of a step, who had corkscrew fingers and were constantly having to massage their hands to keep the arthritic pain down. They had this vastly diminished in two to three weeks.

JM: I've got a question for you on the senolytic therapy. Does it make sense to integrate that with time-restricted eating or even fasting, so in other words do you want to have autophagy activated when you're administering the senolytics or it doesn't matter? It's a different mechanism.

JC: For purposes of our scientific study in science, you want to keep your variables down to the ones that you're studying. We haven't combined it with other treatments. But certainly, turning on autophagy at the same time makes a great deal of sense. Also, making sure – One of the main causes of senescence and early senescent cells is DNA damage. And so that also means that when you have low NAD levels, you can help rectify this. And if you already gone through a period of time with NAD deficiency and you have lots of

DNA damage, and you have a buildup of senescent cells, if the levels are really high, you actually want to get rid of these senescent cells before you take NAD. We've only come across this clinically in a few people who had such high levels of senescent cells and SAS cytokine production.

JM: Are you measuring the cells directly or the SAS? Which are the cytokines because it would seem to me that might be hard to measure.

JC: We're measuring the pro-inflammatory cytokines with immunofluorescent beads. We're using antibodies that attach to them. We can measure it in the blood plasma. This is something, again, pioneered by the Kirkland Lab at the Mayo Clinic. We're incredibly indebted to people like this who have made these discoveries. We're just essentially doing the translational work. We're taking some of their discoveries and trying to get it into clinical trials tested on people rather than mice as quickly as possible.

Because my mother has osteoarthritis. She had both of her knees replaced, so I know what it's like for individuals to go through the suffering of osteoarthritis. I wanted to see, rather than waiting 10 years to hear about FDA trials and approvals, whether this would be something that we can use right now to hack aging and to improve our chances of not having these debilitating morbidities. For example, you and I both know that you need exercise in order to get ENAMPT, endothelial NAMPT, and raise your NAD levels. If you have osteoarthritis and your joints hurt, you're not going to exercise.

JM: Unless you do KAATSU.

JC: Well, even then it's going to be pretty painful for people with very severe osteoarthritis. And of course, it carries along with it additional health problems that we just want to eliminate. Doing all these things, even as a preventative, is what we're aiming at. We're trying to come up with strategies that ducktail together, that reinforce each other to protect our genome, to keep our methylation patterns youthful, that don't essentially accelerate aging, and then another part of my lab is working on altering primarily stem cells.

We're focused on bone marrow stem cells so that we can essentially improve them genetically. Just to give you an example for my own genetic profile, which I know because of its whole gene genome sequence, I was lucky enough to have a 102-year-old aunt, who's very healthy until around 102, she was moved to a nursing home and then she died very rapidly after that. But I had her whole genome sequenced as well. It turned out that I have a 33% greater chance than normal of being diabetic. She has an 18% reduced chance of being diabetic than normal.

That's a 15% difference basically between my 102-year-old aunt's genes and mine. And yet, 50% of all of our genes are the same, between my aunt and me. I know that if I were to make these – This boiled down to only changing three out of eight genes. So by only changing the letters, one letter each of three genes, which is easily done with CRISPR, I could have a 15% change in my genetic propensity to something like diabetes. Why not use CRISPR to change my stem cells and then put those stem cells back in my bone marrow where they're now going to help produce the liver, the kidney, et cetera?

[-----1:40:00-----]

JM: I'll tell you one from my perspective, because I think that's an important analogy because diabetes is so easy to treat. I am confident that you will never get diabetes. There's not a doubt in my mind. You're just not going to get it. But the better analogy might be things like what George is working out, like increasing these incredibly anti-oxygen genes, like forkhead box O3 (FOXO3), and getting multiple copies of those to go in and really address excessive endogenous oxidative stress when needed, not continuously. But that's the whole thing. They've got to –

JC: Absolutely. You and I could talk all day long about molecular mechanisms and protective enzymes and things that we would want to turn up. I've tried to come up with some sort of relatable changes that if you did them to the population at large, for example, you could nearly wipe out diabetes by just impinging. We certainly know that there are people who can consume vast amounts of carbohydrates and sugars and still have blood sugar in the '70s and '80s and seem to be relatively impervious to diabetes. Why not in the long run make sure everybody's just born with these beneficial genes?

JM: Yeah. That might be. But we've got to work out the details. But the point is that the technology exists. This is not something that needs to be – This is a futuristic vision or dream. This is reality today. The details are that we have to work out what it is because you could create something that's far worse than beneficial.

Anyway, thank you for going into that. One final question before we leave you, because this is turning into a long interview, but I just want you to go over the details. It really impressed me in our first meeting, because people don't know the behind-the-scene reality of many of these research labs that are involved in anti-aging and pushing the limits like you are in seeking to minimize the translational period from once something is discovered before it's integrated into clinical medicine, that most of these labs are really doing it to produce a product that they can sell, that many of these labs are funded by VCs, venture capitalists, that are really on a mission to develop a product. They're motivated more by finances than they are motivated about finding the solution, like you are, which impressed the hell out of me when we met because you are the rare bird who is doing this for the right reasons.

JC: Well, I think a lot of – As you know, I went to law school in the Bay Area. I've lived there a good portion of my adult life. I have a lot of friends from the Bay Area that are fellow anti-aging researchers. These are, by and large, younger guys who are just out of grad school and starting their own biotech companies. They get into this with the kind of philosophy that you and I have, which is that we want to see not only for ourselves and our family, but for humanity in general, doing away with the suffering and morbidities of age. And as time passes, chronological years pass, that our morbidity and mortality rates don't increase at all.

But the nature of how one gets funded these days is such that you need investors in general. Everybody goes the route of setting up a company. And then the investors basically say, "What's your product?" So the scientists are now driven to find a particular product and as rapidly as possible, bring that product through research, development and do clinical trials and either sell it, license it or go public and be the company that produces the next insulin product or whatever that might be.

You see this with, for example, AgeX, Unity Biotech, companies that have gone into the anti-aging field, unlike the Buck Institute for Research on Aging, which is a non-profit, these are specific for-profit companies that have one particular target in their quiver, one arrow to essentially aim at this. And so most of my friends get unfortunately locked into spending the next four or five years working on a particular anti-aging pathway that may or may not turn out to be all that important. Whereas as a nonprofit and supported by donors who really want to foster anti-aging, I can say that we're looking at dozens of different completely independent pathways for anti-aging.

JM: Let me just interject here. You shared with me, I think, like 40 or 50 – I've never seen anything like it from your perspective – the trials that you're beginning to engage in. It's just mind-blowing. I mean you're going to have some massive winds in this thing. There's no question. It's just shocking what you're doing.

JC: Well, as we talked about earlier, I've read between 18,000 and 20,000 scientific papers on aging. I've made long notes about the things that were working and what are called model organisms, like flies and mice, for example. In many cases, we know that these same things should work in humans, but the

molecules or the techniques that were used are generic drugs or compounds that you can't patent for various reasons. They've been known about for a long time, for example. Therefore, there's just not a financial incentive for a venture capital company to fund someone researching, like metformin, let's say, and rapamycin, both of which are generic drugs, specifically for anti-aging.

What you see is the venture capital companies are putting money into companies that want to create novel compounds that mimic compounds we already know about. But no one's really studied or optimized those compounds, the rapamycins, dasatinibs, the metformins –

JM: Well, those are drugs, but you've got natural products too, like fisetin and quercetin.

JC: Yes. And because anybody can knock that off, you might see a pharma company trying to create a synthetic molecule that takes attributes of those and has a particular molecular benefit similar to what they do. But my parents, my elderly friends, they don't have 10 years to wait. And then often, these drugs are really powerful. For a lot of people, they aren't appropriate anyway. The natural compound or the generic drug that we already knew about would have probably been a better choice.

What we want to do is take a lot of these compounds that are already proven to work in other organisms, try them on humans, and then if they do seem to work, then we go through a process of optimizing them. If they don't work, we just simply drop it and move on. Because no one's counting on us turning this particular thing into a product, so we don't have that weight over us that somehow the one and only thing that we chose now has to be [inaudible 1:48:45].

JM: You know the other players out there. It seems like well over 90%. What would your guess be of the people who are incumbent to the VCs?

JC: Well, certainly the majority of new organizations that are exploring anti-aging are primarily for-profit companies funded by VCs. There's really nothing wrong with that. But the breakthroughs have been coming from places like the Mayo Clinic, university labs like George's, David Sinclair's and the Salk Institute. Everything that we've talked about today is a result of decades' worth of very intense research by hundreds and hundreds of scientists that are focused on anti-aging and who are not specifically trying to make a profit from a single molecule or cell line or therapy, but merely doing the hard work of telling us what seems to work and what doesn't. And then testing those in model organisms, from C. elegans, worms, drosophila, fruit flies and rodents, like mice and rats.

Much of this is already known that we can rapidly, I think, qualify these things in humans using these clinical trials and just simply know, "Okay. This is worth spending more time on because it has profound anti-aging effects or it helps one particular morbidity pathology." This seems to be something where you need 1,000 people before you even reach technical significance. That means nobody's even going to feel it. If it added anything to their life, it's going to be negligible.

JM: This was one of the things, characteristics that so attracted me to you is that we share the same vision. That is to really radically decrease the time from which something is known to the time it's actually implemented. I'm doing that in the process of educating people. But there's this gap. And you fill in that gap. And you fill it because you've got to do it. Most of the stuff is either theoretical. It's in the lab. It's in-vitro or it's in animals and it's got to be done in humans, and you're doing the human trials. I really greatly appreciate you for that. I appreciate you for writing the book, "The Switch," which goes into a lot of the details that we talked about. It comes out or came out on December 31st. It's available on Amazon or any of your favorite bookstores. If you were intrigued with what we talked about in this interview, I think you're going to love "The Switch." Just pick it up at the bookstore and read it over the holiday weekend. It's a good one.

JC: Thanks very much, Joe.

JM: Alright. Well, I appreciate you. I'm really looking forward. We're probably going to have you on again when we get these NAD studies done. I have a suspicion you're going to be publishing another landmark study in 2020.

JC: We've got a number of really great projects. I'm looking forward to talking with you. I always enjoy our conversations greatly. Thanks for having me on here.

JM: Alright. Sounds good. Alright.

JC: Thank you, Joe.

[END]