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 that if you're more than a hundred years old, you're probably biologically younger than your chronological age. Some researchers at UCLA look at aging as a biological program written on your DNA and they've seen evidence that there's a biological clock that marks milestones along your life's path. These guys are monitoring aging in mice by examining molecular tags called methyl groups which attach to various locations on DNA in a process called methylation. And if you've read any of my books like The Bulletproof Diet or Head Strong, I talk about methylation and how about a third of us suck at methylating, which will make you old and inflamed unless you address it by taking the right forms of nutrients like 5-MTHF. By the way If that was completely Greek to you, that's all right, it's all over the Bulletproof Blog.

Dave: Methylation is an epigenetic modification of your DNA, and that's kind of like flagging a passage in a book with sticky notes. You attach a tag, it doesn't change the information in the book, it just draws attention to those passages and tells you when you can skip the other pages. These researchers at UCLA measured DNA methylation at 353 different spots in the human genetic, we'll call it instruction book, or the genome and as we age 193 locations accumulate tags, kind of like when you see too many fliers posted on a bulletin board, and at 160 other locations, methylation is stripped away as you age. So knowing how much methylation is normally found at each spot, given your chronological age allows researchers to calculate your actual biological age.

Dave: What that means is that maybe we don't just have to look at your telomeres or just at how wrinkly your face is or how saggy different parts of you are to figure out how old you are, we can actually look at very detailed things that go beyond even just looking at your genes. And the researchers at UCLA found that super centenarians, well, they call them semi-supercentenarians if you want to be really technical about it, is the people who are 105 to 109, they tend to be biologically younger than their age, so sort of they're kids compared to other people. So the rate of aging of these people and their kids is slower than normal. Now, that's really exciting because you know what?

Dave: That sounds like a super power in humans, maybe it's one that you and I can also learn how to do just by changing maybe the number of methyl donors in our diets. Why don't we play around with that and live a long time. All right, let's get onto today's show, today's show is with James Payer who the a founder of Apollo Ventures. And you might not have heard of Apollo Ventures, in fact, when you hear it, you probably either think space program or rocky, but he has nothing to do with either one of them. He has to do with life sciences and investing exclusively on breakthrough therapeutics around anti-aging. This is one of the guys allocating dollars to the technologies that are going to give me 50% of the 180 number that you've heard me talk about, I'm going to live to at least 180. I know we can do 120 because I've seen it, in fact, UCLA scientists are studying people who are doing it today. Well, I want the other 50%, I'm counting on guys like James to go out and make investments in areas where we spend very little historically.

Dave: We spend more on all sorts of random political things and things that just don't make a difference, if we applied a tiny percentage of that towards some of the things that

James is actually putting money into, I think we can solve many of the problems of aging. We probably won't be immortal, but we'll be a lot closer to that than we are today. James has a fascinating background and he's one of those guys who's disrupting aging by saying we're going to take what the big pharma companies have done, which is take investment dollars and put it to work on these drugs and say, what if we could tie into that ecosystem and actually make all of us live longer and instead of going out and replacing that stuff, let's just use the existing systems to make ourselves age less. James, welcome to the show.

James: Thank you so much for having me. It's great to be chatting with you and I don't want to disappoint your listeners after that buildup, maybe they all expected that Steve Horvath, who leads that UCLA group would be here, who is also a super, super cool guy talking about methylation and the aging clocks and we can definitely discuss some of that work, but hopefully they'll be satisfied with me here instead.

Dave: Okay. You're not exactly a sloucher, you have a bachelor's degree in immunology, you started the first biotech company to get Kickstarter funding and let's see you have a doctorate from UT and a National Science Foundation Fellow working on the basic biology of stem cells. So I mean, you barely made the cut for Bulletproof Radio, but basically what's cool about you is you're not just a money guy because frankly there's a lot of money guys. I've worked in venture capital and I love what it does to accelerate startups, it's real and I've raised $68,000,000 of venture funding for Bulletproof, so that model works. But a lot of the people doing investment, they're investment professionals, they're not domain experts and then a lot of them are domain experts and then when you get the money people plus the domain experts working on an investment, that seems like that's when magic happens. You are a domain expert.

James: Yeah, I think that's true. My whole group thinks of ourselves as scientists first and investors second, and so we really get super, super excited about a specific mechanism of action or a cool new way to develop a drug or a way to target aging. That's kind of the hook that brings us into a project much more than some of the traditional financial metrics.

Dave: Alright, I got to ask you this question and I'm going to give a little bit of context for people that don't know how venture capital works, which is most of us. Well, so the way venture capitalists work is we go out there and say, "All right, I'm going to find some people with lots of money, they're going to give it to me, I'm going to invest it and I'm going to give them more back." But those people who give the money to the VCs are called limited partners. And half of a VC's job is to go out and say, "Hey, you want to give me some money that I can invest?" Right? So you just said “we're scientists first and investors second,” don't your limited partners run screaming when you say that?

James: So, I would say if we went back 20 years in the biotech ecosystem that existed then from ... then this is all from an investment perspective, right? So from the perspective of these limited partners, then, yeah, they would, because what you had 20 years ago was everybody saying like, "Oh, well, what are the returns? How are the IRR?" Which is the internal rate of return, "What are the IRRs for biotech funds versus other types of funds?" And, "Let's just play a pure financial game." But a series of venture funds that

most people don't know about because they all exist in the footnotes of the innovation economy, right? A couple of biotech venture funds started a model that was all led by groups of scientists who would partner with other scientists from academia to actually start biotech companies together with them around projects that they loved.

James: And because they loved these projects and then built the teams around them, Pharma companies started paying attention and it turns out that in the last 20 years, these scientists-led and science-led venture funds have kicked the ass of all of these finance focused funds by almost a factor of two. And so now the trend in the VC space that thankfully we were able to participate in is that biotech fund should be science led and hypothesis led. And we don't make deals that don't make financial sense, right? We care about all the financials and stuff, but to get us interested in the deal, it's all about the science, and we think that if you can hang your hat on that nugget of truth, if you really, really, really believe in the science, then there's going to be a way to make it work or at least take a good shot on goal on developing a new medicine.

Dave: It makes sense to me and one of the things that frustrated the heck out of me in Silicon Valley, I was a co-founder of a part of the company that held Google's first server and I ran a program at the University of California for five years teaching engineers how to build horizontal scale Internet system, so I'm kind of a deep geek on that stuff. And I just realized over and over the best technologies never won, it was always the best marketing. But when you can get the best technology with the best marketing, that's when you have the biggest impact on the world. So it's not enough if you're a crazy inventor and you make the ability to double rat lifespan or something, if no one hears about it, you failed as an inventor. So you have to have both and the role of having a science led fund like you guys looking in aging is well, maybe you don't want someone who's just marketing because you're going to lose your shirt on that.

James: For sure, and actually we were just talking a little bit before the start of the show about using social media and media reach in these sorts of things, and this is something that I freely confess I know very, very little about, right? It's not at all my domain expertise, but one of the reasons that when we started Apollo, we were thinking, all right, well, are we going to do stuff like what you will get really interested in and what you're doing with [inaudible 00:09:59] are we going to do longevity foods? Are we going to do nutraceuticals? Are going to do supplements, cool devices that can play a role in longevity? Or are we just going to do drugs? And what we realized is that my team is more than 50% Ph.D.s in aging biology, and so what we realized is that we didn't really know a lot about that whole marketing aspect of things-

Dave: You guys must have the coolest dinner parties, right?

James: It's a pretty great group and it has really become a family the last few years since we started. But so we didn't know enough about how to win in that space, right? To do exactly what you're talking about, bring together the efficacy with the right marketing, but one of the cool things about drug development is that for better or for worse, the marketing is done mostly by the pharma companies after you do clinical trials. And until then, there is a marketing component to it and you have to do the right PR and you have to be noticed by the right people, but everyone who you're talking to has deep domain

expertise and is going to be looking at your full data package that you've put together and so we can kind of nerd out on the science and really let the science drive much more of the value of these companies than we could ... we just couldn't invest with confidence in these other domains.

Dave: So what you're basically saying, if I put words in your mouth, is that you are investing in core technologies that you think are going to reverse aging or extend human lifespan and you're going to then take those things that you develop and infiltrate the pharma industry in order to get the pharma companies to start doing that instead of the other stuff they do.

James: That's essentially correct, yeah. And we can talk in a little bit more detail, I think it would be a fun conversation to have of like how we're going to do that because this is something that I think is the core platform or the core concedes of Apollo as a fund is the strategy of how we're going to trick the pharma and biotech industry and I say trick with big air quotes, to really, really investing heavily into drugs that will dramatically extend healthy human lifespan.

Dave: It sounds like, I just got you to admit that you're going to hack big pharma.

James: I wouldn't say that. I like to use the term collaborate, collaborate is good.

Dave: I'm cool with whatever word you choose because there are a good number of people listening to the show right now who come from a functional medicine or a naturopath, or in a lot of anti-aging people who'll listen, and some of them have this if it's a drug it's bad, but the Bulletproof perspective, and certainly my experience is that, you know what, some of these pharmaceuticals are really powerful. You can turn on and off PPAR-Delta and gamma, you can take smart drugs that actually protect your neurons from all sorts of bad things and there are pharmaceuticals, I took three different pharmaceuticals to extend my life this morning and I'm grateful for them, but most pharmaceuticals have more side effects than benefits, especially for regular use. So if you can change that equation, you're actually helping big pharma but helping the rest of us too.

James: Yeah. So I mean, think that that observation is generally true and it's a reflection of the fact that most pharmaceuticals were developed to treat really bad acute conditions, right? Things like even a relatively humble drug, like a statin, right? Which lowers cholesterol. Statins were first developed to treat highly dangerous familial hypercholesterolemia, people who had such high ... genetically had such high cholesterol that they were in danger of having a heart attack or a stroke starting from 15 years old. And they were tested for the safety profile there, and then they made their way to preventing heart attacks and strokes in the rest of us. But you couldn't-

Dave: If they really do that, that might be the marketing guys.

James: Yeah, they definitely do some work on heart disease, but the new data that you're kind of alluding to came out that there's not an overall lifespan extension because they didn't

look at this more holistically, right? There are increases in cancer rates and neurodegeneration rates for people who are long-term statin users.

Dave: It turns out the liver makes cholesterol for a reason.

James: How about that, right? And that's like almost another topic that we could dive into which is how the fundamental shift that's going to have to happen in the medical industry that's occurring in the functional medicine world already and I think will infiltrate the pharma world in the next decade or two, which is this shift from thinking about diseases and individual silos, right? Oh, this is heart disease, we only have to care about the heart, we only have to care about the elasticity of the arteries and that's it, to thinking about, okay, well how does the damage that accumulates to increase the risk of heart disease, what are the similarities between that risk and the risk of Alzheimer's disease and the basic mechanisms linking the two? That's the shift that pharma is going to have to get over in the next 20 years.

Dave: I hope it's a lot faster than 20 years. Being interested in the food side of things and having run an anti-aging nonprofit group for a long time, I also realized that a pharmaceutical company can make this treats a disease claim as a food company and it is, at least in the US, expressly illegal for me to tell people that my stuff, the stuff that I make could possibly, or even in studies that are out there do things like reverse Alzheimer's disease and all that. So I did a calculation in my head, I can't say it was too quantitative, but I said, all right, if I know based on the science that I'm creating a certain set of benefits for people, which I am required by law to be vague about, if I do that marketing job well of driving behavior change in a direction that is in people's best interests, even if I'm not allowed to say everything that it does, I'm morally and ethically okay with that, I'm doing a solid for people. But it's really frustrating because if we could just let food companies say what our stuff does, it would transform everything, but the second I say medical condition and food, the food magically transforms, like with a wave of a wand into a drug,

James: Into a drug. Yeah, you can't make capital C claims, right? Claims of an effect of any kind of tool, whether it's a drug or food or whatever, as if it were a drug.

Dave: Exactly. And even for supplements, the rules, so you really can't do the same thing. Even if there's 500 studies that says the supplement does something to whatever, heart disease or whatever, you simply are not allowed to say that, you can say, "Supports healthy cardiovascular, whatever," but you can't actually say, "90% of people who take this live longer," stuff like that. So it's very frustrating, but as an investor, I think you have to pay attention to that, it's harder to invest in companies who can't say what they do.

James: Absolutely. This is one of the reasons I think we kind of talked a little bit about before that we only invest in stuff that's going to go through an FDA clinical trial system and can eventually make those capital C claims, and one of the reasons that I think it's really important to do this is, also you alluded to this before, is that that 50% of the 180 years that going to get from the 120 to 180 part, that's going to have to come not just from the new medicines that we know are possible right now, like the things that are working

in mice to extend mice lifespan, but it's going to have to be the current generation of things, and then the next iteration of those, and then the next iteration of those. And the thing that makes me most, shall we say concerned or the most ... the thing that animates me about thinking about the future here is trying to make sure that this moment that we're having in longevity and anti-aging and so on is persistent.

James: And the way that I think it will be persistent and spread beyond the experimenters in the world who are willing to try new things and live longer and live healthier, is showing even the most doubtful people, even the most skeptical in the most robust way, that this is really, really, really working and you can't deny this because we went and played by your rules, we went into your system and showed you that this is all real and so now that this is real, let's let this change the whole world. And I think that that's the way we're going to unlock the second and third generation things that aren't invented yet in order to get to that 180 that you want to get.

Dave: How do you overcome the skeptical mindset is one that says, "That can't happen, therefore it didn't happen." So you present evidence in the study that says this just happened. But then based on what we used to believe to be reality, then that's considered the current crop of researchers or doctors or scientists will say, "No, no, no, we simply are going to reject that science and say it's not real because it can't be real." On its face that's anti science, but I've seen that so much in anti-aging and nutrition and everything else. What do you do as investors when you deal with people like that?

James: So, the approach that we have to building companies in this space is even more subtle than having to have those conversations. And we can talk about it maybe first on a theoretical level and then do a little case study. So the way that we approach developing a new medicine for longevity, let's call them longevity therapeutics, right? This whole class of new medicines, is by starting out saying like, "Okay, here's something that can extend healthy lifespan of a mouse or at least target one of the hallmarks of aging that we know are built up in our bodies to cause the diseases of aging. Start with that in a mouse and then find some existing indication that every single medical professional in the world agrees we should be using the drug to treat, and whether that's cardiovascular disease or Alzheimer's disease or in some cases things are not just aging related diseases like rare genetic disorders and these sorts of things and apply that drug to that condition and build a little biotech company just focused on that condition, not necessarily talking about and waving the flag of anti-aging, at least not right away, and then saying, "Oh by the way, after we treat this condition we'll go to a second and a third and a fourth and it turns out that there's all of this evidence in mouse models that this same drug that we're developing will be applicable to 15 different things."

James: And then when you start getting your second and your third and your fourth thing approved, there's a mechanism within the FDA to flip a switch to say, "Oh, well, we should just give this to everybody who has this risk." And that mechanism, thankfully already exists, we don't need to do something as dramatic because redefining aging as a disease or any of these other things that people sometimes talk about, we just have to be very, very strategic in the way that we plan our clinical trials with these drugs. So that's on a theoretical level, not just the [inaudible 00:21:57] companies, but most of

the drug development, biotech companies in this space are following a model somewhat similar to that in their development of new medicines.

Dave: James, how old are you?

James: I'm 32.

Dave: So I got to say this, I really got into anti-aging at around age 29. I'm in this nonprofit, most of the members and certainly their board they're 60, 70, 80, 90, pretty much at least three times my age on average. So why are there so few people under 35 or 40 into anti-aging and why are you one of them?

James: Interesting. Well, it's funny that you say that because I always feel like the demographic distribution is the opposite. If you go to interest group conferences and I guess my world is maybe a little bit different in exposure, but when I go to the big pharmaceutical conferences and talk with a bunch of guys who have been getting cancer drugs approved for the last 30 years, and then I go and spend the next day at a conference talking about aging biology, the guys talking about cancer and Alzheimer's disease tend to be 20 years older than me and the guys talking about aging biology tend to be around the same age.

Dave: Because you're talking to academics.

James: Well, yeah, academics, but also industry professionals, and so-

Dave: Industry professionals, okay.

James: Yeah. Just because drug development is a really tough career to go in, most of the people have M.D.s, Ph.D.s, then they spend time at big pharma companies, then they go into the biotech world then a success takes a long time, so by the time you reach the upper echelons of the biotech ecosystem, most of the CEOs in our companies, for example, are usually 50 and over.

Dave: Just because it takes 20 years to get the experience you need in order to do that job.

James: Exactly, yeah, because those were the guys who by and large have the right experience to take something forward and who can take the energy of a younger guy like me and then combine it with the fact that they have 30 years of experience developing drugs or 25 years of experience developing drugs in order to kind of form a team there. Any case, but getting back to your direct question, I think there is some truth to it, which is that people respond to their incentives and people are inherently short-termists, right? So if you're young, there's this age old thing of you're young and you feel immortal and if you feel immortal, why do you care about age? Once you're getting on a little bit and for many of us, including me, it was kind of triggered by a traumatic experience where kind of age-related diseases hit you in the face, so I got interested in aging when I was 15.

James: My grandfather got cancer and then as he was dealing with his cancer, I was kind of dealing with what that did to my world and the way that I thought about life and what life meant and what we were all moving towards, right? And had emerged from that for a little while in a really dark space where I started thinking, oh my God, the best that we can ever hope for is to spend a little bit of time faffing about and then wait for one of these diseases to hit us and then die.

James: And then after a little bit more reflection and a little ... a lot of reading and so on, I was like, oh wait, there's something I can do here. If I spend my life trying to push that barrier back as far as I can to beat it back with all the force that I can, then that can be something that provides a very nice sense of meaning and sense of purpose for me. I describe it to some people from time to time saying like, "If you had a bomb like an explosive vest strapped to your chest and it was counting down no matter what the timer was on the countdown to detonation, if it was five minutes or if it was 70 years, you would probably not be able to focus on a ton of other things until you took the vest off," and so that's kind of the way I look at aging.

Dave: Okay, that makes good sense. And so you see it affects someone you love and you realize this is unjust. I mean, I got into it because I had pretty much the diseases of aging before I was 30. I got arthritis since I was 14 in my knees, lots of stretch marks from being obese, high blood sugar, prediabetes, all this stuff that is now gone, right? Because a lot of it was optional and it was lifestyle related and now I'm exceptionally healthy and younger than I was, and maybe a little bit wiser.

James: Yeah. The diseases of aging hit you in the face in a really personal ... first Person [crosstalk 00:26:51]

Dave: Yeah. I'm like, I'm not going back, I'm just not ... It kind of sucks to be old and granted, I'm sure I wasn't actually old, but I can tell you, you wake up in the morning and, you ... I sure felt old, that's for sure and it was frightening.

James: It would be interesting to know if the methylation biomarkers that you had changed-

Dave: They probably did. I mean, I did the very early methylation genetic testing with a woman named Amy Yasko who was the first to really call this out in the autism community and I'm a poor methylator and things like that. So I've been on methylating nutrients for 15, 18 years because they make a difference, right? And you can tell like, "Oh, I wake up and I don't feel old, I think I'll do that some more." And since then, so much lab testing has become available and it gets to the point where now we know a third of people don't handle folic acid that's added to our food, for them it's pretty much toxic. It builds up in your cells and you can't get rid of it. For everyone else, it's probably good, so I'm like what if we use the right form for everyone? In fact, things that people wouldn't think about, right now if you wanted to use the biocompatible form of folic acid in food everywhere you couldn't do it.

Dave: And the reason is that there is no accepted way of measuring low levels of that form of folic acid. So if you put on the back of your label that there's 50 milligrams of folic acid in

something, well, if it's the old school folic acid that's bad for a third of us, you can do it. But the new stuff, there's no way to prove it's in there and that it's still in there a year later. So from a labeling law perspective, you can't do it. So there's stuff like that that completely limits, I mean it-

James: I didn't know about that.

Dave: But it's one of millions of things where we're saying, well, we want to do the right thing as food companies and we're working really hard on it, but we're dealing with rules that were written in an era where we didn't have the science we have now and so you see stuff happening in China or Singapore or [inaudible] in India where people are just going ahead and doing what they want to do and it's a little bit frustrating, but also we have a lot of food safety here that is enviable in other countries and that's why you go to China, they pay extra for American foods because they know it doesn't have weird stuff in it, right? So I don't know the answer to that, but it's just an example of that one little nutrient and how deep you could go with it, right?

James: Interesting, yeah. I think that the question of the regulatory aspect and how this will interface with this dramatic shift in how we prevent disease because it's not really going to be about treating disease anymore, right? You and this broader group of thinkers and physicians who are thinking about functional medicine and thinking about health span have already made the shift, but the healthcare system will have to catch up to thinking about prevention and figuring out how we're going to regulate prevention in this aging space is really one of the key driving questions that I think many kind of observers on the fence, so people who aren't hilariously against slowing down the aging process, but who also aren't like you and I so [inaudible 00:30:11] for it, they're like, "Oh, well how are you going to test this? How are you going to get this regulated? How is the drug going to enter common widespread use within the existing system within ... whether it's through good marketing and like a tool there or changes to the FDA and food labeling or changes to the FDA and drug approvals.

James: And I think that it's awesome actually that you started your show with this methylation clock because I think that this technology is actually at the core of one of the things that's going to help drive this, bridge, right? Between the ... we talked before about how Apollo's developing all of these new medicines that we think can get to your 40 or your 60 extra years, from 120 to 180, and there'll be approved for other things. They'll be approved for genetic diseases, there'll be approved for heart attacks and whatever. And then the challenge is you get those drugs approved, you still need to do a clinical trial to get your capital C claims from the FDA and you can't do a trial that's just like a lifespan trial, right? Give it to a bunch of people in their thirties, forties and fifties and see when they drop off or see when they get cancer or see when they start developing mild cognitive decline.

James: And what we'll have to do instead is use things like the aging clock, right? Things that are predictors of what we call multimer morbidity risk. And the FDA has made some signals that they would be willing to accept one of these good biomarkers and use that, and interestingly we're talking about cholesterol earlier, cholesterol did the same thing, right? It was established as a biomarker and then Lipitor and the Statins were approved

based on the ability just to move cholesterol in the blood, which has its problems as we discussed, but it also allowed the pharma companies to justify the cost of the clinical trials because they could then have some time on the patent life span of those drugs so that they can make some money there. Same thing's going to happen with the aging drugs. There's going to be a compressed clinical trial time so that we can prove, quote unquote prove whether they work on these aging biomarkers in shorter trials, two, three, four years, get them approved, and then that's when they'll enter wide distribution. Anyway, that's the idea that we have for the space overall.

Dave: I love it because it's really hard to prove that something will double human lifespan because if you wanted to take it to double yours, you'll be dead before you know that it worked.

James: Exactly, right? That's the key problem there.

Dave: What's your stance on I'm going to call it bio-freedom, and this is the idea that it's your biology and you have a fundamental human right to do whatever you want to manipulate it without anyone telling you, "You're not allowed to do that." Where do you stand on that spectrum?

James: So I put myself completely in favor of it, that I don't want to be and I don't think anybody should be in the business of telling people what they truly can and can't do. I've talked at conferences and so on about the fact that I'm on Metformin because I think that it's an interesting longevity drug even though there's no FDA approved condition that I have that shouldn't allow me to take Metformin.

Dave: Let me define Metformin for people who haven't heard me talk about it before. Metformin is a very common and well understood anti-diabetes drug that in multiple studies is tied to life extension. And I've written about it in *Head Strong*, actually about the pros and cons of it. So anyway keep going.

James: Okay. So, I believe in this idea that we should be able to experiment N equals 1 experiments and self-organize into bigger self-experimentation groups in these sorts of things. I think we should first of all be allowed to do it, and second of all, there is a way to get useful data to make real progress from that, but kind of where I come into the field is that right now there isn't a widely established mechanism to move an entire field of scientific inquiry forward dramatically without the mechanisms that exist of the clinical trials and the capital C claims that we were talking about and this sort of proof. That you'll have little threads of progress where knowledge will be kind of sequestered in groups of people who have tried it on themselves or who have really, really dove quite deeply into the data and figured out something that works, and it's going to be hard to spread it to a wider audience until you play within the existing system.

James: And so I think that there's one huge piece of work to do to try to figure out how to establish that system where we can unite these N of 1 trials into things that can be a convincing enough data sets to make ... to convince skeptical people, but then secondly, figure out how to play within the existing systems so that we can ensure there's funding

and there's development for the second and third and fourth generation of these compounds, which are the ones that are really going to deliver the massive gains in life span extension.

Dave: One of the reasons that I am a huge fan of bio-freedom, that idea that you have the ability to do whatever you want to your body, you don't have to convince the skeptics. They can remain perfectly skeptical, while you basically outlive them. I love talking, this is going to sound rude, but I love talking with fat skeptics. It's like, "Hey man, I used to weigh 300 pounds and I also had a 46 inch waist. I have a 33 inch waist. I don't experience hunger. I can tell you eight different ways that my recommendations work that are borne out by what we understand about biochemistry today and you can try it for two weeks and if I'm wrong, then stop, but the odds of you harming yourself are very low." To be able to do that, it's like, hey, skeptics, you can stay skeptical. Just you'll stay skeptical, fat, tired, and you'll probably die before me, right? And it's okay, right? And by the way, if you try it and it doesn't work, please tell me so that we can figure out what's weird about you and we can hack it.

James: Completely I agree with you there, and we take kind of a similar approach. If you'll forgive the corny reference, it's like there was this line in the second Matrix movie where they're saying like, "Oh, I don't ... not everyone believes things you believe," and he's like, "My beliefs do not require [inaudible 00:37:05] And I think that taking that approach in any kind of innovation development, it is really, really important. You want to be able to pull the world along behind you as opposed to having to convince everyone before there was technology there. The systemic risk that I see in the aging space specifically, is that I think that the tools that we have available to us with the existing amount of aging research and the rate that progress is going is promising, but not as fast as it could be going.

James: So the systemic risk to me is that unless we figure out how to pull those skeptics in as early as possible as we possibly can, they're wall between our industry and billions and billions of dollars of R&D, insurance money, like big insurance companies, pension funds, these are the people who are standing behind the huge walls of money that can be deployed into keeping us healthier longer, and figuring out how to activate those groups of people as early as possible is key, not just for getting the ... figuring out the longevity effects of natural compounds and tools that we can use and this first generation of new drugs that are going to come up, but the second and third generation of those things, we won't have to go through a 20 year development period if we can unlock those people to find the next generation of those things, I want to unlock those things in a four year period after they realize that they're so important.

Dave: I think it's going to happen, and I mean I may be one of those people who gets research compounds that are very well studied, that aren't necessarily approved for use and may decide to use them with or without needles. And I know lots of biohackers and people who speak off the record like, yeah, I did this and my telomeres are way longer than they were before and you can already do things that are in the realm science fiction, but you're not supposed to do these things. And it's sort of like, I'm going to really piss a lot of people off right now, but someone in my mind who is a great hero is Lance Armstrong, okay.

Dave: The guy had testicle cancer and he came back from that and he used every tool available to him as a human being to do the impossible, the truly superhuman. The only thing he did that was wrong is he lied about it and he didn't disclose everything he did so we could all learn from it. But what he did was so impressive regardless of the controversy about all of that stuff, that should not have been possible and the fact that he did all that, what about those of us who didn't have testicular cancer who just took advantage of some of those things to be better parents, to be able to handle whatever life ... do we have a moral obligation to do that? That's a question for you.

James: So let's talk about that a little bit because I share your view, not necessarily of the ethics behind what Armstrong did, but of the ridiculousness of the rules in which we view competition and naturalness in the space. And this [inaudible 00:40:37] ties back to an earlier part of our conversation, which is like if we want to be showcasing and pushing the limits of the best that humankind has to offer, how come an [inaudible 00:40:51] that activates the Wnt signaling pathway, that can count as natural, but a small molecule that activates the Wnt signaling pathway, that doesn't count? How come exercise to increase the rate of red blood stem cell genesis counts as natural, but supplementation with EPO, which creates increased red blood cell genesis doesn't count? And so whether we're thinking about competition or living the good life or optimizing ourselves to our best performance, I think that the distinction between natural and unnatural really have to be broken down.

James: And most importantly, there's this idea of if we want to be our best selves, if we want to maximize our own performance, maximize our own health spans, we'll have to use all of this power that modern medicine has unlocked genetics, genomics, drug development, all of these different things are going to have to be tools in our toolkit just as great foods and lifted modulation and devices to track our calories and meditation and mindfulness and all of these things are tools in that toolbox. I think we're going to have to use all of them if we want to really, really make a dent on aging.

Dave: Aren't you a little bit concerned about this idea? Well, if one competitor uses this, then everyone else has to use it to keep up?

James: A competitor in what sense do you mean? Because usually I think about competitors in terms of companies.

Dave: It could be Tour de France or it could be just competing for resources in this hard scrabble of human life, however you want to look at it.

James: So I'm not a professional competitor in that way and I totally get, right? There is this sense that everybody should be able to do the Tour de France if they tried hard enough and it sucks that you have to do the EPO injections and it especially gets ethically sketchy when you talk about other types of steroids that have positive short term effects, but deleterious long-term effects, there are troubling ethical questions there, I get it, but frankly I'm also not someone who is super interested in sport and competition in that way, and so when I look at it, I'm just like, yeah, but people can be so much better.

Dave: Yes, I'm with you there. The problem is it generalizes to everything and the response that I have there, and I want to hear what you think about this as an investor, I'm like, look, I'm using a laptop right now and a mobile device. So if you look at it, those are massive, unfair advantages over someone who doesn't have this, right? So if they don't have them, they won't be able to keep up, right? What's the difference between using technology or let me can go back, hey, I'm a caveman, I have fire, you don't. It seems like these are just basic technologies and why are we treating them all weirdly?

James: So I mean, my favorite book of all time is probably Richard Dawkins' *Selfish Gene* in which he described and first established the term meme and this idea of mimetics, right? Technologies that behave like genetic traits, but exists in our minds and in our culture and so on. And I think that when we think about our interactions with any sort of competitive system like our society, a game that we're playing, whatever it is, then all memes are functionally equal, right? It's just about how does this improve your fitness towards achieving the end goal? And if your end goal is communication with the other side of the world, then having a laptop is probably going to get you much further than having a piece of paper and a pen. And those are just the mimetic differences. Similarly, if you have, I don't know, a brand new drug that's going to reduce your mTOR signaling and increase autophagy levels and reduce the free radical burnout rates of your mitochondria, then that's probably going to be a better tool for you than a salad with some nice oils on it. That's my take on it.

Dave: I think it's a really nuanced take, but it opens the next question then, and this is one that I know both of those [inaudible 00:45:31] probably answered before, but I want to get your take. What's going to happen to the global population if people live 50% longer?

James: So, I actually just finished doing a research paper with the University of Oxford that's not published yet on exactly this question where we wanted to model both the population effects and the potential impact economically of extending healthy human life. And the short version is that if everything that we think is going to happen kind of comes be, it doesn't change population that dramatically, right? The UN projects that the 12 billionth human will never be born because of the demographic shifts that are happening all over society right now. Every single country is lowering their fertility rates and so right now we're living in a world where the ever shrinking class of working population, right? The people ... we're getting to work later and later because we're doing more and more school, the ever shrinking group of the working population is shouldering more and more elderly and unfortunately often sick people. And so you can convincingly make the argument that not only do we need to continue, there's this old adage, if you're not growing, you're shrinking, if an empire isn't expanding, it's collapsing.

James: And so I think that there's a strong ... that there's some truth in that, that we need to continue enhancing the amount of healthy people we have in our ecosystem, otherwise the society that we've built is in serious jeopardy because we've set up all of these systems where we're relying on an ever shrinking class of people and this is the first time this has ever happened in human history, right? The first year that there were more people over 65 than under five in human history was last year. And I think that because of these demographic shifts, we actually need more people, more healthy people contributing to society and every time we've had any shred of a [inaudible

00:47:52] catastrophe, right? This idea of this population explosion, it's been overblown. Thomas Malthus famously and right before the industrial revolution, the first big population scare was [inaudible 00:48:04] was like, "Oh my God, there's going to be a billion people." And he advocated genocide as a way to stop the fact that there were going to be a billion people because he thought it would lead to the collapse of society. And I think technology can increase the carrying capacity of the world by a lot.

Dave: It certainly can and-

James: That's a bit of rambling [crosstalk 00:48:26] but I hope I made some points there.

Dave: It's a really important point that I'm going to rephrase it, older people who function like younger people are necessary for basically the continuing evolution of our species. The fertility rates are declining precipitously everywhere. So I am not worried about a population problem because basically that was at one in eight couples of childbearing age just can't conceive no matter what they do, which is unprecedented. It'll be one in four in another 20 years, we'll keep doing [inaudible 00:49:01] it will be one and two. And of course the children they're having are less healthy than before as well. So unless you're doing some conscious things before and during pregnancy, I'm not that worried in that when I put on my, I'm going to live 180 years hat, I'm more worried about air quality, soil quality, ocean quality and food quality and things like that. The other thing that I think we're short on now and this is why I'm really passionate about anti-aging is that when I was 28 and I'm sitting down with a guy who was 88 years old who's on an aggressive anti-aging regimen and frankly has more energy than I did at the time, I learned so much and I still do.

Dave: I've interviewed a good number of people over 90, Nobel prize winners like Eric Kandel who are still going strong and they have something that's called wisdom and I want a world with a lot more wisdom. We need old people with functioning brains who've taken enough hits in their lives to gain wisdom and who have enough energy and desire to share it and use that to help the next two or three generations who are still making the same mistakes they did. I greatly value my elders and I think that's missing from society today. We take our older people, we put them in retirement homes and we don't value what they've learned. And you talk to a lot of people, they hit 60, 65 and my parents told me, they said, "You know what, one day I just realized I'm invisible. I walk in the store and it's like people don't see me as a person anymore." I'm like, "Are you kidding?" These are the people who know the most, right?

James: And I think that that's actually the real treasure that's going to hopefully be unlocked by this revolution, is that we'll have people for the first time who can ... imagine someone dedicating a century solving a really, really, really sticky problem that takes a century to unravel, and being able to spar with multiple generations of the creators of a theory and then it's next generation, and then all of a sudden the first generation kind of upsets things 30 years later with new thoughts coming back in, I don't know, I think that that's absolutely right, that the accumulated wisdom that we will have and actually here's the point, that was a bit rambling before, but here's the point that might actually be useful, which is that most scientific breakthroughs happen from a confluence of more than one

discipline, right? There's this famous trope that Nobel Prize winners are five times more likely to play an instrument at the symphony level than any other scientists.

James: I'm not in that category of people who can play an instrument well. But by having very long-lived healthy people who can explore multiple disciplines, you'll get so many more opportunities to have two different disciplines meet in a single mind and come up with something magical that I think if you wanted to go to Ray Kurzweil's thoughts about the singularity and this sort of stuff, certainly that'll be happening in AI to some extent, but really there's something magical to me about unlocking this capacity for human creativity.

Dave: It reminds me of what Naveen Jain says, Naveen runs Viome, he's been on the show a couple times, spoke at the Bulletproof conference, but a Naveen same thing, he said that no great disruption happens except from outside an industry and one of my favorite posts ever, okay, I'm literally a computer hacker, like systems architect deep, like how are we going to make the Internet scale and perform well guy, and it was the most important thing I could think of in my twenties. And [inaudible 00:52:54] said I'm going to change the process of making green coffee to focus on human performance, one of my favorite posts ever was from some coffee snob website, I don't remember which one, and they're like, "It's impossible that Bulletproof has done this because Dave is not a coffee guy." And what you just said, it's like actually those crazy innovations come from people who don't think like the people there.

Dave: And that's why I wanted to interview you because you're looking at aging, but you're taking this aging thing which is different than the way big pharma does, and you're going in and saying, "Hey, I'm going to take my outside your domain expertise, I'm going to bring it into your domain." And that's where real disruption happens. And frankly, drug companies, they kind of deserved disrupting right now. And they got a lot of money, they waste it on ... hundreds of millions of dollars to make a drug that lasts for 10 years before they realize there was a bunch of side effects that any biochemists could have predicted with their eyes closed, If I could just say that, maybe there's a better way and maybe you're bringing it to them and I think that's cool you got to keep doing that.

James: Thanks Dave. Yeah, as you know, I'm a relatively big fan of the pharma companies, to me there are like a really important part of the value chain that ultimately gets these new medicines into the hands of patients, and there's good stories and bad stories that come out of it, I tend to focus on some of the good ones as well-

Dave: I'm with you on the good ones, I'm just saying they waste a lot of money, a lot of money. And I'm not anti-pharmaceutical, I like pharmaceuticals, they're really useful. It's just, could we get them a little bit faster, and a little bit cheaper and a little bit better labeled.

James: I think that those are all fair requests.

Dave: There you go. I'm not asking you to rip on big pharma, I'm just saying that disruption from outside the industry. When you think of aging as a system the way you do, that they look at diseases, individual. Isolated diseases, but that that will change.

James: And this is the big disruption that's going to happen in the pharmaceutical industry. It happened once before, which is when we changed from thinking about infectious diseases from like, "Oh my God, you have swollen lymph nodes," to, "Oh my God, you have a bacteria that's swimming around in your blood that's causing your lymph nodes to be inflamed." This is the same level of disruption. Right now we're thinking like, oh my God, you have a cancer and we're going to change that to Oh my God, your DNA is mutating and you're living in an inflammatory cellular environment and that's increasing your risk of developing an evolutionary anomaly called cancer. That shift is going to hopefully bring about the same sort of reduction in mortality rates that we saw from 1900 to 1950 in infectious diseases that we'll see hopefully from 2000 to 2050 in the age related diseases.

Dave: Beautiful. I fully agree with what you're saying there. Now you've talked about sort of the areas that have the most potential for anti-aging. We have about 10 minutes to do this, so I'm going to list each of these things. I want you to tell me in one sentence that everyone listening can understand what it is and then in another sentence, what's really interesting to you about it and if you have something, what we can do right now about it, so here's number one, genomic instability.

James: Genomic instability is the idea that our DNA is constantly mutating. From the moment that we're fertilized from the single cell stage until we're dead, there is a mutation rate that can both contribute to overall tissue dysfunction and also mainly contribute to cancer. There are a number of things interesting about this, it's one of the trickiest problems to get at from a drug development standpoint, but the way of disrupting this is finding compounds that can enhance DNA repair mechanisms and using those prophylactically. So in the cancer case, you have to do it long before you ever get a cancer, which is going to make them tricky to do clinical trials on, although I think we have some ideas, we don't have an investment in this space yet, and the compound that I know that has been most associated with DNA damage repair is NAD and the nicotinamide, the NAD precursors, which seem to enhance DNA repair.

Dave: I love it. You said NAD, I had a couple of podcasts on that. I've had 20 intravenous infusions of NAD, we do it at Upgrade Labs in Santa Monica and in Beverly Hills. Yes, there's some good science for that and I would double down on NAD or take NAD precursors that you can learn about, just google Bulletproof Radio NAD you'll find all that or it's in the show notes for this. Okay, I love that one. Telomere attrition.

James: So, telomere attrition, related to genome instability, but different cause. Ends of our chromosomes are constantly shrinking. When they shrink too much, they start causing big problems for cells. Cause cancer, but also cause cells to just shut down and not being able to replicate anymore. I think telomere attrition is less of a problem in most aging than we thought it was 20 years ago, we're still really interested in it. One of the things that I'm most interested in it for is figuring out how to use telomere elongation as a way of boosting the effect of cell therapies because one of the big problems in cell therapies

is you take cells out of your body, you have to rejuvenate those cells and expand them out so that you can give a lot more stem cells back in, and I think that actually telomere therapists are going to be most important first in that space, but there's not a lot that I know about that really could work right now there, although we are thinking about making some investments in the space.

Dave: Okay, cool. I think that there's some things where I'm sleeping better, that might give you longer telomeres. That seems to be-

James: For sure, any sort of systemic stress, we know lowers telomeres bit by bit over time as you're constantly exposed to stress. So for example lack of sleep.

Dave: Like being in a bad relationship, it makes you old. There you go.

James: For example.

Dave: Alright. Epigenetic alterations.

James: Like we talked about at the beginning, there are a bunch of different changes, chemical changes to our DNA within ourselves that happen as we get older. This is through the addition or subtraction of these methyl groups which affects these, we have ATGC letters in our DNA, they affect the G's and C's, these pairings and change them so that it silences the DNA. Having those marks around prevents the genes from being properly expressed. And I love that you pointed out at the top of the show that as we age, some things get turned on and other things get turned off. And so this is one that I think is, of all the hallmarks, the trickiest one to deal with because you can't use a blunt instrument to address it. You can't just say, "Oh, we want more methylation," or, "We want less," you have to figure out ways where you can be really targeted with these things. You mentioned a couple of supplements that you take, I don't know that much about those, on our end we haven't seen too much that takes this nuanced approach where you figure out where you need to add things and it doesn't add things so broadly.

Dave: Yeah, [crosstalk 01:00:25] mostly like methylated forms of B vitamins are kind of where it's at for that versus like when you take P5P versus vitamin B6 for instance, or methylfolate or 5-MTHFR versus folic acid, stuff like that. Okay, Loss of proteostasis.

James: So proteostasis is the process by which our proteins are recycled and the amino acids that make up those proteins are used in new things and we kind of keep churn of ... we're constantly making new proteins so we have to be constantly degrading old proteins, otherwise they're going to build up and when you build up too much of anything that you're not using, it can cause problems.

Dave: Like a high protein diet is probably not an anti-aging diet.

James: Exactly. There's some interesting nutrition studies that you can change around the carbon fat loads a lot without having dramatic impacts on mouse health span, but if you get protein diets above 20% or something like that-

Dave: Yeah, it's 20%, like 400% more cancer when you cross 20%, especially for animal protein.

James: So, with proteostasis, the coolest thing about it to me is this process of autophagy, which means self-eating, which is part of this protein breaking down, a process that happens naturally when we fast, right? And the activity of this process of autophagy declines as we age and figuring out ways to boost it however we can seems to be correlated with lifespan in almost all organisms tested. And so we are really, really interested in this space, I think that there are going to be ways of doing chemical [inaudible 01:02:20] really strongly, but in the meantime, I practice fasting regularly, which I think is the best way of turning this off.

Dave: And if you're listening to the show, by now I'm hoping you've read one of my books, first one in 2014, The Bulletproof diet I talked about intermittent fasting. If you haven't at least tried skipping breakfast and having a late lunch every now and then, seriously, it actually saves you money and time and makes you live longer. It's a pretty high ROI activity, you owe it to yourself to try it. All right, I love that one and by the way, yes, give me some autophagy drugs because fasting for three or four days, which is something I do on a regular basis without suffering just for people who are like, oh my God, really, it's not that big of a deal when your metabolism works, so I guess I could eat and it's not a big deal. Okay, altered Intercellular communication. We got to go faster on these two.

James: Okay. Sorry I'm too wordy. So this is a kind of complex one because it means everything about how are cells changing, the way that they're signaling to each other, it can be both inflammation, but I think the one people usually talk about is insulin signaling, right? And as we age, we become less insulin sensitive and this is one of the things that causes type two diabetes really badly. One of the things we're most excited about here is related to autophagy which is mTOR inhibition, which is partially related to proteostasis, but partially also related to the signaling of insulin into the cells. Rapamycin is the famous drug that plays in this space. I don't recommend taking-

Dave: Do you take it?

James: I don't recommend taking Rapa, I think that the side effect ... at the clinically relevant doses, I think the side effect risks are too high when it's been used clinically. We have an investment, in fact, our first investment is in a company that made a version of Rapamycin that does not have side effects.

Dave: Oh sweet. I want some, hook me up.

James: Yeah, it's a really cool.

Dave: Next up, mitochondrial dysfunction, this is my favorite aging thing because it affects how you feel right now. And let's go fast on that one because I think people who've listened to more than probably five or 10 episodes have heard me ranting about [crosstalk 01:04:33]

James: So I [inaudible 01:04:35] really fast, our Mitochondria stop working as we get older. There are a lot of different ways we could potentially target them. I like the idea of enhancing, mitophagy, which is like autophagy but for the mitochondria where you're actually recycling the pieces, the [crosstalk 01:04:55]

Dave: Killing the ones that are weak and make your body grow young ones.

James: Exactly. And we haven't made an investment there yet, I don't know much about drugs, but I think that's the way to play in that space.

Dave: And cryotherapy would be an easy way to do that, if they can't get warm fast enough, the body will get rid of them. So that's, I think, a good way to focus on it, that's cheap. All right, next up, cellular senescence.

James: This is the big one where a lot of people have been making a ton of progress here in the last couple years. So as we get older in all of our tissues, we develop these old zombie cells called senescence cells that secrete inflammatory proteins and seem to cause a ton of problems. You get rid of these cells, you [inaudible 01:05:34] mice live much longer, 35% healthy extended life. The thing that we're excited about here is finding the mechanisms specific to senescence cells that differentiate them from normal cells, exploiting those with drugs to eliminate them from the body. We have an investment called Cleara Biotech that found the first mechanism unique to senescent cells, built a drug based on this and we're getting that, moving that towards the clinic now.

Dave: There are a bunch of supplements that show promise here. One of them is in Smart Mode, which is the cognitive enhancing, the neutral bake that I formulated, it's different than the other stuff on the market, but it's called apigenin. And apigenin in some studies seems to have a pretty good effect on that, so as a senolytic and even quercetin, another [inaudible 01:06:27] antioxidant seems to have effects and I'm talking with a bunch of researchers about those because I think it's the point where given that these compounds have other benefits anyway, taking them knowing they have those benefits and probably help with senescent cells, it's probably not a bad thing.

James: We remain a little bit skeptical about the data that we've seen from the supplement space, but I would agree like with something like quercetin, it's not going to hurt you.

Dave: That's what all you big pharmaceutical companies say, I'm just kidding. And it sucks too because supplements and I have a small part of what [inaudible 01:07:04] does is supplements, but it's a very meaningful part for me as a formulator, I care a lot. A lot of times I'm like, wow, I'd love to run a $50,000,000 clinical trial on this, but as soon as I do, there's no patent protection for it, so the competitors just come out there and steal your stuff and don't even feel shame about it. It's kind of amazing the number of knockoff artists out there who actually think, oh, I'm an entrepreneur. It's like, no, you're not, you're a thief. So that's a big problem in supplements in general, but I hear you, there isn't enough data yet. All right, well it's been so cool to ask you all these questions and I have one more question that I've started asking people just very

recently as I've been turning my attention more towards just talking about longevity and anti-aging, and it's this, how long are you going to live?

James: So I know that you're on record saying that you want to live to 180-

Dave: At least 180-

James: At least 180, okay. As someone who spends a lot of my time talking about this, I tend to think that that's kind of the wrong question because asking a 30-year-old how long he or she wants to live, you'll start getting answers like, not for me, but for an average person like 80, 90. And then when you ask an 80- or 90-year-old how long they want to live, they say like 100, 110 if they're in good health, and so my constant answer for that and I hope it's not dodging the question is at least until tomorrow, and I'll let you know when I changed my mind.

Dave: That is so honest. Here's my real answer, 180 is just based on math and very basic assumptions that are defensible and I believe conservative given the exponential growth in our technologies here, but the real thing is I would like to die at a time and by a method of my choosing. There you go, right? I got to pick when I'm done, I'm done and if I decide to go, it was my choice and that's the ultimate place of freedom or like you don't have to be immortal, which would also kind of suck, there's all sorts of myths about people like that and-

James: So we're fully agreed there at least until tomorrow.

Dave: All right, well it has been a real pleasure to speak with you James, your work is mostly @apollo.vc, I think, where people can find out about what you're working on, really, really appreciate that you're putting so much of your life's energy into getting our financial investments and our drug institutions aligned around this mission to have more people who are older with more wisdom and more health, thank you.

James: Thanks so much for having me on, this has been a ton of fun.

Dave: If you liked today's episode, you know what to do. If you want to be a limited partner in a large VC and you're an accredited investor who absolutely James did not pitch, you should probably call James up and pitch him. So he's not allowed to say that and he didn't ask me to say that and we have no agreement and right now he's going, I can't believe you did this Dave. Anyway, if you're one of the many very successful people listening to this show and you want to put your money where your mouth is, you should talk to guys like James because, come on, if you have more money than you need, you could invest in something that matters, I kind of like that. If you loved this episode, it was worth the hour of your time, please give me 20 seconds of your time by going to Amazon and leaving a review. Thank you.