DUTCH In Conversation with Pendulum
Event Transcript

Jaclyn Smeaton (00:00 - 01:18)
Hi everyone and welcome. I'm really excited to have you join us today as we kick off a new series called DUTCH In Conversation. Our first installment today is with Colleen Cutcliffe, PhD, and she's the CEO of Pendulum Therapeutics. Now, Pendulum is a microbiome focused company. I'm really focused on developing medical probiotics that improve health, particularly around metabolic diseases.

Now, Pendulum has really been at the forefront of putting forward a lot of research, particularly on the akkermansia strain. So we're going to get to talk a lot about that strain today and really expanding on the growing connection between microbiome health and hormone health. And so we're going to talk a lot about that today, particularly in the context of women's wellness. I want to take a minute to first introduce Colleen. ~ She's the CEO and the co-founder of Pendulum. She's got more than 25 years experience leading and managing biology teams across academia, pharmaceuticals, and biotechnology and prior to starting Pendulum, Colleen was a senior manager of biology at Pacific Biosciences and a scientist at Elan Pharmaceuticals. She did her postdoc studies at Northwestern University. She's got a PhD in biochemistry and molecular biology from Johns Hopkins and her BA in biochemistry from Boston School where I'm based, Wellesley College. So Colleen, welcome today. I'm really excited that you're here. So I'd love you to start by just talking a little bit about

Colleen Cutcliffe (01:18 - 01:24)
Thanks so much for having me.

Jaclyn Smeaton (01:24 - 01:32)
the science behind Pendulum. Like when Pendulum was founded, what was your vision and your mission in really creating this company?

Colleen Cutcliffe (01:32 - 02:29)
Well, I think when we started Pendulum, which is about 12 years ago now, the microbiome was still an emerging science. We know that probiotics and yogurts have been on the shelves for a long time, but what microbiome science enabled us to do was to really dig into what are the other 99.99 % of strains that are in our bodies that are playing really important roles in our health and also in disease. And so when we started the company, the whole premise was, we believed that the microbiome was going be the next frontier of human health and discovery for ways that we could intervene. And that was the whole premise. And we just felt like this is going to be the next big wave. This is going to be our way

that we can contribute to the world to help millions of people improve their health through the microbiome. That's been the mission since day one, and that's the mission today. And so a lot of that is what's baked into that is innovation and discovery and bringing new things to market and trying to tackle health beyond just GI issues through the microbiome.

Jaclyn Smeaton (02:29 - 03:05)
Yeah, it's so interesting because I think you're right. mean, 10 years ago, probiotics were not a household name even at that point in time. So the world has really changed and it's really innovative to be thinking about. I think you're totally right. Like it used to be that every brand had a probiotic and it was like a skew, right? But now it's a category and I think that's really growing where just like you have herbal medicine and you have nutrients, probiotics are like its own growing category that I think we're probably still at the leading edge of understanding.

Colleen Cutcliffe (03:05 - 03:12)
Absolutely. think you're right. It is still very early and there's a lot more to discover. So a lot more opportunity for new products in the future.

Jaclyn Smeaton (03:12 - 03:30)
Yeah, so tell me a little bit about the research that was done before you even released a single product into market because, I mean, obviously, a lot's evolved in 10 years. You've probably learned so much, but tell us a little bit about what was done to learn like what probiotic strains should be selected and how did you characterize these and validate them?

Colleen Cutcliffe (03:30 - 04:25)
Well, first of all, it took us almost a decade before we launched our first product to market. So this was not a short endeavor. We've had very patient investors, including the Mayo Clinic, who were our first investors. And really, our starting point was, well, let's DNA sequence all these different microbiomes and start to investigate that data and to try to create these metabolic maps of the microbiome where you can understand what does a person's microbiome look like from a biochemical pathway perspective and how can you start to look for new targets? So in a lot of ways, we approach this the way drug discovery is done in pharmaceuticals, where you're starting with these big data sets, you're trying to identify targets of opportunity, and then you're bringing them into the lab, into preclinical studies, and into clinical trials. And so it really all started with the data, and we've always been driven by what does a person's microbiome look like and how can you change it to improve their health?

Jaclyn Smeaton (04:25 - 04:32)
So what are the main things that you found that were kind of the key insights that helped you bring that product to market?

Colleen Cutcliffe (04:32 - 05:31)
I think the first thing we found was that there was a really big opportunity in metabolism. And when you think about it, most people are actually not thinking about probiotics when it comes to metabolism, but actually everything you eat ~ makes its way to the gut microbiome where a massive amount of metabolism happens, including the stimulation of GLP-1. And so when we first started, it was really ~ understanding that the microbiome could impact metabolism.

And then starting to look for what are the key pathways. And the two really important things that we found that distinguished a healthy person from a person with metabolic issues was one, their ability to metabolize fiber and stimulate GLP-1, and two, their ability to have a structurally sound gut lining. And those two things are sort of the underlying mechanism for ~ our products and ~ really the underlying mechanism for how we were able to demonstrate that you could actually help people with diabetes on par of the efficacy of a pharmaceutical.

Jaclyn Smeaton (05:31 - 05:37)
Interesting. what tell me about like the key ingredients and that first product that you brought to market?

Colleen Cutcliffe (05:37 - 06:14)
The first product they brought to market has, it's a formulation of five strains. ~ So it has a lot of other names that people are not going to recognize because they're not really on the shelves. So we'll start with the one that's sort of the most familiar, is bifidobacterium infantis. Then there's Clostridium butyricum, Clostridium basurinkii, Anero butyricum halii, and Akkermansia mucinifila. And Akkermansia mucinifila has ended up becoming this ~ really, really incredibly well studied strain that is now emerging as a keystone strain for our microbiomes and a bunch of different health issues. And so ~ it was one of five players that was in the initial formulation.

Jaclyn Smeaton (06:14 - 06:24)
Interesting. You know that akkermansia would kind of ~ grow so much in its research body at that time or when you first selected it, it was really kind of early research still?

Colleen Cutcliffe (06:24 - 07:05)
It was super early research and I'll tell you, we so much weren't sure about acrimancy that

if you look at our clinical trial that was published in BMJ, we ran a placebo arm, we ran an arm with all five strains in the formulation, and then we ran an arm where we didn't have akkermansia in one of the other strains because we were like, well, we don't really know if this strain is going to do anything meaningful here. And, you know, what we found out was that you needed all five strains to really get the full efficacy and that when you didn't have akkermansia in this other strain in there, you only got kind of partial efficacy. And so that sort of was our first demonstration that akkermansia might be more important than we initially thought it was. So we were not positive in the beginning how important it was. In fact, we thought it might not be important.

Jaclyn Smeaton (07:05 - 07:26)
That's so interesting. And it does seem to be like when we do GI microbiome testing, stool testing, I see a lot akkermansia is like the missing keystone strain. Like people will have most of the others, but it seems like akkermansia, there's a specific sensitivity. Have you seen that too or what are the things that lead to that strain not being present?

Colleen Cutcliffe (07:26 - 08:21)
Yeah, I think what has made it sort of marked as a keystone strain is, to your point, people are starting to recognize that when you're low in akkermansia or even missing it, you know, can't even see it on a sequencing test, that it's correlated to all these different wide variety of diseases. So not just your typical GI diseases like IBS or IBD, but also metabolic diseases like obesity and diabetes, things like autism and Parkinson's, and even things around immune responses, allergies, asthma. so people are realizing that when you're low in akkermansia, it's correlated to all these different diseases. And over the last 10 years, what we're starting to see is the data supporting the why and what is the mechanism by which akkermansia is having this impact where when you lose it, all of a sudden it shows up in all these different disease states.

Jaclyn Smeaton (08:21 - 08:33)
Well, let's talk a little about the why and the mechanisms. think this is interesting and it's probably multifactorial, but what are some of those key like molecular biochemical effects that akkermansia has on the gut?

Colleen Cutcliffe (08:33 - 10:11)
I think, first of all, I'll a bunch of new stuff is always emerging all the time. so, and I think we're very early in this, but what we know so far is that ~ I think there's sort of maybe three key things that we know about akkermansia. The first is really around the structure of the gut lining. So akkermansia is the only strain that we know to date that can both consume and stimulate the creation of mucin.

So what is mucin? Mucin is basically the glue that holds together your gut lining. So if you think about your gut lining like a wooden fence, ~ which has all these wooden planks that are held together by glue, I actually have a wooden fence in my backyard. And when I first moved in, it was really strong. Everything was fantastic. But what can happen over time and through seasons is that that glue can start to weaken and a plank could start to fall. And now you've got a leaky fence.

Well, your gut lining is structured exactly the same way. You have these epithelial cells, which are those planks, and they're held together by glue, which is called mucin. And over time, and through the loss of the certain strain akkermansia, that ~ glue can start to thin. And when it thins, that lining, those planks, those epithelial cells start to get gaps between them. And so you actually lose the fundamental structure of your gut lining. And the reason that's so bad is because now you have all these things inside the gut microbiome that are supposed to stay inside that are making their way into the bloodstream and vice versa. And so you just had this leaky lining. And so for a lot of people that shows up as GI issues, inflammatory issues, immune response issues, metabolic issues. So that's one of the big reasons that it's such a keystone strain because it is the only strain we know of that really regulates that mucin layer, that glue.

Jaclyn Smeaton (10:11 - 10:59)
That's so interesting. Then when we look at the impact of gut barrier dysfunction, when you talk about the widespread result of of akkermansia deficiency, I don't know what you would call that. Can you call it a deficiency technically?

That dysbiosis where you're lacking akkermansia, then that leads to the gut integrity challenges like you're describing and then from there, it seems like there's a widespread number of effects that have been studied. Let's start maybe with gut health, the most direct correlation. What are some of the symptoms that come up for people with gut health that might lead them to say, you'd mentioned IBS, but what would lead them to say, maybe I need to have this investigated?

Colleen Cutcliffe (10:59 - 12:37)
Yeah, I think that kind of some of the more common things are ~ that people might start to experience is, you know, more diarrhea or even more constipation. So your bowel movements are starting to become really irregular or they've been irregular and you haven't really known why. For some people, it's food sensitivity. So, hey, I used to be able to eat all these different things and now all of a sudden these certain foods are causing me a lot of digestive issues. It could be that ~ you're just your gut lining is out of whack and you just need to fix that.

And then I think there's other things like bloating, know, sometimes belly pains and things. And mostly there's sort of two categories of people. There are people who have been living with it and trying to solve it on their own and really just trial and error, figuring things out and maybe have tried a bunch of different probiotics and prebiotics. And for those people, because akkermansia has never been on the market before, that could be that one missing link that all the hard work that you've been doing just needed this one keystone strain and all of a sudden everything would sort of fall into place. And so for a lot of people that have been trying, they've been on this journey trying to discover like, is the source of my food sensitivities, of my GI sensitivity? ~ It's really could be that it's akkermansia. And then for some people ~ as they, as we age, we know we start to become depleted in akkermansia or when we go on an antibiotic, we know that that...decimates the microbiome and you might not have gotten your acromancia back up and growing after that. So for some people it's like, I used to be okay and now I'm not okay. And it could be that acromancia is depleted and just giving your body back acromancia could be the solve.

Jaclyn Smeaton (12:37 - 14:03)
That's interesting. I'm really glad that you bring up the point of food allergies because as a practicing ND, that's something that I saw all the time and it is such a challenge and what you find is people will start chasing the foods and then they're staying away from one category they're reactive to. So they shift their diet and then if you retest them, they're allergic to those new foods that they're consuming a lot. And this is observations years ago, but really, generally, the foods are not the problem. And that's one thing that I think is a paradigm shift in functional medicine, because we have a lot of food allergy tests, and it might tell you what you're reacting to right now, but that's very dependent upon the diet that you're eating. And I think we're really shifting to take a look at it as a sign of barrier dysfunction, because food allergies do exist, obviously, but not as commonly and as widespread, I think, as the functional medicine world looked at traditionally. It's really more a sign that that barrier that should be keeping larger proteins out of the bloodstream is not working as well. And the foods are getting in and the proteins are too big for the immune system to recognize and that stimulates immune dysfunction. And maybe we can talk about that as well because it's the food, but it's not just food that can end up triggering the immune system activation around the gut, which then leads to so many other problems.

Colleen Cutcliffe (14:03 - 15:14)
Yeah, nutrition and the microbiome are just tied at the hip. So what you eat is metabolized by your microbiome. What you eat also feeds your microbiome and can really be one of the most impactful ways you can change your microbiome is through your nutrition. I would say like first is antibiotics and number, second is nutrition. And I think it's very natural when you start to have these food sensitivities to start trying to cut out the things that are creating

sensitivities and kind of go from there. But I think the goal, if I can turn that on its head, I think the goal for everyone should be resilience. How do I create the most resilient gut microbiome that allows me to consume all these different foods? That might require you to take a step back for a second and start to cut things out and then build your microbiome back up and then build those foods. But really the goal is resilience. And the key to a resilient microbiome is the diversity of the microbiome for these particular biochemical pathways. And so that really is the job of the practitioner who's working with the patient is to figure out how do we get from this place of sensitivity to a place of resilience through, I think, sometimes relatively complex protocols. But the whole goal is resilience.

Jaclyn Smeaton (15:14 - 15:43)
I love that paradigm shift and it seems as like the piece for resilience, the solve is putting the right strains into the gut and also nurturing through food intake and high fiber diets. It is amazing. There is really cool research on people who they do a sharp dietary change like low fiber to high fiber or high fiber to low fiber and they can measure the impact on gut microbiome in like 24 hours. I mean, it's huge.

Colleen Cutcliffe (15:43 - 16:12)
Yeah, it is huge. ~ And I mean, that's why I think the microbiome is such a special, unique opportunity, because you can change it. You are changing it all the time. And so if ever there was a moment where you're like, I'm going to take a stand and I'm going to change my future, the microbiome and nutrition are two just really easy ways to get, if you can get them to work together in the right way, to really jumpstart and change metabolism, immunity, even brain function. So it's an exciting opportunity, I think.

Jaclyn Smeaton (16:12 - 16:31)
So we started with gut health. Let's talk about some of the kind of other bodily systems that we know are heavily impacted by the gut microbiome. So maybe we can start with immune system. Can you talk a little bit more about that connection point with the gut microbiome and inflammation and immune dysfunction?

Colleen Cutcliffe (16:31 - 17:55)
Yeah, think we've all, many people have known for a long time that the microbiome is somehow linked to the immune and the inflammatory responses. And you see a lot of probiotics, especially the, including even the older school probiotics talking about healthy immune system being important. But I think it's actually only recently that we started to understand actually what is this link between these certain strains in the microbiome and our immune system.

And again, just with a caveat that we're really early in research, but I think we're starting to see some compelling literature showing that there are particular strains in the microbiome which can start to impact these inner leukins, IL-6, IL-17, which I know you guys are really familiar with. And that becomes a really important regulator of the immune system and this sort of gut immune ~ axis. I do think it's still really early. And I think that one of the...complicating factors that we don't fully understand is what is the host starting immune system ~ and what are the changes to the microbiome? How are those two things correlated with each other? And I think that's gonna be sort of one of the really big keys. If you're starting with somebody who is already having immune dysfunction, is that the same as starting with someone who is healthy and trying to avoid having immune dysfunction? I think the answer to that is probably no, it's probably not the same, but that's still early research.

Jaclyn Smeaton (17:55 - 18:35)
Yeah, with all these things, like when I'm presenting on – like I did a reproductive microbiome talk last summer and when I opened I said, probably half of what I'm going to share is wrong, but the problem is I don't know which half it is. So just pay attention to the literature. This is just based on what we know today, but a lot of it is early. So keep that in mind. That's a great thing to say. Can we talk a little bit about mental health? Because I think that's another area people are surprised that there are connection points between the gut microbiome.

That's another thing that's been studied, like cognition and mental health. How does akkermansia or other strains influence neurotransmitter production? You hear about the gut as the second brain. Could you talk a little bit more about that?

Colleen Cutcliffe (18:35 - 22:24)
Yeah, I think this is probably one of the most interesting and to your point, non-obvious things that the microbiome is doing. And so there's a few different, ~ you know, pieces of evidence that we have around this gut-brain connection. So the first thing that was discovered was that your microbiome makes massive amounts of neurotransmitters, serotonin, GABA, dopamine, and people are like, why? Why would the microbiome make all these neurotransmitters? ~ The second thing that got discovered was that you actually have neurons in your gut. And so ~ this is sort of fascinating. Everyone has always believed neurons were just in your brain. ~ And we all know about your neurons in your brain. You get what you get when they die, they're done, you don't get them back. And so ~ these neurons that were discovered in the gut were fascinating. Why do you have neurons in your gut? But moreover, they are not like the neurons in your brain because they turn over. They die, they regenerate. So it's this different kind of neuron.

And so, and then the third thing that's important to know is there's literally a direct connection between your gut to your brain called the vagus nerve. So it's like a tunnel that goes straight from one place to the other. And so the current theory is that these neurotransmitters that are being made in the gut are sending signals to the neurons in the gut, but also sending signals to the neurons in the brain. And I think probably two fascinating things that have come out recently are one,

Well, I started my ~ career in the pharmaceutical industry where we were looking for drugs for Parkinson's disease. And we were obsessed with the brain and these plaques that form in the brain when people get Parkinson's. And the whole goal was, can you get rid of these plaques? And is that going to help people ~ either ~ extend the time in which the disease is progressing or maybe even help people reverse? And that was it. We were just trying to reduce those plaques. Well, it turns out that the neurons in your gut also have these plaques. And moreover, in some of these studies, they've shown that the neurons in the gut, these plaques show up before they show up in the brain. So it is possible that the gut is actually what you should be targeting because then when these plaques show up in the gut, there might be some miss signaling that then gets sent to the neurons in the brain and sort of spreads this. And this is all, of course, hypothesis and theory right now, but the data is starting to support this importance of the gut microbiome in things like Parkinson's and Alzheimer's where these plaques are really important. And then if we go kind of one step before that, before we're talking about these diseases of aging, we know that with stress and anxiety, there is an ability to improve those through this small molecule called GABA. And there are recent studies coming out, like literally a conference that we were just at, showing that the administration of akkermansia can reduce ~ stress and reduce anxiety ~ in preclinical models. And so the question is, is that going to translate into humans? And then if we go one more step back in development, the last thing that's really compelling is that when you look at children with autism and you compare them to their healthy siblings, the kids with autism are lower in akkermansia than their healthy siblings.

And I think it's quite well known that when it comes to autism, there are some people who've seen really ~ improved benefits to symptoms through the diet. And of course, as we said, one of the things you change with your diet is your microbiome. So is there this really big unlock in the microbiome that can really help with this, know, autism, which is really, you know, talking about the early stages of neuronal development. So from autism to stress and anxiety to Parkinson's and Alzheimer's, there's emerging evidence coming out demonstrating that the microbiome could be a target here.

Jaclyn Smeaton (22:24 - 23:14)
That's really fascinating and it makes, you when you think about treating the brain, you have

like the blood brain barrier that makes it really difficult to deliver therapeutics into the brain that can be effective. So thinking about treating the gut, which is so much more influenceable, I'm making up that word myself, it can be influenced so much more easily, is really exciting and, you know, where you can see that rapid improvement. But it makes a lot of sense. mean, our gut microbiomes, over the last 50 years as we've seen this transition to hyper-processed use of antibiotics so prolifically, like it really, you can see all the things that have affected the gut microbiome and when we think about the changes we've seen in some of the rates of diseases that you're talking about, it's a really interesting hypothesis to be thinking maybe the problem is stemming in the gut.

Colleen Cutcliffe (23:14 - 23:38)
Exactly, exactly. And I think that's, you know, I don't want to sound like, you know, a hammer that sees everything as a nail, but I do think that is one of the most exciting things about the microbiome. We've always thought about the human body. We're classically taught there are 11 systems in the human body. And what we're realizing now is that the microbiome appears to be tied to all 11 of them. And so is this a way to kind of affect those other systems?

Jaclyn Smeaton (23:38 - 23:54)
Yeah, in a way it's a gateway, It's the entrance point of everything that ends up becoming our body, right? The food we eat becomes the cells in our body. So yeah, it's really fascinating to think about the impact and where things might head in the next 10 years.

Colleen Cutcliffe (23:54 - 23:55)
Absolutely.

Jaclyn Smeaton (23:55 - 24:57)
So I want to shift a little bit to talk about hormones as well, because of course at DUTCH we love hormones and there's a lot of analogous pieces with our businesses. I think that science forward approach and the commitment to looking at whole person medicine and I really see that. I think that's one thing that's so exciting about Pendulum is like you have this hyper focus in the probiotic space but not limited to gut function and really looking at the whole body and how things are connected to the gut microbiome similarly to the way we do with that hormone focus. But I wanna talk, because there are some interesting points of overlay. We have a lot of hormone providers listening to our discussion today because hormonal changes we know can impact the strains in the gut. So can we talk a little bit about that? Like what happens for women specifically when they're pregnant, when they hit menopause? Through these patterns of change, like what are some of the key things we change? And maybe even the differences between men and women.

Colleen Cutcliffe (24:57 - 27:54)
Yeah, it's pretty interesting what we're learning about the role of hormones and the microbiome and kind of this, you know, back and forth interplay between the two of them. You know, at Pendulum, we've been much more focused on metabolism. And so obviously, we know that metabolism changes through every one of these hormonal stages as well. And I think trying to understand how those two things are linked to each other is really interesting and something that we're deeply interested in researching more. But here's what we know about about hormones and the microbiome, we know that before women go through puberty, our microbiomes look kind of like boy microbiomes. And then once women go through puberty, you can tell whether a person is a man or a woman just based on their microbiome. So you could get your microbiome sequenced and you could tell on the other side of that, like this is a man versus a woman. That's pretty amazing. That's how different our microbiomes are. And then...when we go through menopause, on the other side of that, our microbiomes become indistinguishable from men. So if you are looking at a post-menopausal woman, you actually cannot tell is that a man or a woman. And what it all boils down to, the ability to distinguish, are these microbes that interact with estrogen in particular, but with a variety of hormones. Particularly estrogen is what's been, I think, studied the best. And I'll just say, obviously, studied the best. I'll put in quotes because there's really been not a huge amount of literature on it.

And I think we're all hoping and advocating for more research to happen on this front. But what we know is that there are certain strains which interact directly with estrogen. And this is true for some of the other hormones, but I'll just hone in on estrogen because I feel like that data is maybe the strongest at the moment. What we know is there's sort of two forms of estrogen that get created, mostly by our ovaries, but also our adrenal glands. One form is tagged.

And that ~ tag version is basically a signal to get excreted from the body. And then there are microbes that will actually untag. So they'll remove that tag and now you've got a free estrogen molecule. And that's a signal when it doesn't have its tag on it to go back into the bloodstream and become free ~ estrogen in your bloodstream. So what your microbiome is doing is effectively deciding who's remaining tag and who's going to get untagged and therefore has an impact on how much free estrogen is in your body and how much of it is getting secreted out. And so when your microbiome changes, you actually lose that control over the tagging or untagging of estrogen. And so I think, you know, how does that all fit together? How do you start to create interventions that can help people transition from these like sharp increases in estrogen and sharp decreases in estrogen through the microbiome? I think that's still TBD, but it's just fascinating that you have these particular strains that can influence how much free-floating estrogen you've got.

Jaclyn Smeaton (27:54 - 30:54)
Yeah, we've actually seen that also on DUTCH testing and we haven't published on it. We probably should publish the data because it's quite fascinating. But about two to three years ago, we added a marker, a urine marker called Indicin, which is a non-specific marker. It's an organic acid that elevates with dysbiosis, but it's not a specific diagnostic screening tool, but it is associated with like people with dysbiosis can have elevated Indicin in their urine.

We added that as an additional marker on the DUTCH test to let people know because it's a urine-based test. It's not a stool test, so it's not diagnostic, but it helps providers identify when gut testing might be more appropriate for a patient, especially when their patients are asymptomatic, which is kind of an interesting aside because people's perception of what normal gut function looks like is pretty widespread. I'll just tell a little side story. Before we dive into that, I'll never forget I did most of my practice with fertility and I was sitting with a couple and I do a review of systems for both partners. When I asked the male partner about his digestion, he's like, my digestion is fine. His wife said, your digestion is not fine. It became this thing and I said, well, tell me a little bit about what it's like. He's like, well, I go to the bathroom, I have a bowel movement maybe like seven or eight times a day and it's like liquidy, but that's how my mom is too and that's like what my family has always had for normal digestion.

And the wife was like, just because your mom has it doesn't mean it's healthy. But he grew up with that culturally, and because we don't talk that much about what should be expected, he had no idea what normal looked like or not. My point being, sometimes that marker on the lab test is the first sign to someone that, OK, maybe what I'm experiencing isn't normal. And sometimes dysbiosis can be asymptomatic for people if they're not really perceptive to it. But what was interesting was that when we looked at the research of people who've done the DUTCH test who have elevated Indicin, we actually saw a trend to higher estrogen levels in the overall test results. And this is looking at tens of thousands of samples that we've run, men and women. So it is really interesting because we can see that that dysbiotic pattern does result typically in a higher estrogen level in the body. And like you're talking about, we know that estrogen is metabolized through phase one where it adds like a glu... It gets glucuronidated, then methylated, and then it goes to the gallbladder, and then it gets kind of packaged up and sent to the gut. And yes, certain strains that produce a lot of beta-glucuronidase can kind of cut that package open and allow that estrogen to be resorbed. it's definitely a very interesting connection point. ~ So you're looking at that connection from hormones and gut in two directions, both the way that the gut function and the microbiome impacts your hormone level,

And then so interestingly like you highlighted, the way that hormones impact the gut microbiome.

Colleen Cutcliffe (30:54 - 32:19)
Yeah, and it's amazing, and you guys probably have seen this data too. You can literally draw a plot of, know, for a woman over time, our estrogen levels, which, you know, goes up and then it goes down when you start going through paramenopause. And you can overlay these beta strains that produce beta glucuronidase on top of that. And it's literally an exact overlay. They go up when we start to go through puberty and they start to go down when you're through perimenopause. So they're exactly correlated. Now that's still just a correlation, but because we understand this mechanism that you just pointed out, it's really compelling to think about, okay, well that correlation is something to follow up on. ~ And I think one of the other interesting things with the DUTCH test is that with the urinalysis, ~ because the microbiome is tied to so many of our organ systems, you actually can see, you can detect changes that are happening in the microbiome through other parts of the body. And so there is good evidence supporting that. Obviously you can see changes in the stool or telling you something about the gut, but also changes in the urine, changes in plasma, blood levels. In fact, we found that we were trying to increase butyrate levels and we found that you could see it more in the plasma than even in the stool, so-and that's been published by other people as well. And so, you know, the signals for what's happening in our gut microbiome are coming out in all of our fluids, I guess.

Jaclyn Smeaton (32:19 - 32:32)
Well, it makes sense because all of the molecules and compounds that they make through their own metabolic processes enter the bloodstream, which then enters the urine. So that makes a lot of sense.

Colleen Cutcliffe (32:32 - 32:36)
Exactly. If they're doing their job right, they're getting into the bloodstream and into the urine.

Jaclyn Smeaton (32:36 - 33:18)
Totally. Now, another thing that I found fascinating in data is that during pregnancy, the gut microbiome actually mimics someone that has metabolic syndrome. Have you seen that data, like more of that metabolic dysfunction ~ pattern where it's, you know, lower diversity and things like that, which is really fascinating because you think about the need to extract nutrition and calories from your food when you're pregnant really goes up because you're growing another human really cool. think that is very early observational data, but very interesting to think about how hormones influence the gut microbiome in order to assist us through different phases of life.

Colleen Cutcliffe (33:18 - 34:11)
Absolutely. And again, to the point that you made earlier that the microbiome is so malleable, it is really transitioning with us through these different stages of life and there to assist. mean, we've co-evolved with this entire other system in our body in order to optimize and maximize our health. And so it makes sense that these things would show up. you know, one of the, just to go back to akkermansia for one second, because we're talking about pregnancy, one of the most interesting things about akkermansia is that people have been looking for

Well, let's say it's this keystone strain. It's so important for your body in so many ways. So people have been looking for what foods have acromancia in it, because obviously that would be, ~ you think it would be everywhere. Like we should be getting access to this everywhere. And to date, there has been no food that has been found that has acromancia except for one, and that's mother's breast milk.

Jaclyn Smeaton (34:11 - 34:25)
It's so interesting. Yes. I mean, how does it get seeded for people? Because do we see – have they looked at like formula-fed children and whether they tend to have lower acrimantia later? Or how do you think that that gets seeded for people?

Colleen Cutcliffe (34:25 - 35:16)
Yeah, well, I think the current theory is that it's when you're nursing, so mother's breast milk provides the first seeds of akkermansia, and then you spend the rest of your life trying not to lose it. And so I don't know that I've seen any really compelling studies which compare children who haven't been breastfed at all versus children who are 100 % formula fed. don't think that there's, I think that as long as there's some breast milk being given, that that's probably good enough for the seeding. And many infant formulas contain the prebiotics that are going to feed these strains. so I think there's, I don't want to come across as like people have to be breastfed 100%. Of course. But I think that I haven't seen a good study that showed that, if you did no breastfeeding, what does that look like for some of these strains?

Jaclyn Smeaton (35:16 - 35:42)
Yeah, I mean, I think it's okay to talk about the benefits we know of breastfeeding and also recognize that people don't choose that sometimes or it's not possible. So, you know, it's great to talk about what else can be done. And it makes me think about when women are pregnant or when they are nursing, whether there's a really important role of improving mom's akkermansia at that time. I wonder if that impacts how much comes into the breast milk.

Colleen Cutcliffe (35:42 - 37:07)
Yeah, we're really interested in that. how can you, you know, even when you're ~ trying to get pregnant, how can you start to seed your body for ~ having the right strains that are going to help your baby? you know, I think the other thing too is just practical knowledge. So my first daughter was born really prematurely. She actually never had the jaw strength to be able to nurse properly. So every ounce of breast smoke that kid got, I pumped and then fed to her. And so sometimes I would just literally feed to her directly, but most of it was got stored in the freezer and then thawed. And I think a lot of people do this. You're storing breast milk, you're thawing it out, you're feeding it to the baby. Well, ~ I'm a relatively impatient person. So I would turn that thing up to high and try to like as quickly as possible, get some of it thawed out, know, mix it up so was the right temperature and give it to the baby. But I now realize that if I had to do that over again, I would never do that because the fact is that when you go up to that really high temperature, you are likely killing the strains that are in there and you're likely unfolding a bunch of the proteins that are really important for that breast milk to have in place. So I would say just on a really practical ~ piece of advice that if I were doing that today, I would just get a little more organized and try to do it ahead of time. I would not put it on that super high temperature because I think you're probably killing a lot of things that you actually want to have in there.

Jaclyn Smeaton (37:07 - 38:45)
I'm so glad that you mentioned that and that is such practical advice that so many of us can relate to that kind of how quickly can you get a bottle warmed for the baby. ~ So I'm glad you mentioned that, like even just thawing what you need the next day in the fridge the day before, that way you can have minimal warming. mean, those things are simple changes that if they can improve the impact, that's enormous. That's great. Well, I do want to spend some time talking about.

Really the key therapeutic area that Pendulum has focused on, metabolic health. There's so much happening right now and so much conversations around weight management, insulin sensitivity, pre-diabetes and diabetes, and just metabolic health in general that it really, the fact that you have this product in market, aligning with the timing of this just consumer discussion, even with GLP-1, it's really you know, it's kiss-met in a lot of ways. Like the way that these things have come together, because it's really nice that I think that for me, my patients have an alternative to injectable GLP medications in a way that they can really leverage the improvements that are seen through their own body's production. I wanna talk a little bit about, maybe you can paint the picture first about GLP-1 ~ peptides and just like what's happening in the gut with other related peptides too, because it's not just GLP-1, peptides in the gut, and then talk a little bit about what you've learned, since

this is such a critical area of research for you around the role of akkermansia and other strains.

Colleen Cutcliffe (38:45 - 42:33)
Absolutely. mean, I think for a long time we've known that ~ diet is really important for metabolic syndrome. So you have all these products that are really centered around high fiber and fiber supplementation that really have ~ benefits to metabolic syndrome. And then we've known there are these pharmaceuticals, insulin, GLP-1, that have... Even though the GLP-1 drugs are kind of having a heyday in the moment, they've actually been around for decades. And so we know that those small molecules also have a great impact.

What has been missing is the fact that you eat food, it's metabolized by your gut, and then these hormones get created, is that gut microbiome component. And over the last few years, what's been discovered is that there are two strains that have been published in peer review journals showing that they can directly stimulate GLP-1 secretion. This is now we're talking about your body's natural GLP-1 hormone. And that is akkermansia and mucinophila and clostridium butyricum.

And so these two strains in your microbiome, what happens is when you eat food, that food gets metabolized by a bunch of different microbes, but these two create the signals that tell your L cells, ~ okay, release GLP-1. And the GLP-1 hormone has two important roles. One is that it goes on to stimulate the entire downstream set of ~ signals that help you metabolize sugar. And so that's really important for the ~ metabolism of the sugar you just ate.

And then the second really important thing that that GLP-1 hormone does is it sends a signal to your brain to say, hey, we just ate, we're full, we don't need to eat anymore. And when you think about how important that is to evolution, it's that you eat a meal with sugar in it. Now you've got this one hormone that says metabolize that sugar and we're full, we don't need to eat anymore. Your natural GLP-1 hormone, therefore, it goes up after you eat, it does all its important signaling, and then it goes down.

And then you get hungry again and you eat and it goes back up and down. So GLP-1 hormone is supposed to be on this cycle of up and down and up and down. That is the healthy, natural, normal way that your body is supposed to create GLP-1 hormone. The pharmaceuticals have sort of taken that and said, my gosh, let's mimic this hormone because it has all these important roles. And so when you take an injectable GLP-1 ~ mimic, what you are doing is you're basically ~ putting into your bloodstream high levels of a GLP-1 ~ chemical that ~ actually cannot be metabolized the same way that your hormone is metabolized. instead of this cycle, it's just at really high levels all the time. The upside of that is you get this immediate impact that people feel.

And in a lot of ways, that's super important for getting people jump started onto better metabolism. But the downside is that in the long run, this could potentially have negative impacts to your body. And the way I think about it is like, if I was talking to you through a megaphone right now, you would definitely hear me better and you'd hear me right away. But if I kept talking to you through that megaphone, eventually you're gonna go deaf and your body is actually the same way. We know that your beta cells can become sort of deaf to signaling, to insulin signaling. And that's why a lot of times over time, people have to keep increasing how much of these drugs they have to give themselves because your signaling pathways can become deaf to that. And I think nobody wants to end up in that world.

How can you start to help people, know, the drugs are super helpful and important for people, but how can you start to help them also stimulate their body's natural GLP-1 hormone? And that's really the center of how pendulum glucose control works, how pendulum metabolic daily works, and even our single-strain akkermansia, that's one of the two strains that's been shown to be able to stimulate GLP-1 hormone. And, you know, people like you who really understand how do these things really work together are so important for people to know all the different tools that are in their toolbox for helping to stimulate GLP-1 and help them manage their metabolism.

Jaclyn Smeaton (42:33 - 44:15)
Yeah, it's really, really a fascinating thing to be thinking about as we're seeing more widespread use because, like you said, if we have receptor function decline, then it's gonna be really hard to get off of those medications and that is one of the concerns that's commonly raised as these are considered lifelong. So that might be appropriate for someone who's obese or has kind of end state disease or in type 2 diabetes. They have severe metabolic syndrome.

But when we see them used in the population that just wants to lose 10 pounds, I really think there's a huge risk of, like you said, that overuse that can be really difficult to get off of versus thinking about stimulating endogenous production, which is such a safer way with other benefits. Like we've talked about, improving the microbiome has so many other downstream benefits versus that one targeted approach. So yeah, I just want to reinforce that.

I will say, interestingly, like I've been taking the glucose control product for probably six months and like I feel a huge difference in my hunger and I lift weights and work out a lot. So there are times where I'm like ravenous. Yeah. But I've actually seen that just change or even with cravings and things like that that are minor. And I mean, I'm an N of one. So take it

with a grain of salt. You've done a lot more. You've had a lot more look at a broader perspective of people.

I do think, you know, I'm just giving you my personal experience for people who are listening because I think if you have patients that are asking for that kind of support, there's really nice alternatives available that I would highly recommend like the pendulum product to have them try first. Again, not just for that one benefit but because there's so many other downstream benefits of improving the gut microbiome.

Colleen Cutcliffe (44:15 - 45:51)
And you're not alone in that food craving thing. So we actually did a study ~ using the food cravings inventory. So that's a test for food cravings. And we found that after being on these strains for three months, so 90 days, ~ 91 % of people had statistically significant improvements in their food cravings. And that was across the four major cravings types, sugars, high fat foods, and...carbs. I forgot the one that is my craving problem.

And so I think that ~ that shows that, you know, when you can actually help your body improve the microbiome, you can also help these food cravings. And that's a great jumpstart to help people to make better food choices. And I'll again just advocate that it's not just about your microbiome, it's also about your nutrition. So if you compare higher fibers, higher polyphenols in your diet with a microbiome intervention, or you have a microbiome intervention that helps you choose those higher fiber, higher polyphenol foods, you're really gonna be helping your body in these ways that are sort of your natural body's way to stimulate GLP-1 hormone. And one other use case we've had from practitioners that we've heard from them is a bunch of them are using them to help their patients reduce the amount of drugs that they're on or if they want to do an on-off that during the off, so it doesn't feel like a big cliff, you can start to introduce your body's natural GLP-1 hormone producers. And that's a great way to help people kind of not be on this super high dose all the time for long periods of time.

Jaclyn Smeaton (45:51 - 46:30)
That's great, great advice. I'm really glad you shared that, because I think learning from the field, the best ways to use it from other providers is great for you to facilitate the sharing of that, so thank you. So I want to talk a little bit about the future of probiotics. I beyond probiotics, I'm hearing more about things like postbiotics or the next generation symbiotics, kind of the combination of probiotics and prebiotics to enhance gut health. Can you talk a little bit about what you see in the future in this space. I know it's an educated guess, but foreshadowing, like what's coming down the pipeline that providers can expect to see?

Colleen Cutcliffe (46:30 - 51:00)
Yeah, well, so if we start kind of with a definition of terms, because I think it is sort of a confusing space for a lot of people. You what are all these different things? And it feels like there's marketing innovation happening all the time that, you know, is it real science or not? And so I think the first thing is the probiotics are the actual strains. So everything we've been talking about here are the actual strains that are in your, in this case, the gut microbiome that do all the activity.

Prebiotics are the foods that feed those strains. So we've talked about high fiber diet, high polyphenol diet. Those are the foods that you can either get in the form of actual foods or in the form of supplementation. Those are prebiotics that feed the strains. And then the postbiotics are all the small molecules that are created by the strains themselves. So the prebiotics feed the probiotics, which create postbiotics.

We don't talk about this a lot, but actually most of our products are synbiotics. We have observed in preclinical studies that if you don't have the prebiotic with the strains, you actually don't get as much efficacy. And the kind of analogy for that is that if you were going to drop me off on a deserted island, I'd rather you drop me off with a cooler full of sandwiches and beers than by myself. And so we're kind of delivering the food with the probiotics themselves in order to help them get jump started when they make their way back into the gut microbiome.

And I think that there will be an ever increasing role for both prebiotics and probiotics ~ as we kind of look at the most effective ways to impact the gut microbiome. I'm a lot more skeptical about postbiotics. These are the small molecules created by the microbiome. And the reason I'm more skeptical about them is just simply delivery.

What's supposed to happen in your microbiome? This is an ecosystem of different strains that are interacting with each other in real time and temporally and also ~ in proximity to each other. So they're literally handing things off to each other as they create them. so if you're just trying to put this thing in, you've to make sure it's getting delivered to the right place at the right time. And probably the most compelling data that we have, just the decades of research, is around the small molecule or the postbiotic called butyrate.

Butyrate has been around for a very long time. Even though the term postbiotic is new, it is not. Yeah. And butyrate has been around for a long time because there are incredible studies showing that if you deliver butyrate in preclinical, in mouse models, ~ and in vitro, in the lab kind of test tube setting, ~ it can stimulate all these super important hormones for metabolism, know, including GLP-1, there have not really been strong, compelling clinical trials showing that the delivery of butyrate, either orally or through enema, have the

same impact as you're seeing in those animal models and in the lab. And the question is why? Why is it not as good in humans? And it's because, well, I will say this is the hypothesis, it's because of delivery. So you have these strains that create butyrate.

The way butyrate works is it has to bind to these receptors that then stimulate these downstream molecules to secrete GLP-1. So when butyrate is not handed off directly to that receptor and it's just free-floating, it's not going to create that pathway stimulation. Moreover, every cell in your body uses glucose as its primary source of energy except for your colon. Your colon cells use butyrate as their primary source of energy.

So when you think about you're trying to deliver this small molecule to this very specific receptor and all along the way, all these colonic cells really want to use that butyrate and take it up. It's like if I said to you, I'm going to give you a million dollars. Would you rather I put it in a suitcase, knocked on your door and handed it to you, or would you rather I scattered it all over highway 101 and said, it's on highway 101, go pick it up. You would much rather I delivered it to you in a suitcase because you know that if I scattered it all over the freeway, everyone would be pulling their cars over and taking your money.

And that's really the problem with, I think, butyrate delivery the way we have it now. It's in a capsule. It's literally the money. As it's getting through the colon, all those cells want that butyrate. And so is it ever going to make it to that doorstep, to that receptor? I think that's why the efficacy looks really different. Whereas in the lab, you can have that direct interaction. And even in mouse models, the way it's fed, it's gavage fed, it goes directly into the microbiome. And so I think that that is one of the reasons why postbiotics are going to be really hard to have the same efficacy as prebiotics and probiotics. It's just simply that delivery problem.

Jaclyn Smeaton (51:00 - 51:34)
Yeah, I appreciate you sharing that example. And it seems as though, you know, there is so much synergy that we don't know about between the prebiotics, the microbiome itself, and then the compounds that are produced by the microbiome. It's ~ a feedback loop in an ecosystem that it makes sense that things would have to be aligned across the spectrum of it versus just delivering a postbiotic and expecting to see the same change. So that's really, really fascinating and I'm sure we're going to know a lot more about it in the future as far as what's working and not working.

Colleen Cutcliffe (51:34 - 51:40)
And I'm happy to be proven wrong there because the more tools we have, the better. That's why I'm skeptical about it.

Jaclyn Smeaton (51:40 - 51:57)
No, I think the skepticism is a healthy skepticism and if we can work on that root cause of microbiome diversity and balance and really getting that to be healthy in the long run, that it reduces the need for all of these post-biotic applications as well. Yeah, wonderful. Well, it's been awesome having you. I had so much fun when we recorded the podcast at A4M in December and again, really expanded on our knowledge here. So I really appreciate.
Colleen Cutcliffe (51:57 - 52:10)
Exactly.

Jaclyn Smeaton (52:10 - 52:21)
your time today. If people want to learn more about your work or about Pendulum or about the research that you guys are doing, what are the best ways for them to stay in the know?

Colleen Cutcliffe (52:21 - 52:57)
Yes, please come check out pendulumlife.com. We have all the data on there. We have papers on there. And if you're a practitioner, we actually have a special portal for you where we share all these protocols from your peers. So we basically create a way in which people who are using these products can share how they're using them in their practice. And so a lot of practical knowledge there. And so ~ please come check us out. And also feel free to reach out to us. We love hearing stories about what's working and also what's not working so that we can of learn together as we learn more about the microbiome. so pendulumlife.com, please come check us out.

Jaclyn Smeaton (52:57- 52:59)
So thanks so much, Colleen. For those of you who are listening, I'm sure that this emerging science has stimulated a lot of questions for you. It definitely does for me. It's like you know a little bit and now you want to know a lot more. We will be following up with a live Q &A. It'll be on IG live.

Colleen Cutcliffe (52:59 - 53:18)
Thanks so much.

Jaclyn Smeaton (53:18)
It'll be May 9th at 11:15, Pacific, which is 2:15 Eastern and all your time zones in between. And also when you join the IG live, you'll be able to submit questions live and be part of the discussion. So we really invite you to join us there. So thank you so much and we will see you there.