**How Hacking Your Gut Bacteria Can Regulate Your Blood Sugar – Dr. Coleen Cutcliffe with Dave Asprey – #767**

Announcer:

Bulletproof Radio, a state of high performance.

Dave Asprey:

You're listening to Bulletproof Radio with Dave Asprey. Hey guys, this is a really cool interview that you're about to hear and I recorded this after the interview for you because I want to make sure that you know a certain number. If you go to pendulumlife.com and use code DAVE25, you can save 25% on the specific magic probiotic that you're going to hear about in this episode. It's got the most research behind it, and it does things for blood sugar regulation that you would not believe. So write that down right now, and then let's go into the interview. And by the end of the interview, you'll know why you wrote this down. This stuff is really interesting.

Today we're going to talk about one of my favorite topics, your poop. Okay, not really, your microbiome is what we're going to talk about. And we're going to talk about using the microbiome almost like a drug, using artificial intelligence as a part of this. It is really cutting edge stuff and it's things that I believe are in a position to change the world and change how we function.

Our guest today is Colleen Cutcliffe, who is CEO and co-founder of Pendulum Therapeutics. What they're doing that's different and interesting is that they're using biological and computational insights into what the microbiome does so that they can target specific species of bacteria for health and disease things. They're isolating, identifying new strains, mixing them up to create unique probiotics, and then doing clinical grade research on them. They have the world's first microbiome intervention for people with type 2 diabetes, for instance, which is really cool. This is so much different than I would take this drug to lower your blood sugar. This is hack your gut bacteria. So this is super disruptive technology, and we have a very, very intelligent PhD, Colleen Cutcliffe, on the show. Colleen, welcome.

Colleen Cutcliffe:

Thanks so much for having me.

Dave:

Now, you studied biochemistry and then molecular biology. What got you into gut bacteria of all the places you could go with a background like that?

Colleen:

Well, with a background like that, I actually have a pretty traditional career path. I did a postdoc. I worked as a scientist in a pharmaceutical company. And then I worked in an early stage biotech company that was building DNA sequencing instruments. And while I was at that company, the microbiome space really started to emerge as a science in the academic realm and it was all premised on DNA sequencing. And this is what's really cool is that DNA sequencing technologies really started to become affordable in the mid 2000s. And that's actually when you start to see microbiome become a science. Prior to then, there really wasn't a way to probe the microbiome. It's all of these thousands and thousands of bacteria and other microbes that exist inside your gut, and the only way to really understand them is to get their DNA sequences.

And so before we could actually sequence DNA affordably, we couldn't actually look at the microbiome. And so I got really interested in this concept of this deep sequencing challenge really. You have 100 times more microbes than you do human cells. And so when you think about the human genome, you're really looking at log orders more data. And so how do you probe that microbiome to really understand what are targets in there? And that was sort of the intellectual question. And being at a DNA sequencing company, me and my two co-founders had the ability to think about how to apply DNA sequencing into this realm.

But on a more personal note, what really got me into this space had to do with my daughter. My daughter was born almost eight weeks premature and when you have a baby that's born that early, you get to see them for a few seconds and then they get taken away from you and go to the ICM. And that's where she spent the first month of her life hooked up to all these machines and monitors and actually receiving multiple doses of antibiotics. And they don't do that because the baby has an infection, they do that as a prophylactic treatment so that they don't get an infection because they're so fragile.

And as my daughter started to get older, I realized that she had things about her that were different from the rest of our family. Certain food sensitivities, certain issues with metabolizing those foods. And as I learned more about the microbiome, I realized there is this huge opportunity that we've been overlooking for decades and decades in science, which is this microbiome, and how could we target that to improve health. And so for both the technical reasons, the interest in the emerging science and my daughter, it seemed like a no brainer to jump two feet into this space.

Dave:

Well, there's so much that happens around birth with bacteria that we don't know. And for so long we thought inside the placenta it's going to be sterile, but there's actually a baby, a microbiome inside the body, and we just didn't know. I look back, 13 years ago we were putting Lactobacillus infantalis on Lana's nipples while our daughter was feeding to make sure she'd get some of the good bacteria, even though she had a natural birth. And we all do our best but it feels like, certainly about 10 years ago, we really started getting so much more science that's showing what's going on. And you guys use something called long-read DNA sequencing, which has led you to some of your discoveries. What is that and why is it different than what we've always done?

Colleen:

Well, you can think about the way we do DNA... So first of all, I will just say the fact that you were already using lactobacillus is pretty advanced. So I'm impressed.

Dave:

I did write a book on fertility.

Colleen:

Yeah. I don't know how many people are doing that, but that's pretty, that's awesome. So we think about DNA sequencing, your DNA are sort of these really long strands of these ATCG sequences. And when we do DNA sequencing, there's two ways to look at that. One is to kind of chop it up in all these little fragments, and then you get all these little reads. And you get a ton of those reads because you're chopping a little fragments and you get all that data. The other way is to try to get as long of a single read as you can. But you get a lot fewer because it's a longer read. I sort of think about it like if we think about taking a page of a book and cutting it up into a bunch of small pieces and then trying to paste it back together again, versus just cutting it into two pieces and trying to paste it back together again.

The brilliance of marketing, which is something that I'm learning more and more about every day, is that when you chop it up into a bunch of pieces, you can say to someone, "Hey man, here's a hundred pieces of this book. Wouldn't you love to have this?" Whereas somebody else might say, "Well, I only have two pieces." Actually those two pieces are much easier to paste together than those hundred pieces. And so what we said is, "All right, let's take the long read sequencing. We can integrate it with these short read sequences, but actually get the full picture of what this book actually looks like." And that's something that not a lot of people are doing because it costs more, it feels like it costs more. And the value proposition feels like, well, you only get two pieces for your money instead of a hundred pieces for your money. So it was that really not that clever insight that that was what we were making on with the technology.

Dave:

That was a really good explanation. I've been struggling with how to explain the difference between peptides and complete proteins in some of my books and listeners have probably heard me say that before, but I'm like, if you had words and you had sentences and you had paragraphs, they're of different value. So I like your explanation a lot. And so reading the book cover to cover instead of one word randomly at a time will give you a different result from the book. Okay. Now, I was a little surprised that I hadn't heard about you guys because you've raised $57 million so far from venture capital firms I've worked with like Sequoia Capital, Coastal Ventures. What's it like to go through a big fundraise, having done it myself?

Colleen:

Then having done it yourself, you know there's just one word, it's painful. In some ways it's great to go through a fundraise because it forces you to condense your story down into something that really gets punchy and to the point. But I think for those of us who like to build things and create things, it's the tough part. It's the pan handling. It's the trying to get people to put money behind your idea. It can feel very personal when people decide not to put money behind your idea. I'll tell you a funny story. The first time we... So I have all signs in my background, no fundraising in my background.

And so when we started this company we had no idea how to raise money from venture capital. And I finally got a meeting with this kind of young VC, his name was Adam D'Augelli, over at True Ventures. And he came into the building and we met, he said, "Well, Colleen, I'm super excited about this meeting because I have now heard about you from three or four different people who are not connected to each other who've all contacted me and said you're this amazing entrepreneur with this great idea. I can't wait to meet you." And I made the joke that, "Oh, well then if after this meeting you decide not to fund us, then I guess it's all me because you're already excited about the idea."

And then we sort of laughed and I gave the pitch of the company and he got to the end and he said, "Well, I'm not going to give you money." And I thought, "Oh man, that joke up front that it's all me is really playing out now." But he gave me some guidance on focusing in from just being this kind of almost R&D feeling discovery company to pick a disease that you think you're going to be able to make a headway in and then come back to me. And so we did that and we actually ended up getting funding from the Mayo Clinic to really go after that and figure out what is the disease that's interesting. So our first investors were actually the Mayo Clinic not an institutional VC. And that's when we decided to hone in on metabolic syndrome, which of course personally was very tied to my daughter in thinking about that and we came back and that was actually when we got our first round of funding.

Dave:

Do you feel like you were treated fairly in Silicon Valley?

Colleen:

I think generally all entrepreneurs are treated unfairly in Silicon Valley.

Dave:

That is the truest thing ever.

Colleen:

It's a supply and demand issue.

Dave:

Yeah. A lot of entrepreneurs, less VCs.

Colleen:

Yes.

Dave:

There was a problem 10 plus years ago, and there's probably still some of it today where female founders were really having a hard time. And I'm looking at this, you've got tier one VCs and you did it. I've sensed that there's a growing awareness among venture capital firms to behave themselves and just to be a little bit more fair. I'm hoping that that's the case, but I would never see it because I'm a white dude. So generally it was rough but reasonable, is that what I'm hearing?

Colleen:

As you have only your experience, I only have mine too, so I can't really compare to what it would be like to be a white dude. I can say that I think everybody has a trail of tears around fundraising. We've been really lucky. I think the people who've gotten behind us, they see the vision, they see the promise of the microbiome space. They see the concept of being able to make these natural products that are efficacious and that you can bring these directly to people rather than being stuck on in this rut of small molecule chemicals. And I think one of the things about venture capitalists, for all the negative things you can say about them, they're super smart and they can see a vision. And so we've been really lucky. We've got great people behind us that are in it for the long game.

Dave:

That's exactly what you want on your board. That's so cool. Now, one of the things that I imagine led to your success there, and just you've spent a lot of time working on this, but I was looking through the studies. Nine of 10 customers for your first probiotic report lowered HbA1c and improved glucose levels. Now, that's better than any diabetic or diabetes drug that's out there on the market right now, is it not?

Colleen:

Well, there's variability in efficacy of drugs. Yeah. But it is on par, absolutely.

Dave:

I think you're kicking Metformin's ass if I'm just saying.

Colleen:

Well, many people, as you know, are already on Metformin. What's really cool about this is that the efficacy in our clinical trial was on top of Metformin. And so it's been great to see the people who've come interested in the product. We have people, of course, with type 2 diabetes on multiple drugs. We have people with pre-diabetes who are looking to avoid crossing over into taking drugs. And we've had people who are healthy that are really concerned about how is my body metabolizing sugar and fibers. And so we offer free A1c testing, actually at baseline, and then three months in so that people can see their results. And I think that really helps people kind of believe the results that they're experiencing.

Dave:

Now, this is something that I'm going to add to my anti-aging regimen. And I take a good number of probiotics because I know that it's useful to have the right species around, but I've also seen all of the studies that say taking probiotics doesn't work because they have nothing to eat and if you don't eat the right substrates, then they won't grow. Do you have to take prebiotics with Pendulum or does it grow no matter what you eat?

Colleen:

Well, I definitely believe that you need the food in there. I always say if I were going to be dropped on a deserted island, I'd rather be dropped with a cooler of sandwiches and beers than just by myself. And when we developed the product, we had the same philosophy. So we actually, in the pill it has the probiotics, the microbial strains, and the prebiotics that feed those strains all in the same capsule. And in our preclinical work, what we found was that if you didn't have them together and you just had the probiotic strains themselves, we didn't see the same efficacy. So you really did need both the probiotics and their food, the prebiotics, together in order to deliver this. But to answer your question, of course having things like a high fiber diet and eating well are all beneficial. But for this, you don't actually need to add to it. It's all encompassed in that one pill.

Dave:

When is the best time to take it?

Colleen:

That's a loaded question and maybe points to how little we know about the microbiome.

Dave:

You are a CEO like every five minutes all day long.

Colleen:

Exactly.

Dave:

Just kidding.

Colleen:

Just pill popping all day. There's a couple of things to consider. The first is actually the acidity of your stomach, and you're trying to get these things delivered into the colon. We have an interior coated capsule so that it will get through the stomach acidity, but we also recommend that people take it while they're eating food. And that's because your stomach is extremely acidic. When you eat a meal, it makes it less acidic. And so then the capsule has an increased chance of getting to the colon, which is where you want to deliver it. And in our clinical trials we've asked people to take it in the morning and in the evening.

And what's been really interesting is the translation of things from a clinical trial into real life is always you never really know when you're released into the wild what's going to happen. And one of the interesting things that happened is this idea of morning and evening pills. And it started actually with my husband who of course by virtue of being my husband, he has to try the sawfish that I've been making.

Dave:

So Guinea pig, right?

Colleen:

Easy Guinea pig. A few days in he said, "I've been having a hard time sleeping at night and I think it's because of these pills." And I said, "Are you crazy? It's definitely not the pills. It's something else you're doing. You're drinking coffee at night. You're having too much dessert. It's definitely not the pills." And then there were other customers who were sort of saying the same thing, I'm having a hard time sleeping at night. So my co-founders and I sort of sat down and said, why might this be happening?

And it turns out that one of the strains in our formulation is capable of producing GABA, which is a neurotransmitter, and the idea is that if you're having these neurotransmitters that are being created in your body because you're taking this pill right before bed, that can cause people to have issues with sleep. So actually for some people, it's better to kind of take them in the morning and not take them at night. And in fact I myself I take my pills in the morning and it helps me, I think, specifically with that post-lunch drag. I don't know if you've ever experienced that, but-

Dave:

Back when I ate lunch, if people haven't had a fast, I tell you... Okay.

Colleen:

It's true. Those of us mere mortals are still eating lunch.

Dave:

I ate lunch those days, I'm totally kidding.

Colleen:

But I always say like I'm a lot smarter at 9:00 AM than at 2:00 PM and it's because of that post lunch kind of drag. So I've found for me when I take the pills in the morning, it kind of helps me stabilize my blood sugars throughout the day and I don't have that early afternoon low.

Dave:

Why would GABA, which is in a lot of sleep formulas, why would that keep you up? I'm not clear on that. Don't you want GABA at night?

Colleen:

Well, I think it's a complicated... This again I'll say like the microbiome neurology. So my first job in the pharmaceutical industry was trying to develop drugs for Parkinson's disease. And it's another kind of place where I think we think we know a lot about the brain and how it all works and how these neurotransmitters work, but a lot of it is situational. And so it depends on all the other things that are happening whether these particular small molecules can have one effect or sometimes actually the exact opposite effect. So like I said, it's sort of a loose hypothesis. We haven't tested it, but what we know is that when we ask people to shift to just the morning, they don't have these sleep issues anymore.

Dave:

Well, sometimes having extra energy during the day is just fine. In fact I know a guy who really likes coffee in the morning. It's crazy how that is. So in the morning is a good thing. And there's also a circadian rhythm to bacteria in the gut as well. There's a couple of studies that I came across while writing some of my books that showed that when you stay up all night or you get jet lag, your gut bacteria also get jet lag and then they make more lipopolysaccharides, that toxin that contributes to brain fog and cravings and all of that. So maybe they just don't like growing at night because they should be grown during the day and that's just how it is. Okay. Tell me about the history of the probiotic industry. How did it get to be the way it is now?

Colleen:

The probiotic industry is very interesting. I think all of us kind of somehow intuitively or inherently know that these gut bugs are important for us. And that's sort of why I think probiotics and yogurts and things like that have been able to really thrive despite kind of the lack of clinical evidence or really going after a particular mechanism or target. I think we just all sort of know there's something important there and we haven't really known exactly how to target it yet. So I think up until the time in which we could do DNA sequencing, it was about, well, what can we grow? What microbes can we grow at scale that we can commercialize and try to help deliver these beneficial microbes to people?

It really hasn't been until the last decade that there's been science behind it that says, well, what are the functions you're looking for? And then how do you grow those microbes and how you deliver them to people? And then how do you measure what those microbes are doing and what impact they're having on health? That's what's really been happening in the microbiome emerging scientific space over the last decade that wasn't happening before.

Dave:

Even going back to when I first was putting together the Bulletproof Diet, I went really deep on probiotics because my gut had been screwed up by over 15 years of taking antibiotics every month for chronic sinus infections and living in a house with toxic mold. Tends to maybe negatively affect your gut bacteria just a tiny bit. And I was kind of disturbed because I would read the research about some of the species that were in common probiotics and some of them were histamine formers, some of them were making stuff in the gut that you really didn't want. I'm like, why are we taking these ones? And there was actually a section in the book where I said, if you're not feeling good after meal, maybe you should have more of these and less of these.

So most of the stuff that you could find, especially at the low end on the market, probably was doing some good but probably was doing some harm. And then a lot of it wasn't even going in because either it was dead or didn't have enough CFUs or it didn't have prebiotics. But I feel like in the last 10

years it's been just a sea change and we still have all the old strains out there, some of which have some evidence. And then we have all these new kind of Ninja species like the ones you're working with. What do you think the future's going to look like? Are we going to wake up in the morning and have 72 different probiotic pills for each of the different states we want? How are we going to manage the growing number of things? When you have like 10 different things, like all the major diseases, am I going to have like all these different stacks of probiotics?

Colleen:

It's a great question. I mean, I would say kind of what you're experiencing with taking antibiotics and living in a house with mold and all those things, you probably know quite well that the microbiome is an ecosystem and kind of like a garden, right? And so as you're killing one type of plant, you're enabling another type of plant to kind of sprout up there. And the whole game of the game is keeping this garden thriving. And when we lose certain types of flora, we lose certain types of bacterial functions, that's when we start to experience different diseases. And I think actually where we're headed is rather than calling a disease by what the symptoms are, we are actually looking at the microbiome as an underlying infrastructure within our body.

And so as you think about losing these functions and what that shows up for people, it could be the same loss of function results in showing up as a different disease for different people. Let me give you an example. If you're losing some of the functionality that's related to inflammation, you might feel like, wow, I'm getting all these skin rashes and inflammation is showing up for me in that way. And somebody else might feel a great deal of joint pain. At the root cause is actually an inflammatory issue, but people are experiencing it in different ways. And I think where we're heading is understanding that the microbiome is foundational in a lot of things like the immune response, allergies, digestion, metabolism, and that once you start to make sure that you have the right flora and all the right plants in your garden, you're actually going to be tackling a lot of these different things. And so you won't have to have a specific thing for every disease because I think we're going to transform the way we think about disease.

Dave:

Wow. I agree with you. So much of it is happening in the gut or in the environment around us. And I'm hoping that as you figure out some of the other combinations that you'll just make me a master Ninja, a whole platoon of Ninja, even if it's a few pills. And they'll just say we've taken, in my case the big four killers. I wrote my anti-aging book, I'm saying the first step to living a long time, don't die. So let's play the odds. What is most likely to kill you? Number one, diabetes, because we see other three things that kill you: cancer, cardiovascular disease, and Alzheimer's. And if you just don't die from one of those, you'll probably live a lot longer and you'll probably like your life better along the way. So let's start there and then let's look at all these advanced stem cells and all this other crazy stuff, including modulating the human gut bacteria.

Are there some species of bacteria in the gut that we just should never have in there other than obvious like toxic e-coli and stuff like that. But things that we kind of think are normal that we should really just kick our ass and remove them. Like generally stop doing what's harmful before you add more of the good ones, is that a part of your strategy?

Colleen:

I think, again, because it's an ecosystem, if you're inundating with the good stuff, you will dilute out the bad stuff. But I think you've talked about this also, which is one of the things with this sort of anti-aging

or healthy aging, one of the things that's at the heart of it is how we metabolize sugars and how we metabolize kind of natural sugars. And so you've probably also seen the papers that talk about how taking artificial sweeteners and things like that really alter your gut microbiome. Your microbiome is really adapting to your environment and all the things that you're doing. And so as we think about healthy eating and good nutrition and trying to lead less stressful lives to the extent that we can, these are all the things that are altering our microbiome probably more than anything else. And so diet and environment have such a big impact on your microbiome that trying to eradicate a particular specific species is probably less relevant than thinking about it holistically and saying, all right, how do I put the right flora into my microbiome?

Dave:

I like that idea of just diluting out the bad stuff and that does seem to work. What about fasting? When you fast, there's nothing for the bacteria to eat, what happens? A lot of people with diabetes, a lot of people with pre-diabetes are adapting fasting. I've very transparent plug for my new book on fasting called Fast This Way. What's the role of the gut biome and specifically the species you work with when we're actually fasting?

Colleen:

Well, fasting, of course it's a super interesting phenomenon and getting back to almost our caveman days of how our body was intended to function, not a constant stream of food all day long. I think we don't fully understand the impact of fasting on the microbiome. Obviously there are certain microbes that are colonized in your microbiome that are less susceptible or more susceptible to not having food there. It is a competition because it's an ecosystem. And so the question is maybe after you stop fasting, what's the first thing you eat? Who are you feeding first? But this is really in its infancy stage. A lot of interesting things to study there.

Dave:

I love that you said that. One of the reasons that I hypothesized that Bulletproof Coffee does what it does is that caprylic acid, which is another fancy name for the specific subset of MCT oil that Bulletproof makes, it and even just butter are anti-microbial. So you take those on an empty stomach you're going to knock everything down. But then some species will grow faster based on polyphenols versus others. So the polyphenols in the coffee feed the Bacteroidetes versus the Firmicutes and that's a shift that you actually want to do because at least that's the shift that people who are thinner have.

So what you just said there really ties into one of the six reasons that I think it's doing this stuff. And it's fascinating because we have no evidence, no clinical trials, no one knows what to do. We have mechanistic thoughts, and you can sort of try one versus the other, but is that the kind of trial that you think will ever be funded where we start looking at how to break a fast from a microbiome perspective, or is that just one of those things that no company's ever going to fund?

Colleen:

What's really interesting about the microbiome is the ability to create a product that is natural and can be brought directly to consumers. And the reason that's interesting is because it allows a consumer to now test whatever they want to test. And there are microbiome sequencing companies where you can get information about microbiome changes that are happening, you can get blood tests done. You can basically measure and of course it's a phenomenal world we live in now where there's all these new

measurement devices that we as consumers have access to. You can measure anything that you want to measure.

And so by offering different types of microbes you're enabling people to really run their own experiments. And so you Dave could take this set of probiotics and then you could fast and you could for two weeks break your fast with one particular type of coffee, and you could then choose to break your fast with a bunch of scrambled eggs, and you could literally see what is the difference between doing those two things. So well, will a company fund that? I think companies are funding it already in enabling people to measure this themselves, but it's really it is the future is the way personalized medicine is actually going to play out is through these measurement devices.

Dave:

I've just recently made an investment in Levels Health as an angel investor and I'm an advisor. This is a continuous glucose monitoring thing. I've done CGM and before that I'd prick my fingers. I was probably pre-diabetic when I was in my 20s according to some measures, but I don't particularly have issues with that now, but I just like to manage it. And with Levels, what I can do is say this was the effect of this meal. And what I'm really excited to do is say, okay, now that I know how I respond to white rice and sushi or something, I can go do the same thing when I'm on Pendulum and then look at the difference. I haven't done that yet because I wanted to get you on the show. I have my Pendulum in the mail.

I'm in Canada, so I have to figure out how to do all this stuff that I do so that I can get it, but I'm really excited about that. And this is something that anyone who's listening can do, and you can get a finger prick type 2 diabetes-ish sort of thing, a glucose monitor that's 25 bucks at the pharmacy. Like they're very, very easy to get. So you can measure this, and if you want to do one thing to really live a long time, controlling your blood sugar should be very high on the list along with not getting hit by a truck. I like that one too. Select that personalized thing, you can see if it works. What amplifies the effect of the bacteria that you guys are using in your first product here. Is there any food that you should eat with it or not eat with it? What does alcohol do to it? What do you know about the environment that it's going to grow in?

Colleen:

I know, I've always said we should never make a product that doesn't work with alcohol. That's just a big problem. The prebiotics for these strains are fibers. So things like inulin. If you eat foods that are high in fibers with these probiotics, it ought to boost the efficacy. But again, it is really different for different people. I love the idea of continuous glucose monitors. I wore one to run the experiment on myself that you're talking about wanting to do. We have many customers who have done the same thing and reported back their before and after. I had the luxury of being able to get a placebo pill. And so I could really measure taking a placebo pill versus our pill with all those strains in it.

And what I saw for myself, even though I don't have diabetes or pre-diabetes, was... Of course all of us when we eat sugar we have the sugar spike and then the sugar crash. And I saw for myself that once I was on the pills, all those sugar spikes and crashes were minimized. And to your point about managing blood sugars, that's literally what the product is doing. And so it's really helping you with those highs and lows throughout the day. And that's something that other people have also experienced or reported back and shared and broadcast out to other people.

And so I think that's really the beauty of the product. And wearing a continuous glucose monitor, I'd also give a plug for that because it does allow you to see the effect of everything you're doing. And so I literally was like, well, if I eat a cup of grapefruit juice versus a cup of orange juice, what's the difference in my glucose spike. And you really learn it is different from person to person. And so I do

think what Levels Health is doing is really cool and enabling people to see very directly what you're doing, what impact that is having on your blood sugars.

Dave:

When seatbelts first came out in cars, and then lock brakes, a lot of people were like, oh, this is going to reduce deaths from car accidents, and it did. But people also started driving faster because they were safer. I'm pretty sure that Pendulum is going to allow me to eat cake sometimes and not pay the price, is that true?

Colleen:

Okay. You know I can't say that. However I will say this. It is helping metabolize your sugars, I know. I'll share a story with you which is that my daughter, the one that was born prematurely that really inspired me to start the company, she's been on these pills. It's actually pretty cool because we've made this product that my 13-year-old daughter is on, I'm on, and actually my 70-year-old mother is on. Everybody should be trying to manage their blood sugars. But anyway, my 13-year-old daughter has been taking these pills and she came home one day and we'd actually run out of them. They weren't in the fridge. And she said, "Mom, where are the pills?" And I said, "I need to get more. We need to order more." And she said, "Ugh, because I was going to go to Baskin-Robbins with my friends this afternoon, and now I can't do that." And that's when we had to have a talk about, this is not an enabler of bad behavior.

Dave:

Well, actually it is though. I'm just going to have to say it that way. Look, everyone who's keto, everyone who's fasted, everyone who's been on a healthy diet, whatever it is, every now and then they do something that probably wasn't very wise and you could do it with an airbag or without an airbag, right? So I look at this, there are times I'm going to eat some carbs, like way more carbs than is advisable if I follow my own advice. But what I will do is I'll take a handful of herbs and various things like chromium and all that stuff and I'll blunt my blood sugar spike.

Like I just had a whole episode on how to manage your blood glucose and it's really interesting because will this then, when I'm going to do something bad, may only take an extra one of these and some extra prebiotic fibers in my Bulletproof Coffee? Yeah, I think I will. I was going to do it anyway. I just maybe my blood sugar went up 33% less the way it shows in clinical trials and maybe I'll live longer as a result. It seems really logical and rational, doesn't it?

Colleen:

It does.

Dave:

I didn't make you say anything, did I?

Colleen:

Thank you.

Dave:

How regulated are you as a probiotic company? Keep in mind, okay, I started Bulletproof, I've done the VC dance and we're regulated by the FDA because it's food, but are you on the food side or the drug side or the supplement side? Like how regulated is your industry?

Colleen:

Yeah, I think we all kind of pretty well know the drug side, which is very, very heavily regulated by the FDA, especially around the claims that you want to be able to make around those products. And then there's the dietary supplement side, which has very little regulation, but you cannot really make any claims around the products. There's actually a third path, which is called medical food. And that enables you to bring the product directly to consumers with the supervision of their physician. But if you have the clinical data to support what your product is doing, it enables you to make those claims. And I think this is really foundational for the microbiome space because you can create these natural products that will have this kind of efficacy. So we're in a regulated space. We can only make claims on things that we have actual data to support, but we are not a drug.

Dave:

That means that you can sell direct to consumers?

Colleen:

Correct.

Dave:

Why did you not make it a medical food? Because medical foods have to be prescribed, right?

Colleen:

No, medical foods do not have to be prescribed.

Dave:

Interesting. I thought they were.

Colleen:

Yeah, you have to take them under the supervision of your physician, but you can get them without a prescription.

Dave:

Got it. Okay, cool. Well, I'm really impressed with the amount of research that you guys have put into this, and this is only one of the conditions that you're going after and you've had, I mean, your people with diabetes had a 0.6% decrease in HbA1c which is a really meaningful decrease. Percentage wise, about what was that, do you know? That should be like at least 10, 15%, depending on where it was.

Colleen:

Yeah, depending on where the starting point was. And our people were relatively early in diabetes, so most of them were on Metformin pretty early stage. And so, yeah, that's about the-

Dave:

Probably around 6 or something, 6.2.

Colleen:

Yeah. But that actually for some of them who were on the lower side. It meant the difference between having diabetes and moving into the pre-diabetes space. So it can really move you out of the diabetes spectrum.

Dave:

The anti-aging and functional medicine doctors that I work with, ones who have interviewed on the show, many of them are using HbA1c as a general marker for aging because we lose blood glucose regulation as we age. And they're looking at that as one of the biggest areas where they can intervene and help a patient. And so, you're seeing like 33% decrease in post-meal blood glucose spikes. Those are the ones that age your tissues, AGE, advanced glycation end products that gum up your cell works and damage your cell lining and all that stuff. Like those are monstrous changes to be really straightforward from just a bacteria. What is the next target for you guys? Let's say you've hacked this one. What's up next? Can you talk about it?

Colleen:

We have a pipeline of different things that we're working on that are pretty early stage, but the next one up is actually a product we're working on as a pretty strong collaboration with Johns Hopkins looking at IBS, irritable bowel syndrome, which is a really complicated, it's not even a disease, it's a syndrome. It's essentially if you go to the doctor and you have the symptoms of bloating, cramping, irregular stool movements, there'll be a bunch of tests that your doctor will run to try to figure out what is the disease that you have. And if they run every one of those tests and they can't figure out what you have, you get bucketed as having IBS. And so it's very complicated to go after this because it's basically, I don't know what you have. You've got these symptoms but I don't know what's wrong with you.

But it's super interesting for the microbiome because essentially for these people it could simply be microbiome is not something that anybody's really been going after in IBS or any disease up until now. It could be that you simply have an imbalance in your microbiome that is causing you to have these shifts in pain and bowel movements. And so there's a big opportunity there to kind of use the microbiome target. And so we've been doing this with Johns Hopkins, as I said, and we've just gotten positive preclinical results back, which is super exciting.

Dave:

Wow, congrats.

Colleen:

Yeah. And so we're really looking forward to tackling that next illness.

Dave:

I suspect you're also going to magically see a bunch of people with eczema and psoriasis are going, oh, look what just happened, because when you start dealing with IBS, there's other membranes in the body that are also irritated. So that could be a really powerful thing. What I'm looking to do is get that mega pill. Every time you add a new thing to the arsenal, I want you to have like the one pill to heal

them all. Not that you could actually say heal, because that might be a claim. The one pill to make you master over your own biology of them all.

I want that one. That is my request. That every time you get something, hey, most people have this, it's a problem. We're just going to put the good stuff in there. And here's why I want you to do that. Okay. I don't want any of that crap. I probably have some of it I didn't know about, but I'm pretty good at my million dollars with the labs and stuff, but I want that because it's protective. But also if we have large numbers of people taking large numbers of healthy bacteria, what would that do to the microbiome around us?

Colleen:

Yeah. It's interesting, sort of the microbiome pill that has it all is maybe akin to the multivitamin that has all the different vitamins that we're looking for. And so I do think that that's an interesting good long-term vision. The microbiome around us is a whole nother issue. And we think about metabolic syndrome, which is a chronic disease of aging. Because as we age, we start to lose our ability to metabolize these sugars. When we think about the environment that we all live in and the stress that we live under and the inability to cook meals all the time, to eat farm to table, and all the sort of food colorings and unnatural things that are in our diet, all of those things are not only affecting our microbiome, but affecting the microbiome of our environment. And so really I think what we're seeing is a movement towards bringing back the microbes and the environment that we were intended to live in. And that is really the shift that has to be made. It's a big one but...

Dave:

It's a giant one and one of my favorite headlines of all time was from a wired magazine article a while back and it said you are surrounded by a cloud of fart and skin bacteria. You really are like, oh my God, I'm so horrified. I have to read this article. And what they were saying is you can actually sequence the air in a room where someone's been in two hours after they've been in there. Just by analyzing with a lot of expensive tests what's in it there, you can identify the person if you have the microbiome signature. So we're carrying this all around us. It's unavoidable. It's a part of the human condition and no amount of hand sanitizer is going to make any difference in that. So I feel like if I charge myself up with all of the best bacteria, they become a part of essentially the world around me as well as a part of me.

One of my companies, Homebiotic, makes bacteria that eat toxic mold for a reason. I spray them around my house because I'm really sensitive to toxic mold and this stuff has trashed me. So I'm really hopeful that we get lots of people taking really good probiotics because honestly our sewer system will have better bacteria in it. Like they become a part of the world around us. It feels like no one's talking about the biome around us as much as it should be. But when you take things like Pendulum, inevitably eventually they become a part of your family whether you like it or not. Have you studied anything about transmissibility of good gut bacteria? How long does it take to make them part of the environment?

Colleen:

Yeah, we haven't. But what you're talking about is really interesting. There's definitely been work done. Like you're sitting in a room and there's probably other rooms that are on the same ventilation system. And there've been studies showing that if you take the air in your room and you look at the rooms where the air ventilation is all circulating in, that the microbiome in those rooms will look more similar than another room which could be in your same building that's on a different ventilation system. And so

it is true that your microbiome is passing through your vent system to other people that are on that same ventilation system, and those are passing back to you.

There was a cool study that was done around people looking at their microbiomes of people that have dogs versus people who don't have dogs. And in this study, they showed that if you have a dog, you tend to have a more diverse microbiome than if you don't have a dog.

Dave:

Have you seen what dogs like?

Colleen:

Have you seen what dogs like and how dog owners behave with their dogs? I mean, I'm a dog lover and those dogs are in my bed. We're snuggling. We're definitely exchanging microbiomes all the time. And so you can imagine that you think about your immediate family, pets included, your microbiome start to converge based on how much you're interacting with each other and really sharing foods and hugs and all of that.

Dave:

Right. I kind of laugh at the idea that some people are doing now. They're saying, "I'm going to create this bubble." I'm like, there's a bubble, it's called the earth. We're all here and we're all sharing this stuff and that's just kind of how it is. We really don't have much control over it because it's just fundamental to being alive where that stuff moves around. And the trick then is to have a resilient system. And the number one factor for resilience from an immune perspective, and you know what I'm talking about without actually saying any specific names of anything here, is blood sugar regulation.

Because if you have diabetes, you're at massive risk of dying from all those killers we talked about and any kind of infectious agent, whether it's bacteria or viral, right? Lack of blood sugar regulation equals an immune system that cannot turn on power in the mitochondria when it's necessary to fight something. And so you fix your blood sugar regulation, you lower your risk of all-cause mortality. In other words, you're harder to kill when your blood sugar is more normal. True statement?

Colleen:

Absolutely. Managing your blood sugar is at the core of so many health issues, including very much your immune system. And you talked about the other big killer diseases. Those are all linked to each other. I mean, think about it. If your body is spending all of its time trying to figure out how to manage these blood sugar spikes that are in control, it's not spending time and energy on these other things. And so you really are more vulnerable and susceptible when you're not managing your blood sugars properly.

Dave:

What do you eat?

Colleen:

This is a terrible question, especially after you just asked me those questions about the pills being enabling. I will admit-

Dave:

You are on the [inaudible 00:44:49] diet, aren't you?

Colleen:

I love to eat and I love to drink whatever I want to. And so I'm constantly having to battle that with trying to create products that target the microbiome, exercise and then trying to eat well every once in a while too. It's hard though. I'm definitely susceptible to bad foods.

Dave:

What's your HbA1c?

Colleen:

I actually don't know what my current HbA1c is.

Dave:

Oh, that's a good answer. I've actually taken one strain, I'm not going to name which one, of genetically engineered gut bacteria that was specifically tweaked to do specific things. Is there a future of not just finding species but just pulling one apart, putting in the genes you want and releasing it into our guts?

Colleen:

Yeah, not to get too sci-fi, but I think that's a not... There are many companies that are already working on genetically engineering microbes and of course there's a huge opportunity there too. As you're pointing out, could I take all the good functions and cram them into one pill, cram them into one microbe, that would be amazing. So I think there's a huge opportunity to do that. I think we have to be careful to not believe we know more than we know, because there's the obvious downsides which Hollywood has shown us in abundance.

Dave:

We also have the food pyramid. We became convinced that we knew what made people fat and they were wrong. And so they did a lot of damage to hundreds of millions of people's health because they thought they knew what they didn't know. I'm a little concerned about releasing these things out there because there is transfer of skills between bacteria via plasmids. Can you talk about plasmid level sharing and what that is and whether we need to worry about that in our guts?

Colleen:

Yeah, it's not just plasmids but actually there's a substantial amount of gene transfer that happens between microbes that doesn't really happen... We don't gene transfer with a dog that we're sitting next to but our microbes when they're next to each other will sometimes transfer genes. And that's why this long read sequencing was so important is because it enables you to get the full assembly of a genome of a bacteria and all the different genes that are in there without having to make guesses about, well, I know that if it has this short sequence, it must have all these other genes in it because there's constant gene transfer happening. And so I think this is the other reason to try to populate with microbes that are performing specific functions because those genes, they are hotspots for gene transfer and those genes could be transferred to some of the other microbes.

But similarly on the downside of this is the transfer of anti-microbial agents and things like that. Antibiotic resistance is something that I think we all worry about a lot because the genetic engineering of a microbe in itself shouldn't be an issue because you should be able to kill that microbe with an antibiotic. The problem is if that microbe happens to gene transfer an antibiotic resistance gene into it.

Now all of a sudden you can't kill it with an antibiotic and now it becomes really problematic. So I think that's the beauty of gene transfer in the microbiome. You can start to get good genes propagating, but it's also kind of the scary part. We don't know exactly how that gene transfer happens and when.

Dave:

I like to look at as sort of like the X-Men all get together and they're like, hey, do you want to trade my super power for yours? And then they swap it all and what comes out of they're like, oh my God, like that's going to be a little bit harder to deal with than it already was. But it's also inevitable, right?

Colleen:

Well, yes. Or maybe it's like, I don't know if you ever did this as a kid, but you would go to a swap meet and you'd bring all your toys that you didn't want. And everyone else would bring all the toys they didn't want and you'd swap. And then you'd go home with a new box of just junky toys. So they were different.

Dave:

They were different but in this case you still get to keep your old ones for the most part, I think, anyway, don't you? So you're kind of additive versus just swapping. Like you copy your toys and hand them over. It seems like since that's been a part of all life evolution forever and it's been happening in our guts forever, there really isn't much to be done about that and that it's just something normal. So put more of the good guys in there and even if you had say the Pendulum stuff, and if it picked up antibiotic resistance, you're like, oh darn, now I have this thing that protects me from high blood sugar and it's harder to kill. Like it's not that big of a deal. Is that a good way to think about it or is there a possibility for the good guys to go bad guys, granted there's hundreds of probiotics out there, I'm not talking about just yours?

Colleen:

Yeah. I mean, I think the whole point of gene transfer is that you can transfer in good things and you can transfer in problematic things. And again, I might think about it like a garden where you have this ecosystem. You can make your garden look however you want to, but then if there's all these transfers happening that are out of your control, you might end up with something that's not exactly what you're looking for.

Dave:

Well, I believe the best way to protect yourself from that is to keep taking fresh and well-formed probiotics, which has been a regular practice of mine for 20 something years. I've taken a lot of stuff that didn't do anything and I quit taking it. And you guys have the most robust evidence behind this, and I should have shared this earlier in the show too. You have kindly offered 25% off for their first bottle for people, pendulumlife.com. Use DAVE25 for the code. That's pendulumlife.com. Use code DAVE25. And guys, I really think you should give this a try because if you've read my anti-aging book, if you have already ordered fast this way, you know how important blood sugar is not just for living a long time, but for having a brain that works because if it spikes like crazy, it's also going to crash like crazy and you're going to get that 2:00 PM fog in the afternoon.

And also if you want to have a brain that works and cells that lasts a long time, you got to get on top of this one part of your biology. So pendulumlife.com and code DAVE25. And hey, save some money. Just try it for a month. See how you feel, see the difference. A question for you, Colleen. Do

people lose weight? Normally when your blood glucose regulates better, you lose weight or you maintain a healthier weight better. Did you see any of that in your trials? Did you measure it?

Colleen:

In our trials we did it for 12 weeks. We did not see a substantial change in weight. We started to see a trend and sort of the belief is that if we ran it longer, we would see a change. But again, that's a clinical trial setting. What we've heard from customers reporting back are some really interesting things. Not only do people see lowered A1c in blood glucose, seven out of 10 people are reporting improved reduced sugar cravings. And we have nine out of people reporting improved GI issues. And we have one out of two people reporting weight loss.

Dave:

Incredible. So 50% of the people are finding that. And some people with type 2 diabetes aren't fat anyway. They're the skinny fat where it's all around their organs. So very impressive. Well, I want to just extend my thanks to you for doing hardcore real science around probiotics and going really deep on it and doing the incredible amount of work it takes to do a clinical trial the way you've done it, double-blind and all that. And this I'm hoping will just put the critics just to rest where they're saying, "Oh, probiotics don't do anything."

It's kind of like saying vitamins don't do anything. You can say it all you want, and it doesn't make it true, no matter what elected office you hold. It's one of the things either it is or it isn't. And in this case, there's robust evidence that the right species of gut bacteria can lower your blood sugar because you found the evidence and you found the species and you matched it up, but it took some work to do that and it took years to do that. And I'm super happy to be able to add this into my stack because it's really cool stuff. So thank you.

Colleen:

Thank you. Yeah, it's an investment. It's easy to sort of take things that are already existing and package them up nicely. This is almost a decade of hard R&D in clinical work. And the truth is you never really know if the work you're doing is going to result in something that has efficacy. There's a great deal of luck involved. And I've also been lucky to have investors to back the company and really invest in it and then an amazing team to build it out. So it's an exciting new opportunity this microbiome thing.

Dave:

It takes people believing you and have access to capital for sure. I mean, I wouldn't have predicted 10 years ago that you could have a company doing what Bulletproof did in far west central and all, and $80 million of people trusting you later and okay, it can happen. But it is a 10 year plus thing to build a company the way you've built it, which is really cool. And what's coolest of all is once I get my Pendulum in the mail, I think I can eat all the gummy worms I want and I'm totally protected, right?

Colleen:

As long as you have your Bulletproof Coffee in the morning.

Dave:

I actually blend them into the Bulletproof Coffee there now. Gross. Is there anything else you'd like to share with our listeners about the future of probiotics?

Colleen:

I think as we think about probiotics and the microbiome, the thing to really ask is, it's not about how many CFUs a probiotic has, it's really about what are the strains in this probiotic and what are the functions that those strains are doing. And I think we're about to get a lot more sophisticated about how we ask and answer those questions. And so looking back, probiotics have been about general health and, gee, it's better to have more diversity and more microbes. Looking forward it's going to be about what is the problem I'm trying to solve and what are the microbes that are going to solve that problem for me. And so I think that's really where we're heading and what we're trying to build out around.

Dave:

Well said. Diversity is stupid. I'm just going to have to say it because if your diversity increases the percentage of serial killers, psychopaths, sociopaths, and all the other kinds of bad bacteria out there, I have no idea what other kinds there are. But no, you want a diverse, good group of bacteria, not just a random diverse group. So we just couldn't tell the difference. So we said, okay, let's have diversity in our gut, but we just don't really know. And we just know that that's better than having a few species. But your target there, which is diversity of the good guys, that's the future. And it's one that we're building right now and people get all depressed because 2020 has been a little bit of, in technical term a shit show.

But at the same time you've been working on this for 10 years. It's just come to market and we couldn't do this 10 years ago. And so the amount of human knowledge and information that we have right now, it's bigger and better and more awesome than it's ever been. And so we look in a future where we have the diversity of the good guys in our guts and we kick the bad guys out and we're going to do that all over the place. So I'm super excited about what you're doing. It is really groundbreaking. You just put it on the market, what, a few months ago? I think about five months ago.

Colleen:

Yes, we just brought it to market this year. In the middle of a pandemic, no problem.

Dave:

Well, given that lowering your blood sugar is probably the most important thing you could do in the middle of a pandemic, good timing. And it's now added as of this interview as a regular part of my stack. So I'm super excited about this and it's something that I plan to be taking for years. Come out with some more good stuff. And if you could do some ones, let's see, just make a bacteria that stops the other seven causes of aging. If you could just figure that one out real quick, I'll take the anti-aging ones.

Colleen:

We're on it.

Dave:

Colleen, thanks for being a guest and a good sport on Bulletproof Radio with me today. And guys, if you didn't get the code, use DAVE25 on pendulumlife.com. Literally this is so worth it. Let's just look at the numbers, look at the research, it's awesome.

Colleen:

Thank you. Thank you for having me.