Dr. Jill

Your Functional Medicine Expert®

Jill Carnahan, MD ABIHM, ABoIM, IFMCP

#81: Dr. Jill Interviews Kiran Krishnan About New Psychobiotic Probiotics

Dr. Jill 00:15

Hey everybody, good afternoon! It's so good to be back. I've been traveling and filming a documentary and have been a little busy, so the episodes haven't been coming quite as freely. But we're back. We're here with one of my absolute favorite people in the world, Kiran from Microbiome Labs. We're going to talk about some new products they have and why you need to know about this content. It's so cutting edge and I just love the science that he always brings to our conversations.

Dr. Jill 00:43

I'm going to formally introduce him, but before I do, you guys know where to find me. If you've missed any past episodes, you can find them all on iTunes, Stitcher, or wherever you listen to podcasts. Those are the audio versions, and if you want to see the videos, you can find them on my YouTube channel, which is just under my name. We now have over 80 episodes, so they're all there for your watching pleasure. We've been on before with Kiran, so please go back and check out that episode. It was fantastic and full of great content. We were talking about all kinds of things, including spraying probiotics up the nose. You'll want to catch that and what we talked about there. You can find me at JillCarnahan.com. There are free blogs and free resources there. If you want any of these products, I'll be sure to include the links, but you can find them at Microbiome Labs or on my website, DrJillHealth.com.

Dr. Jill 01:33

Without further ado, I will introduce Kiran Krishnan. He's a research microbiologist who's been involved in the dietary supplement and nutritional market for the past 18 years. He comes from a university research background, having spent several years hands-on in the R&D fields of molecular medicine and microbiology at the University of Iowa. He established a clinical research organization where he designed and conducted dozens of human clinical trials in human nutrition. He's also a co-founder and partner in Nu Science Trading, LLC, a nutritional technology development and research company. He's the Co-Founder and Chief Science

Officer at Microbiome Labs.

Dr. Jill 02:11
He is a frequent lecturer on the human microbiome. I always love your content, Kiran! Again, I love talking to you because you bring great research there. He's been an expert guest on many, many outlet shows, national and satellite radio, and podcasts. You name it, he's been there. I always love those lectures. He's currently involved in 16 novel human clinical trials on probiotics and the human microbiome, and he's on the scientific advisory board for seven other companies in the industry. This is one of the reasons I love talking with you, because you bring this great science.

Dr. Jill 02:45
I never support companies I don't believe in. You're not paying me to do this interview. I just want people to know that, because I think I said this before, but I'm just going to start briefly. Twenty years ago, I was diagnosed with Crohn's disease, right after breast cancer. It was super aggressive. The only thing I knew was that there was this one weird probiotic that worked when everything else failed. And guess what? It was a spore. I didn't know at the time that it was a Bacillus spore. I had no idea why it worked or why I only needed one capsule to do the same as these other ones. The other ones made me worse. They were the typical Lactobacillus bifidobacterium that is being pedaled. There's no problem with that for some people. But there's something very different about spores. You've told your story before, too. What I want to do is just briefly review: How did you get into this? And then let's dive into this new line. How did you get into looking at probiotics that can affect the brain, sleep, and stress?

Kiran Krishnan 03:40
Yes, of course. First of all, thank you so much for having me, Jill! It's always an honor and a pleasure. I always love our conversations, whether they're on or off air. It is always a pleasure to be on. So thank you so much for having me.

Kiran Krishnan 03:54
I got into this because my passion in microbiology is about exploring the unseen universe around us. I was either going to be a physicist or a microbiologist. That was one of the two paths I was going down. In both cases, you're exploring

unknown forces that impact our lives on a daily basis without most people realizing it. When you get to study it, you realize how profound it is for our outcomes.

Kiran Krishnan 04:23
Since my math is not as great as it should be, I went the microbiology route, which worked out better for me anyway. When you get into studying microbiology—especially when you get into clinical microbiology—the focus is often on pathogens and the pathology of the pathogenic disease. How do microbes infect? And what is the process of infection? And all of that was very interesting to me. That was one of the most exciting areas of research work that I was doing early on in my career.

Kiran Krishnan 04:57
You soon come to realize that of all the microorganisms discovered, 99.9% of them are either benign or beneficial in some way. The small 0.1% or so that can cause illness in a specific way get a lot of the limelight. That's who we all think about when we think about organisms. It became a real natural fit for me to go: "What about the other 99.9%? We need to know and understand those a little bit better." So my whole world started shifting toward wanting to understand the rest of the microbes—in fact, the ones that make up the vast majority of what we encounter.

Kiran Krishnan 05:45
Soon around then, the Human Microbiome Project started kicking off by the NIH, which was trying to study our ecosystem, which is a big chunk of that 99.9% of beneficial benign bacteria. For me, the human microbiome became the place to go into. It was this dark abyss of unknowns, which is exactly what drives me. It's [about] starting off being lost in this immense space and then looking for solutions and connections and connecting the dots. So for me, it was a natural fit.

Kiran Krishnan 06:20
The whole idea of why we founded the company Microbiome Labs is to take doctors like yourself who are on the front lines, working with patients with complex issues, and then utilizing the power of the microbiome to provide therapeutics that can make a difference. You don't have the time to do that work. Your patient is not doing that work. You are working with patients. We're not doing that work, so we have to be behind the scenes working through the research to line up all the dots so

that the patient has a solution. I found that to be a great fit for us and for me personally. So that's where we've been for the last 10 years or so, focusing on it.

Dr. Jill 07:05
Yes, and from my experience, I didn't know what this thing was that helped me 20 years ago. It was just a strange one-strain thing. It's a spore. But the thing that's so fascinating to me is that you guys brought very compelling research. It's always been that way. One of the things I respect about you is that you bring great research to this world and this realm that hasn't always had great research. A lot of the companies, I don't feel, have that same level. That matters, but what matters to me is in the clinic. If I give it to a patient, does it work? And over and over and over and over again, what I saw, which is why I'm here talking to you, is that it works. It works. The spores work.

Dr. Jill 07:42
Before we go into these new ones and talk about the stress response and the gut-brain axis—I have another little story about that, and we'll go to that in a minute—let's just talk about spores in general. We've talked about this before, but I think it's so critical for patients to understand that the number of millions of colonies isn't where it's all at. Why is that? And what makes spores different?

Kiran Krishnan 08:04
The CFU count is not the basis of the efficacy of a product. The market went crazy and haywire because it was not driven by science. It was driven by megalomaniacal marketing thinking, where the idea is that if three is good, six must be better, and if 10 billion is good, 50 billion must be better. As companies started to compete with each other on the shelf for what looked better on the label, they just kept upping the game for higher and higher and higher potency. No establishment governs probiotic dosing and all of that stuff. We have an RDI for vitamins so you know the minimum daily amount you need. "Here's the recommended daily allowance." And you have maximum threshold doses and all that for most of these vitamins. We didn't have that kind of structure for the probiotic industry, so then marketing just drove it haywire.

Kiran Krishnan 09:05
I've been a consultant for lots of companies in the last decade and a half. I've been

the scientific voice in many of these formulation discussions. You'd sit in the meetings and they'd be like: "Okay, we're going to do a product. We're going to have 17 strains and 50 billion CFUs." They've already decided. I'm like: "What is the basis for 17 strains? Where'd you come up with that number?" It's that their closest competitor that they're fighting with for shelf space has 15 strains so they want just a little bit more.

Kiran Krishnan 09:35
"They have 30 billion, so we want 50 billion, but we want 50 billion and 17 strains for the same price as the 30 billion and 15 strains," which means that you need to get lower quality strains at a lower price to meet that amount. So then you're buying tanker loads of lactobacillus and acidophilus for nothing. You can buy a shipping container of this stuff out of China that costs nothing. And you could make millions of bottles for $1, sell it at $9, and make a killing. That's where the probiotic industry started going. It was unfortunate.

Dr. Jill 10:15
Clinically, what I see is: Number one, there are strains of lactobacillus that increase histamine. I have patients with mast cell activation. I have patients with mold illness. And some of these patients get worse on the wrong strain, so it does matter. It's not that they're all cheap, but some of these strains—like Lactobacillus casei, for example—often increase histamine. That matters. Then number two, if you have dysfunction with digestion, absorption, motility, and proneness to overgrowth of small bowel bacteria, sometimes adding to that mix with good normal strains that are human-compatible does not help patients; it makes them worse. Have you seen that as well?

Kiran Krishnan 10:53
Yes, absolutely. That's been one of our big gripes with the industry in general: You can't just combine dozens of strains that are not well characterized. There was a study published in *Nature* in 2017 where they took a bunch of kids' probiotic products off the shelf and analyzed them. And 94% of them had the wrong strains in the capsule than what was claimed on the label because people are not doing the genetic analysis that's required to verify that what they're buying in that container load is the actual strain that they think it is. It just looks like a powder. How can you tell? Is it acidophilus? Is it casei? Is it reuteri? What is it? Or is it any of those at all? And what is the contamination level and so on?

Kiran Krishnan 11:43
What we were always griping against is that if you're just loading your system with tens of billions of CFUs of these unknown, uncharacterized species, you may be competing with your own indigenous bacteria. If the lactobacilli that's coming in is somewhat similar to your lactobacilli, and we don't know the exact mechanism of action of how it works, it may be competing for binding sites and all that with your own endogenous species. And if nothing else, if they're just dying through the stomach, they're loading your microbiome and your system with genetic material that is unknown. We don't know what that is because these companies are not doing proper genetic analysis, gene typing, or BLAST searches on these bacteria to understand what they hold within them.

Kiran Krishnan 12:37
That genetic part of it, to me, is even scarier because you don't know what genes these microbes are carrying. As you dump tens of billions of these bacteria into your system every single day and expose your microbiome to those genes, it can make foundational changes to how your microbiome functions in ways that we couldn't predict at the moment without them doing the studies. For us, it's always been critically important that any company that makes a probiotic product—it doesn't matter what species it is; there are many different effective species—has to study it. You have to show what it does in the microbiome. You have to show what it does to the rest of the microbiome. You have to show what it does to the immune system. You have to characterize the bacteria properly. We just have way too much in this industry of what I call kitchen sink formulas:
"Throw everything together and let's make it the biggest sounding number, and that means it's really effective." And hopefully what we're trying to do is set the bar high to go: "Okay, guys, here are the basics we need to do to have an efficacious probiotic."

Dr. Jill 13:49
I love that. I would rather have someone not take a probiotic than just grab one off the counter at Walgreens and not know what they're taking. Now, some of those strains have been studied, but not all of them. Two questions come to my mind, and then I still want to get to the new products. I've heard a lot in the last decade about soil-based probiotics. Those do contain spores, but my understanding is that a lot of times they're not studied. I recall there was a case of pancreatitis with these strains that had no evidence behind them because some of them became very

aggressive. What's your comment on why the strains that you guys have studied, which are spores and are from the soil at the root... But these random, large, soil-based things—I deter patients away from them because we don't know. Do you want to comment on soil-based organisms?

Kiran Krishnan 14:38
Yes. There was an early product when we first came out that we were always very nervous about. That product eventually came off the market, I believe. But it's because they had this mass of uncharacterized organisms that they just characterized as soil-based. You just don't know what's in there. Unless you know what each of the players are, you don't understand what the functionality is going to be in the gut. And it's true, some of those could be opportunistic. Some of those could have virulence factors that we don't know about.

Kiran Krishnan 15:14
Most companies in our space don't have the scientific capability to study these types of things. That's the big problem. They don't know how to take a microbe, do full end-to-end sequencing and gene blasting, and understand all of the proteins that the microbes produce and all that. But what they do well at is very quickly put the marketing story together, grab a bunch of ingredients from a bunch of different suppliers, put it all together, and call it a product.

Kiran Krishnan 15:43
When this whole phenomenon of soil-based probiotics came about, the general idea behind it was okay. The problem is that you cannot have a big mix of uncharacterized bacteria. You just don't know. You're setting yourself up for disaster because there's going to be something in there that's going to cause somebody some illness. And that's a big problem. Now, with our products, even though Bacillus endospores are known to be ubiquitous in the environment, we went the further step of specifically isolating Bacillus endospores that are commensal to the gut microbiome. All of the spores that we work with came from healthy human volunteers rather than from the environment. Initially, they probably came from the environment, ended up in humans, and adapted to being much more savvy within the human microbiome than the outside.

Kiran Krishnan 16:41

You'll find, for example, subtilis that is better adapted to be outside than subtilis that's adapted to be in the gut. What we wanted was subtilis that's adapted to be in the gut. Then you have to take them, and then you have to do a full genome analysis to make sure there are no virulence factors and no toxin production. Their chromosomes are very stable, meaning that through irradiation, antibiotic use, and all that, they don't shift and create antibiotic resistance. You have to do all of those kinds of studies to make sure these are safe bacteria. Unfortunately, 99% of the companies in our space just don't do that kind of stuff.

Dr. Jill 17:21
No, this is great because now people understand what goes into making a great product and why I think they're so effective. It's interesting. Just a little tidbit on inflammatory bowel disease. We know patients like myself with the genetics—NOD genes—for Crohn's. This background, I think, will help people understand our conversation. All it is is that someone like me has an abnormal immune response to a normal microbiome, which means I could have a very inflammatory response to something that's a resident in my gut that's not a pathogen. Also, you and I talk a lot about endotoxemia. Just briefly, if you're listening, endotoxemia is when the bacterial coatings leak from the gut lumen into the bloodstream. They are one of the most potent inflammatory triggers for heart disease, obesity, and mood disorders, which we're going to get to in a second.

Dr. Jill 18:11
It's so relevant because it's not just about planting a seed like a probiotic and having it grow and flourish; it's about communication in the body. These probiotics are messengers and they communicate with the immune system. If you have a permeable gut, immune dysfunction, or proneness to autoimmunity, it matters because it could send the wrong message, and then all of a sudden you're down the road to some autoimmune disease because you've got the wrong milieu of microbiome. Just a little bit of framing that so that patients understand why we're talking so much about the species.

Dr. Jill 18:44
I'm so excited about Zenbiome COPE and Zenbiome SLEEP. Tell us first: How did you get into this? We know the gut-brain connection. Then, let's talk about these products and what they might do for patients.

Kiran Krishnan 18:57
Yes. This is a super exciting area for us. The gut-brain connection has always been something that's been on my radar and the Microbiome Labs team's radar for years because of the incredible prevalence of anxiety, depression, and sleep disorders in society today. We're not even talking about people with major depressive disorders or really bad anxiety who can't leave the house. Unfortunately, I think somewhere around 30–40% of the total population suffers from functional depression and anxiety. Meaning that they're experiencing daily anxiousness. They're facing daily levels of depression. And in many cases, they're self-medicating in many different ways. Whether it's drinking wine all day long or it's addiction to food or addiction to other substances, whatever it may be, they're self-medicating most of the time. And they're in this weird limbo where their condition is not severe enough for them to go: "I need to go see a psychiatrist and get a diagnosis and go through all of that process."

Kiran Krishnan 20:11
Number two, they don't want to get a diagnosis because once you get a diagnosis, then you're on that drug regimen. I know the vast majority of the population is very concerned about starting down that path of SSRIs, anti-anxiety medications, and so on. In an attempt to avoid all of that, they try to deal with it. There are meditation apps, wellness things, mindfulness work, and then lots of self-medication, too. We realize that that's a big issue. We also realize that, from a therapeutic standpoint, nothing has changed in the world of psychiatric medicine. It's been the same class of drugs for 50 to 60 years—the same SSRIs, the same anti-anxiety medications, just different flavors to them to certain degrees.

Kiran Krishnan 21:04
The microbiome presents a unique opportunity to get a grasp on the things that the average person is dealing with. To me, that's where we can make the difference. It's not necessarily the patient who's so severe that needs to be hospitalized. It's the mom, it's the dad, it's the student at school—the people who are experiencing sleeplessness, daily anxiety, and daily stress. You and I know—because we read the studies and we do the lectures—that stress and anxiety are also driving things like leaky gut, chronic inflammation, and endotoxemia, setting them up for all kinds of other chronic illnesses down the road. For us, this is a really important gap in therapeutics, even within functional medicine. It became an area of focus for us.

Kiran Krishnan 21:54
When we break down the pathology and look at the gut-brain connection and what within the gut is either missing or creating a problem, we find two big areas. Area number one is LPS, which we've already been dealing with through the spore-based probiotics from MegaSpore. We know that high levels of LPS through endotoxemia—leaking into the blood—will be significantly disruptive to brain function. LPS interferes with dopamine binding and it interferes with serotonin binding. It can turn things like tryptophan metabolism from being made into serotonin and melatonin instead into things like kynurenine and quinolinic acid, which are neurotoxic. We know that it creates inflammation in the brain. We know it triggers microglial activation. So, we know LPS is highly toxic to the brain and has all kinds of mood and depressive disorders as a consequence. But we're already dealing with LPS really well with the spores.

Kiran Krishnan 22:54
There's a second part that we weren't quite dealing with with the MegaSpore as well that we wanted to dig into. And fortunately for us, we have an amazing partnership with a group out of Ireland called PrecisionBiotics. They've been specializing in this work for the last 15 years. They've been working with a group called the APC, which is the world's most renowned gut-brained research area in Cork, Ireland. A lot of this research has come out of there and our collaboration with them. Of course, they've been working on this for the last decade and a half as well. What we've come to find out and what seems quite clear, is that there is an inflammation-mediated stress response.

Kiran Krishnan 23:41
For your audience to understand how that happens, let's say you're driving down the road to work one day, and then somebody cuts you off. That pisses you off, so you honk your horn, you flip the bird, you have an exchange or whatever through the windshield. That creates a bunch of stress in your system. That's an external stressor. The first thing it's going to trigger is for your hypothalamus to start releasing corticotropin-releasing hormone. Then you've got activation of your pituitary. Then, finally, your adrenals get activated and your adrenals release cortisol. We'll pause there at the cortisol level.

Kiran Krishnan 24:17

The other side of that activation of the HPA is the activation of the sympathetic nervous system. The sympathetic nervous system's job is to get the body ready for a flight-or-fight response. One of the things it's doing is increasing heart rate, respiration rate, and vasodilation. But the sympathetic nervous system releases all these catecholamines, which end up activating the immune system. And it ends up activating macrophages and microglia cells, which are kind of macrophages in the brain, if you will. Those cells then release all of these inflammatory cytokines—things like NF-κB, interleukin-6, and interferon-α—and create massive inflammation in the brain and massive inflammation throughout the body as well, which can be measured. Part of that sympathetic activation is about driving inflammation in the brain, driving excitotoxicity activity, and shutting down anything that would calm the system. All of that is just to get the body amped up and ready to go to fight or flight from whatever the danger is.

Kiran Krishnan 25:26
Inflammation, of course, causes perfusion. One of the things that I think the body is adapted to do is use the immune system as a way to drive blood to areas where the body feels it needs it. You've had that external stressor, so now you have two outcomes working in parallel: Cortisol levels are going up because of HPA activation, and you've got inflammation going up. Your respiratory rate, heart rate, and all that are going up as well. Now you feel stress. This is the physiological feeling of stress. You're amped up; you're stressed out.

Kiran Krishnan 26:03
Feeling stress is perfectly fine. That's a normal physiological feeling. We are geared to feel stress. The normal response that tends to happen then is that cortisol keeps going up. As cortisol goes up, it starts to create a negative feedback loop for that whole mechanism. We have these receptors throughout our body called glucocorticoid receptors. As cortisol levels go up, it starts binding all the glucocorticoid receptors, which then send a negative feedback signal to shut down the whole system. That becomes our recovery from that amped-up stress.

Kiran Krishnan 26:42
The whole idea is that we're walking through the grass, we see something scary, it amps us up, cortisol flies up, and the sympathetic system flies up. We run from the danger and we climb up a tree and hide. And once we're sitting up on the tree, we're supposed to be able to come down from all of it because if we don't come

down from it, then we are constantly in a state of being amped up. The sympathetic system works against the parasympathetic system, which means that we can't rest, digest, or rebuild. We're always amped up, moving, seeing a lot of breakdown of tissue, the creation of reactive oxygen species, and oxidative stress. We're also full of inflammation because now the immune system is amped up and the macrophages and all that are kicking off all of these inflammatory cytokines.

Kiran Krishnan 27:32
All of this system is dependent on elevated cortisol reaching a point where it starts binding glucocorticoid receptors and then providing the negative feedback to bring down the whole system. But here's an interesting aspect of how that whole system works: The trigger or the linchpin for whether or not negative feedback occurs hangs in the balance in the gut. There's a component in the gut that is absolutely critical to making sure the negative feedback happens. And we've outsourced this to microbes in the gut.

Kiran Krishnan 28:09
It's super interesting when you think about it from an evolutionary standpoint. Our ability to experience stress, react to it, and then come down from it is dependent on the types of microbes we have within our gut. Whether we are constantly stressed and can never come down from the stress... The stress progresses towards generalized anxiety, and then depression with generalized anxiety and lack of sleep, of course, because we can't sleep when we're stressed and our sympathetic system is up. Whether it progresses to that all depends on whether or not you have a particular type of microbial system in your gut. And we'll talk about what that is in a second. That's where modern society is going. Modern society is at that place where we experience stress, but we just can't come down from it. It keeps building and building and building [inaudible].

Dr. Jill 29:04
Really quickly, I was just going to say that in the sense of the pandemic, people have been on this high alert with fear of getting sick and they're isolating. And it's just going on and on and on and on. So, depending on where you are in the world, it doesn't matter. We're in a time and era where this is the most relevant it's ever been.

Kiran Krishnan 29:23
Absolutely. The timing couldn't be better. We need these kinds of thoughts and solutions more now than we ever have. And our microbiomes are probably more damaged now than they've ever been in recent history because of all of the over-sanitization and isolation [inaudible].

Dr. Jill 29:41
You know this, but just a little fun fact: Anger and fear can preferentially destroy Lactobacillus and allow things like Clostridia to proliferate. Even our emotions negatively change aspects of our microbiome.

Kiran Krishnan 29:56
They do. And since you bring that up, there are lots of opportunistic organisms within the gut microbiome and the total microbiome that respond to stress hormone signaling, whether it's cortisol, epinephrine, or norepinephrine. They respond and exercise their virulence factors when those levels are high because they know that the host's immune and metabolic systems are suppressed, so that's their opportunity to express themselves and win in the population fight. Studies have shown over and over again that multiple continuous bouts of stress and the stress response will end up creating more pathogenic bacteria, viruses, and so on in your system because of the stress itself and the way they respond to stress. It couldn't be more relevant now.

Kiran Krishnan 30:53
The linchpin I was talking about—here's what tends to happen if your gut is dysbiotic and you don't have the microbial component in the gut: As cortisol levels build up, as we were talking about, part of it enters the gut. When cortisol goes into the gut, it increases intestinal permeability. Cortisol leads to gut permeability. The problem with that is that it does so when your gut is dysbiotic and there isn't this checkpoint, and I'll talk about what that checkpoint is. But as your gut becomes permeable, endotoxins flow through. Of course, LPS now has free reign to move up to your brain and screw up your brain even more, like we talked about earlier. But the other consequence of intestinal permeability or leaky gut is a huge elevation of interleukin-6. Interleukin-6 (IL-6) is the quintessential cytokine for inflammation. When interleukin-6 is elevated, what it tends to do is go and trigger the HPA axis again. So, IL-6 by itself can activate the HPA axis.

Kiran Krishnan 31:58
Now you've got a good amount of rising cortisol levels dumping into the gut, causing a leaky gut and an increase in IL-6. IL-6 activates the HPA axis again, causing more release of cortisol, which causes more leaky gut, which causes more HPA activation. And here's the other kicker: Not only does it trigger HPA activation, but it also reduces the expression of glucocorticoid receptors. Those are the receptors that cortisol is supposed to bind to to provide the negative feedback to shut all this down. Not only is the negative feedback loop now cut off, but the continuous amplification of the HPA axis is happening. Your gut is becoming more leaky. You're becoming more inflamed. You've got more LPS now dumping into the system, which puts you at risk for all of the chronic illnesses that we've talked about. And you're moving towards this area of significant chronic illness.

Kiran Krishnan 32:59
Of course, all the while, you're not dealing with the stress. The coping centers of the brain for stress are not functioning and are not firing. You're not in the theta wave state. Your brainwave activation is all off. It's just a mess. But that's where the average person is right now with stress, mood disorders, sleep disorders, and all that.

Kiran Krishnan 33:21
Here is that linchpin in the gut that makes all of the difference when cortisol enters the GI tract: The big thing is something called bacterial peptidoglycans. Peptidoglycans are fascinating compounds that bacteria make that are like amino acids with sugars on them. Some bacteria make it. And peptidoglycans, as it turns out, are important to you and your central nervous system from day one. If you're pregnant and have a baby in utero, on your placenta, you have bacterial peptidoglycan receptors and transporters.

Kiran Krishnan 34:05
Mom's gut bacteria, which make peptidoglycan, will release peptidoglycan into mom's circulation. That bacterial peptidoglycan will make its way to the placenta. It'll be bound by the peptidoglycan receptors. It'll be grabbed by the peptidoglycan transporters and taken through the cord blood into the baby's brain. The baby's brain has peptidoglycan receptors and transporters. And as the studies show, when the baby's brain binds these bacterial peptidoglycans, that becomes a key stimuli

for the proliferation of brain cells and the creation of synapsis, so synaptogenesis, and the myelination of the baby's central nervous system—that's the putting on of the insulation on the nervous system, on the neurons—and then the formation of the blood-brain barrier.

Kiran Krishnan 34:54
The development of our baby's brains and central nervous system is dependent on a bacterial byproduct. Just think about the symbiosis of that. It's insane. We have outsourced one of the most important aspects of human development: Bacteria and a byproduct of bacteria. To me, that's the mind-bogglingness of this connection that we have with microbes. It's super important when you're in utero, but it's equally important when you're an adult as well, because peptidoglycans from bacteria are the checkpoint for how cortisol impacts the gut microbiome and the leakiness in the gut.

Kiran Krishnan 35:54
If you have adequate levels of peptidoglycan being produced in the gut by the right type of bacteria, that peptidoglycan will check the inflammation and permeability that cortisol creates. It prevents the creation of intestinal permeability, and it prevents the activation of that inflammatory process in the gut. So it prevents the brain inflammation that cortisol can create through the gut microbiome. In fact, the peptidoglycan will go as far as binding to certain types of cells on the intestinal lining that create neurotransmitters that move up the vagus nerve and change brain wave activity during moments of stress to improve stress coping mechanisms.

Kiran Krishnan 36:22
This bacterial peptidoglycan goes so far as to prevent the escalation of HPA activation, the leakiness of the gut from cortisol, and the inflammation that's induced by that stressor, especially the cortisol component of it. It also changes brain wave function. That's the component that we grabbed onto and said, "That's the second part of this story." The first part is that we're dealing with LPS. You've got to stop LPS from moving through. The second part is that we've got to get a handle on the inflammation-driven stress response and continuous HPA activation. So that's the second part, and it's mind-boggling what we're seeing now when people utilize the product.

Dr. Jill 37:06
That's amazing—what you just shared—and is so relevant! I just see that from 10 years ago, when some of this started, it's just [been] exponentially [growing]. When I look up IL-6 and depression, there are thousands of studies relating to that. And that's relevant to COVID because IL-6 is one of the main cytokines related to this not only long-haul [COVID] but also bad outcomes. These are all connected.

Dr. Jill 37:28
Let's talk in our last few minutes about how there are these strains that have peptidoglycans in them, but what about the other ingredients? Let's talk about Zenbiome COPE first and then Zenbiome SLEEP. It made sense because I've used those ingredients, but talk just a little bit about what's in Zenbiome COPE. And why did you choose these other ingredients?

Kiran Krishnan 37:49
We have this strain called Bifidobacterium longum 1714. It's a very unique bifidobacteria with what we call an exopolysaccharide. Like the spores that have this unique capability of providing this coating on themselves, this is a unique strain that also coats itself with peptidoglycans. It's an exopolysaccharide. That's the source of the awesome peptidoglycans that you get in the gut when you take this species. And that's what's doing all of the checkpoints—bringing down the cortisol, improving sleep, and changing the brainwave function. We have two studies showing that when you get exposed to this bacterial peptidoglycan through that species, it changes your brainwave to theta wave function, which is that flow state that everyone wants to be in.

Kiran Krishnan 38:35
Because the strain works both in improving sleep parameters—like the time to sleep and the quality of sleep—it also helps with coping with stress day-to-day and reducing cortisol. It can work throughout the day, both daytime and nighttime. We looked at the population and we said: "There are a lot of people that have issues with both sleeping and day-to-day coping. But some are like, 'I sleep fine, but during the day, I need a lot of support,' or 'During the day, I'm fine, but I need help sleeping.'" Either way, the microbe is going to help. Then what we did to distinguish the product was utilize a couple of key ingredients that we've loved in the past. We've all, within Microbiome Labs, used them personally. On the sleep side, we use

theanine. Theanine is just such an amazing, powerful product. I'm sure you've used it.

Dr. Jill 39:28
I love it. I use it, yes.

Kiran Krishnan 39:33
We think it pairs so well with the mechanism of action of how the peptidoglycan-rich strain works. What we're finding in people who are using it is that they're noticing a change in their ability to fall asleep and then the quality of their sleep. In fact, what we get the most response from is the vivid dreams that people have because you're in deeper, higher quality sleep for longer. We get that response within the first week or so. On the other side, with Zenbiome COPE, we also started using lemon balm and saffron. Those are both such awesome, gentle, high-quality ingredients, with lots of studies showing their ability to simmer down the sympathetic nervous system, which tends to be activated in people who are dealing with stress all the time. While the probiotic bacteria are working on the root cause—continuous HPA activation and gut-brain inflammation—we've got these ingredients to provide support to give a more short-term, immediate effect. You get a two-pronged deal here, where you're dealing with the root cause, but in the meantime, you're also getting more immediate relief and more immediate effects.

Kiran Krishnan 40:52
That's how we formulated it. We could have just put the strain in there, but we wanted to have people feel relief much sooner as well. When you combine the underlying root cause solution with the peptidoglycan and the exopolysaccharide strain, and then these cool herbals that are well documented and well studied, you get the most bang for your buck, really.

Dr. Jill 41:20
Yes, I am really excited. These are brand new, so I haven't had a huge year of patients to see yet. But what I'm doing is [recommending] the Zenbiome COPE more during the day and the Zenbiome SLEEP, of course, at night. Some people will take both. Some people will choose. Just by interviewing them, I usually know which piece is a bigger issue. But you can take both, correct?

Kiran Krishnan 41:38
Yes. I've been taking both. Because I've been traveling a lot overseas to Europe and all that, I've been using both. Zenbiome COPE has 60 capsules. If you were taking just the Zenbiome COPE and you were like, "I don't need the sleep help," then you would take two capsules a day of the Zenbiome COPE. You take it during the day with food, which is normal with your MegaSpore. If you were taking both, you would take one capsule of Zenbiome COPE and one capsule of Zenbiome SLEEP at night. If you're just taking Zenbiome SLEEP, you just take one capsule of it at night. And then you're in a good place. We're finding that about 80% of people are taking both. Only about 20% of people are taking just Zenbiome COPE. We don't know anyone yet who has taken just Zenbiome SLEEP. Everybody seems to have a good amount of daytime stress [inaudible].

Dr. Jill 42:34
I was going to say that this is so relevant to the era we're in. We talked right before we got on here, and anyone in functional medicine knows this, but the demand for services and people who are suffering is exponentially rising. A lot of it's related to the stress response because people are so under stress, and we're getting pushed from all sides—in making decisions, family, school, kids, and COVID. So this is so relevant.

Dr. Jill 43:01
So many people, like myself, have tracking rings or other devices. For me, when I do an intervention, I can see changes in real-time. I can see the changes in deep sleep. I'm excited as well, too. Maybe in 30 or 60 days, I'll give you some feedback.

Kiran Krishnan 43:16
Yes, that's awesome! We've been getting people reporting from their Oura rings and all of that, which has been super exciting. And keep in mind one thing that's really exciting and interesting here: Even though we're trying to get a quick response, because the species are working on the underlying root cause, you're also getting all kinds of long-term health benefits by fixing that root cause problem.

Dr. Jill 43:52
Right, because of the LPS, the IL-6, and all the stuff you're dealing with. I think—I'm sure you do too, and we may be very few—LPS, endotoxemia, IL-6, and some of these things that we're talking about are the crises in medicine and health. We're

dealing with the core. You take cardiovascular disease, obesity, metabolic syndrome, mood disorders, sleep disorders—they all relate to endotoxemia. Many of them relate to excess cytokines. So it's kind of coming together. It's not like a silo approach anymore. There are commonalities in the mechanisms of stuff as diverse as heart disease and depression. It all comes together.

Dr. Jill 44:32
This is, as always, so fascinating. I am so excited to share your products with patients, listeners, and everything. I'm just super excited. Anything else? The last time, we talked about these being on the horizon and now they're out. We will be watching for good results in our patients. Anything else on the horizon? Are you looking at more ways to deal with inflammation and mood? Is there anything else that we should be looking toward in the future?

Kiran Krishnan 44:59
Yes. We have two very unique strains coming out. One that's coming out by the end of the year is called PyloGuard. This is attenuated lactobacilli, so it's not alive. It's a postbiotic or ghost probiotic. It has a very strong affinity to bind up H. pylori in your stomach. From doing microbiome studies and tests, we think H. pylori is a forgotten driver of so many conditions. It's so prevalent. More than 50% of the population has infectious levels of it. Of course, most people knew about it through peptic ulcers and things like that. But now that the studies are coming out, there's a lot more. Even more recently, a study came out showing its correlation to prostate cancer. It screws up the entire digestive system, starting in the stomach, starting at the very front of it.

Kiran Krishnan 46:06
To us, H. pylori is a massive, massive issue. The treatments for it are super aggressive. The triple therapy is super aggressive. That has all kinds of other implications to it. For us, the idea is like [this]: Is there a first-line, more gentle way of trying to go about reducing those numbers? Here's a probiotic strain that will disperse in the stomach. Then, it has an affinity to grab onto and bind H. pylori and take that whole complex out so you can defecate it out without touching anything else or damaging anything else. It's a mind-blowing probiotic strain when you think about it.

Kiran Krishnan 46:49
In that same vein, we have another one coming out called MegaMetalliQ. The reason it's called MegaMetalliQ is because heavy metals are another big issue that we're dealing with. A big congressional report just came out. I think it was the beginning of this year, showing how all of these kid foods and baby foods are laced with crazy amounts of lead and other heavy metals. Of course, so many households in the US still have lead pipes and all that. Lead is a really big problem in terms of toxicity and impacts the microbiome. We have a species of attenuated bacteria—it doesn't have to be alive—that can go into the gut and bind up all of the lead, arsenic, and cadmium from the liquid, the diet, and the foods that you're eating, and take it out of the system.

Dr. Jill 47:37
Wow! This is fantastic because those are two huge problems. Those are two things that I deal with every day and they're not easy to treat. As always, I love your cutting-edge approach. Kiran, thank you. Thank you for your time, your expertise, and your work! It is always a joy to spend time with you. We will continue sharing. And thank you all so much for joining us today!