180: Resiliency Radio with Dr. Jill: Key Updates in LONG COVID with Dr. Bruce Patterson, MD

Dr. Jill 00:12
Hello, everyone, and welcome to another episode of Resiliency Radio with Dr. Jill! Today, you're in for a real treat for multiple reasons. In this post-pandemic era, we have more complex chronic illnesses than ever before and more sequelae of this virus called COVID, and today we're going to dive deep with one of the world's leading experts. If you listen to us on iTunes, Spotify, or YouTube, please stop and leave a review. There are many more episodes that you can find there.

Dr. Jill 00:42
Today, without further ado, I want to introduce my guest, Dr. Bruce Patterson. Dr. Bruce Patterson, a medical doctor, received his undergraduate degree and training in molecular biology from the University of Michigan in Ann Arbor. He then received his MD at the Northwestern University Feinberg School of Medicine, followed by a residency in pathology. During the early stages of the AIDS epidemic, Dr. Patterson began investigating cellular reservoirs of HIV using molecular and in situ cell-based technology patented in his laboratory and used today around the world. He determined that enough HIV virus was present in infected individuals to account for the massive destruction of the immune system. This paradigm-altering work was published in Science in 1993 and was featured in *Scientific American*, *Rolling Stone*, and on the *Discovery Channel*.

Dr. Jill 01:35
Dr. Patterson has authored over 150 manuscripts and book chapters focusing on single-cell biology and diagnostics. He was formerly Associate Professor of Pathology and Infectious Diseases and Director of Virology at Stanford University. He currently serves as CEO and founder of IncellDx, Inc., a growth-stage company that has translated his research discoveries into state-of-the-art single-cell diagnostics in cancer, immuno-oncology, infectious diseases, and especially in our topic of today, COVID. Welcome, Dr. Patterson. That is quite a history! I'm so glad to have you here today.

Dr. Bruce Patterson 02:11
Thank you, Dr. Jill. It's a pleasure to be here.

Dr. Jill 02:14
And I mentioned this before we got on: You have quite the journey. It's interesting because you were at Northwestern and I was at Loyola, so we were both in Chicago for some time during residency and training. But on this journey through all that you've been through, tell us first of all, how did you get into medicine? Then, what was your path to all the scientific discoveries that you made through the years with HIV?

Dr. Bruce Patterson 02:40
It's a family affair. My grandfather and my aunt are both PhD scientists. My aunt was a classical virologist from the '60s and '70s, back in the day, when we didn't have all this great molecular biology and you had to grow the viruses on chick embryos. That was her thing. I think I was about 17 or 18 and I went to her lab and she showed me an electron microscope with a magnified virus 100,000 times. I was sold. I was like, "This is what I want to do for the rest of my life."

Dr. Bruce Patterson 03:22
What's interesting is that back then, they called it the Norwalk agent. It's the norovirus, which is a cruise ship virus that landed on a few cruise ships in port unexpectedly. That was the start of it. Then, of course, molecular biology was in its infancy. I had been riding that molecular wave as it infiltrated medicine all that time. The interesting thing is that the AIDS epidemic pushed the envelope on molecular medicine, molecular diagnostics, and those techniques—much like COVID, as we'll talk about. It has pushed the envelope on new-wave immunology techniques and discoveries.

Dr. Jill 04:13
I love that because it's been such a lifelong [journey]. And you can tell. I always say that curiosity is the mark of genius. But you clearly had that way back at 14 or the first time you looked at the microscope. Especially in a new era of medicine with these complex and crazy viruses like COVID, you have to be curious and think outside the box to get the answers that you've been coming up with. I read a little bit in your bio about your work. You made some massive discoveries with HIV. Do you want to tell us a little bit about that?—because I think it's fascinating.

Dr. Bruce Patterson 04:47
When I first started in HIV [research], there were two different things: Patients

were dying of these horrible immune deficiency syndromes [such as] Kaposi sarcoma, lymphomas, etc; then, of course, there was this virus. But putting it together: Is the virus causing AIDS? That was the big question when I first started. There were even very prominent scientists saying that the HIV virus doesn't cause AIDS. My training in molecular biology and pathology was instrumental in saying: "Maybe we're just not finding it. Maybe we're missing it."

Dr. Bruce Patterson 05:39
I think that was the big thing that I was working on at the time: "Maybe we can't find it. I'm going to try and do molecular biology in these single cells of the body instead of fluids, etc., and try to find where the virus is hiding." We were able to do that and quantify that, which allowed a lot of early work in antiretrovirals. I was just talking the other day about my involvement when they were developing the protease inhibitors and figuring out that it took people that had CD4 counts of single digits—7 or [even] 10—a few months of therapy and they were back up in the hundreds. It's one of those moments that you never forget. You look back and say: "Wow, that changed the course of everything, as HIV-infected individuals are living healthy, long lives now." They still have it, but we've been effective at treating it with drug therapy."

Dr. Jill 06:54
It is amazing that you have that background. Again, now we're in this new era where we need to think outside the box. What's the big overview? COVID is such a different thing than we've encountered before. Do you want to frame it? I told you before that we have a lot of physicians and people interested—patients and clients. Give us a framework for this virus. Why is it so different from things that we've experienced in the past?

Dr. Bruce Patterson 07:18
It's different but it's not in some ways. I was in China in January of 2020. We developed a new immune profiling test with over 150 different biomarkers, both cell-based and plasma-based for looking at CAR T therapy in cancer. We were in China talking to a company over there in Shanghai. I was supposed to go to Wuhan the next day to visit another lab, another customer of IncellDx's. It was canceled because there was this virus and everyone was talking about it. I saw one of the really, really early papers on this virus and some of the lab results. The immune system was just on fire. As we later learned: The cytokine storm.

Dr. Bruce Patterson 08:27
In immunology, we have all these different arms of the immune system: The adaptive immune system, humoral cellular immunity, hypersensitivity, etc. But this was clearly an innate immune response, which is what our body has when it hasn't seen an infectious agent before. It was heavily macrophage-burdened, meaning macrophages were playing a very significant role. That was one of my major areas of research on HIV. You had this massive immune activation of macrophages and the production of interleukin 6 and TNF-α, which were part of the initial pathogenesis in acute COVID. And elements of that still exist in long COVID as well and are part of what we target with some of our diagnostics as well as some of our therapeutics.

Dr. Bruce Patterson 09:32
In our first study of acute COVID, we found that the CD8 T cells were just as low as the CD4 T cells were in HIV. Acute COVID patients with the alpha variant were supremely immunosuppressed. That is the nugget that people aren't considering as we're dealing with the post-acute sequelae of COVID—people are immunosuppressed to varying degrees with acute COVID. What does that do? It reactivates chronic herpes family viruses: EBV, CMV, HHV-6, herpes simplex, etc. Also, in patients who have either undiagnosed or poorly treated Lyme, the bugs start to replicate again. What happens is that all this is going on and all of a sudden we find that there's this post-infectious syndrome that has fatigue, brain fog, post-exertional malaise, joint muscle pain, headaches, etc.

Dr. Bruce Patterson 10:47
That's all well and good. We first described it in long COVID. But the fact of the matter is that all of those chronic inflammatory diseases have the same primary symptoms. Symptom-based diagnosis of long COVID is highly, highly nonspecific. It could be long COVID. It could be long Lyme, as we call it. It could be ME/CFS. It could be fibromyalgia. It could be long vax. All of those have the same primary symptoms. The necessity for a diagnostic was critical. The fact is, we have it and nobody is saying, "We have a diagnostic for long COVID." It's absolutely absurd. We published it two and a half years ago, this signature for long COVID.

Dr. Bruce Patterson 11:39

We developed the Long Hauler Index, and it's still highly sensitive and highly specific for long COVID. Now, in our latest paper, we can differentiate long COVID from Lyme, ME/CFS, long vax, and fibromyalgia. And you know what? It is the most critical tool that we have. I hate to be long-winded, but—

Dr. Jill 12:02
No, this is so relevant. I get excited because you're right. I deal with this complex, chronic disease—ME/CFS, long Lyme, long COVID. I heard you speak in depth about the cytokine patterns, which we'll talk about, and your lab tests and how to differentiate. I've been using your lab tests for a while, but the more data that you guys bring out and the more patterns that you're showing us, [the more] it is a game changer for those of us dealing in this chronic world. Because [of them] we can say, "This is much more likely to be your Lyme or Borrelia reactivated," or "It's more likely to be a true long COVID panel." And it's treated differently.

Dr. Bruce Patterson 12:37
Absolutely. Another important aspect is the negative predictive value. As physicians and scientists, everyone loves to talk about sensitivity and specificity. As I used to teach residents both at Northwestern and Stanford, I always said that sensitivity and specificity work after-the-fact statistics. You do a study and you look back and say, "What was the sensitivity and specificity?" But as a physician, you get a lab report; you're looking at a number and a test result. What is going through your mind and what you're saying is, "What are the chances of that being positive?" Or, "What are the chances of that being negative?" What your mind is doing is [considering] positive predictive value and negative predictive value.

Dr. Bruce Patterson 13:26
Having a negative predictive value for long COVID of 98%, we can say, "Who doesn't have long COVID?" And you know what? In the days of all this inflammation and the major symptom being fatigue, it's almost as important to say, "Who doesn't have long COVID?" as it is to say, "Who does have long COVID?"—because as you say, the treatment is subtly different. We had this other discovery, which showed that all four of those chronic inflammatory conditions have vascular inflammation at their heart. But there are also subtle differences and subtle changes in this drug combination that we just submitted to the FDA for our clinical trial.

Dr. Jill 14:18

Hey, everybody. I just stopped by to let you know that my new book, *Unexpected: Finding Resilience through Functional Medicine, Science, and Faith*, is now available for order wherever you purchase books. In this book, I share my own journey of overcoming a life-threatening illness and the tools, tips, tricks, hope, and resilience I found along the way. This book includes practical advice for things like cancer and Crohn's disease and other autoimmune conditions, infections like Lyme or Epstein-Barr, and mold- and biotoxin-related illnesses. What I really hope is that as you read this book, you find transformational wisdom for health and healing. If you want to get your own copy, stop by ReadUnexpected.com. There, you can also collect your free bonuses. So grab your copy today and begin your own transformational journey through functional medicine and finding resilience.

Dr. Jill 15:17
Gosh, there's so much I want to cover here. First of all, just for those listening, what you're talking about is the innate immune system, which I've been dealing with for decades with mold and Lyme and complex chronic illness. Most of our patients have had some things like that or know someone who has. Many of our physicians who listen treat these conditions, so a lot of our listeners are going to be aware of that. But just to frame it, this is this arm of the immune system, like you said, that's the first activator or first responder that maybe doesn't have antibodies already made or those kinds of things. It's typically cytokine-driven. It's like the activation of our own systems and cytokines are killing us because they're in this cycle of activation.

Dr. Bruce Patterson 16:01
Right. It's an imperfect system and it's just trying to do something. My colleague, Joe [inaudible], always talks about damaging immunity. The reality is, yes, some of these inflammatory products that are indeed trying to help clear up a virus, clear up a bacterium, or otherwise are tissue damaging. IL-6 and TNF-α are two great examples. Our February paper showed that TNF-α is the major driver of fatigue. If anyone remembers, with acute COVID, fatigue and respiratory symptoms were the major findings. But when you looked at the pathology more closely, it was blood vessel inflammation. What was happening was that these activated non-classical monocytes and macrophages, where we later found the S1 protein months after infection, bind to blood vessels through the fractalkine/fractalkine receptor.

Dr. Bruce Patterson 17:16
One of the reasons we use statins is because they decrease fractalkine so they don't bind the pro-inflammatory white blood cells to your blood vessels and cause endotheliitis. The other thing is that maraviroc, the CCR5 antagonist, is elegant in the immune system because it does two things: It restricts the migration of inflammatory cells all over your body, including through your blood-brain barrier; it also repolarizes monocytes and macrophages away from that pro-inflammatory phenotype, where it's making interleukin 6 and TNF-α. This drug combination we use is exquisite in terms of targeting the pathways that are underlying the symptoms in long COVID, long Lyme, ME/CFS. That's driven by the fact that the blood vessels are inflamed and dilated. What do dilated blood vessels do? [They cause] headaches, migraines, brain fog, and tinnitus.

Dr. Jill 18:19
Post-exertional fatigue.

Dr. Bruce Patterson 18:24
Hot and cold sensitivity. I can't tell you how many times on telemedicine I've seen a patient come on with a blanket over their shoulders because they're so cold. Temperature regulation is just completely thrown off. And that's my window into their blood vessels before I even look at their lab report.

Dr. Jill 18:46
That makes so much sense. Because of your research, I've been talking to patients, [mentioning] that COVID is like a disease of the endothelium, which is what you're saying. At the core, there's macrophage activation. Let's talk just briefly because one of the things you're testing in your panels as well is the retention of the spike protein in these atypical macrophages. Part of the problem is that they become activated, and then they go. Do you want to talk just a little bit about what happens in the macrophages with that spike protein?

Dr. Bruce Patterson 19:16
Flashback to 2020. [inaudible] 158-file marker panel. We used it on acute COVID, and we followed these patients: 30 days, 60 days, 90 days. In 90 days, a lot of them got better. They were home. But by no stretch of the imagination was their immune system the same. It was abnormal, but it was abnormal in a very different way than in acute COVID. That's where we used machine learning and AI to say, "How is it different? Why is it different?" That's where we found this signature for the long

COVID. The Long Hauler Index is interleukin 2 plus interferon-gamma divided by CCl4.

Dr. Bruce Patterson 20:07
If you look at literature from the early 2000s [on] atherosclerosis, when non-classical monocytes bind to blood vessels and migrate into the blood vessels, what's liberated are type 1 cytokines, interleukin 2, and interferon-gamma. It happens to be the numerator of our Long Hauler Index, which was found by machine-learning in AI 20-something years later.

Dr. Jill 20:36
Wow! Unbelievable. Also, I've heard you speak multiple times about this triad of vascular inflammation with the sCD40L, the CCL5/RANTES, and then the VEGF. Are those the three? Can you tell me about those and what pattern you've seen with that triad?

Dr. Bruce Patterson 20:54
That was very helpful because the first protein of the thrombotic pathway and blood vessels is sCD40L. CCL5 and VEGF—

Dr. Jill 21:02
That's like the instigator. You know the macrophages have activated the endothelium if that is elevated. Do you see the timeline as well? Do you see that up first and then the rest of them follow over time?

Dr. Bruce Patterson 21:14
Usually, by the time the patients come to us, they've had long COVID for three months or 18 months. I just had a patient; she had it for three years. It was an unbelievable telemedicine session a couple of days ago that, after eight weeks of therapy, she was 95% back to normal after having suffered for three years. These stories are almost daily during our telemedicine of patients getting better. The reason is that we're treating the underlying cause and we're not treating [inaudible]. Anyway, these macrophages bind to the blood vessels.

Dr. Jill 22:02
Let me just be clear for those listening—because a lot of people think the virus is still around—the virus is long gone, correct? This is not about the virus retaining its fragments and then activating the immune system. Is that right?

Dr. Bruce Patterson 22:12
That's been debated [inaudible]. It's an RNA virus. You don't expect it to be around for a long time. It doesn't have the latency machinery that the chronic herpes family viruses have. We were the only ones who'd done whole-genome sequencing of the entire SARS-CoV-2 genome. We did that in the non-classical monocytes when we published that two years ago. Then we looked into the tissues of long COVID patients before all these reinfections were going on. We found fragments just like we found in monocytes and macrophages. Those fragments represented less than 5% of the genome.

Dr. Bruce Patterson 23:04
My point is that you can't build a building with 5% of the bricks. And all the techniques that they're using to say, "There's viral persistence in tissue," which I believe… We published it. There's the persistence of fragments of RNA and the persistence of protein S1 in the non-classical monocytes. But at the end of the day, they're all using techniques like droplet digital PCR, very short fragments, or in situ hybridization, [which are] short fragments. They're not doing whole-genome sequencing. And it's a big stretch. I keep saying this over and over again: We can talk about persistence; I love talking about persistence. But it's the persistence of fragments or, as [inaudible] said, "viral debris." I love that. But the fact is, there's a huge difference between persistence and replication competence.

Dr. Jill 24:04
Yes. It makes sense to me. Even on a microbiome level, we know fragments like LPS cause a massive immune response. We can have fragments of viral particles that cause an immune response, which is very different from the virus continuing to replicate.

Dr. Bruce Patterson 24:20
And the Paxlovid trial failed at several universities for long COVID. The reason is that there isn't any viral replication, except for the caveat. We published this in 2021: We found viral replication out to 87 days in one long COVID patient who had very low CD8 counts—at three months, which is the cutoff for long COVID. I'll always admit that if you're at three months or four months of long COVID, yes, there could be viral replication. But when you're talking [about] 6, 12, 18 months, or three years, you're not going to see it. I'm still waiting for that paper that says,

"Whole-genome sequencing reveals alpha variant RNA in long COVID patient three years after infection." I haven't seen it and it's not coming.

Dr. Jill 25:20
That makes sense. I've been doing 20 years of chronic fatigue, fibromyalgia, long Lyme, and all those things before COVID and we've been seeing these immune dysfunction activations. And the same question has been [raised] in the Lyme community. Yes, we know these spirochetes persist, but is it truly that infection, or is it the immune response that's creating inflammation? I agree. I think more and more we're determining it's this long immune response and a dysfunctional and weakened immune system that's more likely to be part of the culprit than just purely the infection.

Dr. Bruce Patterson 25:52
Absolutely. I brought that question to the Lyme community. Articles show the cell wall peptidoglycan in the arthritic joints of patients with Lyme [disease] or arthritis. I'm like, "Those are just setups for phagocytosis by monocyte-macrophage lineage cells and persistent presentation to the immune system." That would be another mechanism for post-treatment Lyme disease, chronic Lyme disease, whatever you want to call it, where your refractory antibiotics... That's where we come into play because we found the blood vessel inflammation in chronic Lyme.

Dr. Jill 26:35
Yes. And you kind of alluded to it, but I want to be clear for those listening. First of all, you can determine, through the Long Hauler Index, the likelihood. And what are the percentages of sensitivity and specificity of how accurate that test is? This is the Long Hauler panel, the Cytokine 14 panel, through your lab. Tell us a little bit about that and the specific cytokines and patterns.

Dr. Bruce Patterson 27:02
Like I said, machine learning in AI brought our 158 panel down to 14. We're now using that in all of our machine learning for different immune conditions. Now we're getting a little bit into some of the autoimmune diseases, like Sjogren's and others. When I look at a panel, I look at several things. Number one, I look for the sCD40L, CCL5, and VEGF pattern of vascular inflammation. Undoubtedly, I'm going to find it. There are different [levels of] severity. Maybe they just have sCD40L, like you said, at the beginning or maybe there's a little bit of lingering VEGF. That's the

first thing I look for. The second thing I look for is the Long Hauler Index. Is it in the normal range or is it elevated?

Dr. Bruce Patterson 27:53
How elevated is important based on our new algorithms. When I start searching for Lyme patterns, my three bullet points are elevated interleukin 8 plus elevated interferon-gamma, elevated interleukin 13 plus elevated interferon-gamma, or a Long Hauler Index greater than 6.

Dr. Jill 28:16
Okay, that makes sense.

Dr. Bruce Patterson 28:17
If it's [inaudible], it's probably long COVID. If it's really high, I'm sending it off for Lyme testing.

Dr. Jill 28:27
I'm having this aha [moment] listening to you because I've been treating Bartonella, Babesia, and Borrelia forever. What I know about Bartonella in particular is that I'll use VEGF as a marker of activity. And I haven't because I haven't had access to your panel for that long. I've been regularly using the other vascular markers and some of the new stuff you just mentioned. But it makes sense because Bartonella in particular causes more vasculitis than any others. Again, I only knew about the VEGF, but this is making so much sense because what I was starting to see was my own little, tiny one-marker indicator of vasculitis, which is what you're seeing in different ways with COVID. We have the symptoms' buckets. It's the same for Lyme, long COVID, and chronic fatigue. And you're basically saying that now we can look at cytokine patterns and say which is which.

Dr. Bruce Patterson 29:21
Exactly. The latest in this is coming out in a new paper, which I should be sending off to a preprint server after the holidays. But we have a new Lyme index, much like the Long Hauler Index. The Lyme index, interestingly, in the numerator is TNF-α and interleukin [inaudible]. TNF-α, we published in February in our outcome study with treating long COVID patients. TNF-α and interleukin 2 are the major drivers of fatigue.

Dr. Jill 30:01
Now you can start to correlate which cytokines are a representation of those symptom

clusters, like migraines versus fatigue versus brain fog. It's fascinating. [inaudible] for a second, but did you say IL-2 and TNF-α are the two that are the most correlated with fatigue?

Dr. Bruce Patterson 30:18
Yes, it's in our February paper in *Frontiers in Medicine*. That was a 20-patient study: Maraviroc, statins, and long COVID. We did five different symptom scores: Fatigue, dysautonomia, neuro, cardiac, and shortness of breath, or dyspnea. Then we looked at our entire panel and looked at those biomarkers and how they would respond to 6 to 12 weeks of maraviroc and statins. We expected the fatigue score to go down and maybe even dysautonomia, because we've seen a correction of those symptoms. All five symptom scores went down with statistical significance. But most importantly, we didn't stop there; we told our biostatisticians to then correlate what symptoms correlated with reductions in what biomarkers. We closed that loop of infection-inflammation-symptoms-treatment, infection-inflammation-symptoms-treatment.

Dr. Bruce Patterson 31:28
I have not seen that circle closed for any other marker in any of these chronic diseases. Especially early on in long COVID, "Oh, there's this autoantibody and that autoantibody." My first question was, "Okay, what symptoms does it cause?" If you bring that autoantibody down with IVIg, for instance, do the symptoms get better? No one closed that circle. It was important for us to close that circle between biomarker, symptom, and treatment with a very targeted approach, with our two drugs at the actual proteins that are causing the symptoms—not the symptoms. For instance, here's a great example. This new paper comes out [on] serotonin. "We did this clinical study": "Long COVID patients are responding to Prozac because it elevates serotonin." Do you know what the most important thing is that lowers serotonin levels? Chronic inflammation. Cytokines lower serotonin levels, interleukin-1 beta, and TNF-α.

Dr. Jill 32:51
Yes. IL-6 too. All the studies on depression and IL-6, right? I don't know that that correlates with serotonin, but depression absolutely correlates in the studies with IL-6.

Dr. Bruce Patterson 33:01
I'm glad you mentioned them because, from a mental health aspect, among our

40,000+ patients, the amount of anxiety and depression is incredible. Their physician wants to throw them on this and that—this drug, that drug. But at the end of the day, when you resolve the inflammation, it goes away.

Dr. Jill 33:27
Yes, I've been known to say that I think that all depression and anxiety are organic in nature in the sense that there's some other cause for them. I shouldn't say all, because there are always exceptions—genetics and stuff. But I feel like more and more that toxic load, infectious burden, cytokines, and immune inflammation are at the root. I would say that with 80% of my clinical mood disorders and any sort of psychiatric diagnosis, frequently, if we get to that root cause, it's a game changer.

Dr. Bruce Patterson 33:54
It's amazing. I just read a paper the other day about dysautonomia and Lyme. All of a sudden, [with] long COVID, we opened this Pandora's box for these chronic inflammatory conditions. You know what? There were differences that allowed us to model that. But there are also a lot of similarities. You see anxiety and depression in chronic Lyme. All of this stuff is starting to come together under the rubric of an altered immune system and chronic inflammation.

Dr. Bruce Patterson 34:37
Here's another example: PANS/PANDAS. I probably have somewhere around 50 PANS/PANDAS patients. The classic was, "Let's immunosuppress them and then give them IVIg." The problem is that it's post infectious and you don't know if the infection is cleared. They always say PANS/PANDAS is from strep and recurrent strep. Well, you know what? I have a handful of PANS/PANDAS patients who all have a chronic herpes family virus that, when it reactivates, ticks the symptoms and everything gets worse. When you suppress the chronic herpes family viruses, it gets better. But the other thing we found in PANS/PANDAS, and the reason why I think it was hit or miss for IVIg treatment, was that there's a chronic inflammatory component that nobody had ever identified before. So just taking away autoantibodies wasn't doing it. It wasn't doing it because there's also pretty significant chronic inflammation. But when you treat chronic inflammation, for instance, with maraviroc and statins, and then you do IVIg at the same time, these kids are responding.

Dr. Jill 35:56
I love that. When you talk about IVIg, I have a lot of patients that are on that and they do well. But here's the deal: We think it's just the immune system, but the truth is, it has a very potent anti-inflammatory mechanism as well. The same with the statin; it's kind of an equivalent. We're thinking about this cholesterol issue. That's really the side note. It's really this anti-inflammatory. Maybe you could talk briefly—because you alluded to this—about statins. Your mechanism of action is much more directed to the endothelium. What is it that blocks exactly? You mentioned it earlier with the statins.

Dr. Bruce Patterson 36:26
There is a protein called fractalkine. It's made by [inaudible] cells. Believe it or not, these pro-inflammatory non-classical monocytes have a fractalkine receptor. To keep them from binding to the blood vessels and causing inflammation, let's down-regulate fractalkine. Well, statins down-regulate fractalkine. We don't use cholesterol-lowering doses of statin.

Dr. Jill 36:59
Yes. You use quite low doses, right?

Dr. Bruce Patterson 37:01
[inaudible] I'm like, "No, we're not giving you massive doses of statins for the rest of your life." It's 6–12 weeks with a quarter of the dose that you would give for cholesterol lowering. It's just an exquisite anti-vascular inflammation agent. It's a great combination. We're making it into a single pill. Maraviroc and like I said, our RCT will…

Dr. Jill 37:29
Which statin did you choose for the trials?

Dr. Bruce Patterson 37:32
We chose atorvastatin. The reason was that when I was treating kids with long COVID, they responded so well. I would say 6–12 weeks—people with more neurologic symptoms maybe even longer than 12 weeks. But [for] kids, some [with] as little as four weeks [of treatment], and they're better—they're completely better. Four to eight weeks is about the standard for kids, because they probably don't have a lot of other comorbidities. But I was using atorvastatin because there are studies

published on the safety of atorvastatin in kids. They were getting better faster, so then I started to use atorvastatin for adults.

Dr. Jill 38:18
Would sCD40L be the main marker of that fractalkine inactivation or is there any correlation with one of your cytokines with knowing that the...

Dr. Bruce Patterson 38:31
I wish we had fractalkine [inaudible].

Dr. Jill 38:32
Right. That's what I'm wondering. How do we know for sure?—even though we can understand the mechanism and see that. Is it that triad that you mentioned before?

Dr. Bruce Patterson 38:38
That's right. Yes.

Dr. Jill 38:41
So the sCD40L, the VEGF, and the CCL5/RANTES.

Dr. Bruce Patterson 38:45
[inaudible]

Dr. Jill 38:48
Okay, got it. In that way, you know if someone has those high, it's very likely they have the fractalkine and the atypical macrophages. I suppose it could be another mechanism besides long COVID, but that mechanism is absolutely involved in most long COVID, right?

Dr. Bruce Patterson 39:04
Absolutely. It's also involved in chronic Lyme, ME/CFS, and maybe many others. We've had some significant success with Sjogren's syndrome.

Dr. Jill 39:20
Yes, I've been seeing that too. Let me take the jump here because I'm in this functional world and seeing the diagnoses. POTS dysautonomia is at an all-time high for all of these underlying reasons. Is that because of the vascular inflammation? Is that usually the link to POTS?

Dr. Bruce Patterson 39:37
Yes. When blood vessels are inflamed, they dilate. When they dilate, your blood pressure goes down. When your blood pressure goes down, your heart rate goes up. It's classic physiology. The other thing is that I've seen infiltrates of the inflammatory cells around the vagus nerve.

Dr. Jill 40:00
Yes. We're going after these vagal nerve stimulators, which is a nice idea, but I'm like, "That's not going to fix the root cause," right?

Dr. Bruce Patterson 40:09
There's so much out there on what works, but most of them are very transient. [inaudible], vagus nerve stimulation. There's this microclot stuff for a while. I'm not a big supporter of that because the anticoagulants aren't working. We tried Plavix a year or two ago with all of our protocols, and it wasn't adding anything. Microclots are difficult to look at. I've seen pictures of microclots, and as a pathologist, I said that those look like epithelial-mesenchymal transition cells or EMTs.

Dr. Jill 40:58
You can hardly even tell under a microscope, huh?

Dr. Bruce Patterson 41:03
Yes, don't give me a microscope because [inaudible]. These EMTs are formed when there's tissue damage. Of course, if there's an acute COVID—

Dr. Jill 41:16
That makes so much sense, because at the core, our immune systems are damaging the endothelium, and that's this whole cascade. The only reason the clots happen is because it's our repair mechanism trying to repair the damage to the endothelium. So it's doing what it's supposed to do, but of course, in the...

Dr. Bruce Patterson 41:34
Absolutely. Then these epithelial cells fuse with macrophages and cause an EMT. Do you know what they express? CCL5 and CCR5. Then they migrate to areas of inflammation.

Dr. Jill 41:41
Are macrophages expressing VEGF, or is that just a signal to get more blood flow?

Dr. Bruce Patterson 41:58
They express VEGF. That's why when you talk about the tumor microenvironment in tumors, and the inflammatory infiltrates that come into the tumor microenvironment, you're talking about producing high levels of VEGF, which allows the tumors to increase their blood supply. And do you know what directly decreases VEGF? Maraviroc. [inaudible] All of this is just exquisite. As I was sitting there in a hotel room in China, I was thinking about the cancer literature and our work on cancer and CCR5. I initially started with some of the early trials of maraviroc, vicriviroc, and others in the early 2000s for HIV. But then we started talking about this more exquisite role in the immune system, basically as the quarterback. It's telling the immune system's cells where to go and when to go. It can be both good and bad.

Dr. Bruce Patterson 43:07
It's our job to exploit the good aspects of it. The bottom line is that it's not immunosuppressive. Everyone is throwing people on steroids. Yet again, another long COVID paper in *Nature* with low cortisol. I'm like, "Because everybody's on steroids." Steroids and LDN. It's like a reflex: "Here's your LDN. Here's your steroids."

Dr. Jill 43:36
We're not going to the root. In my world, if I could, I'd love to use curcumin, lumbrokinase, or any of these things. Is there anything that you've seen that has any effect even remotely close to the medications that you've been successful with that are in the realm of natural agents?

Dr. Bruce Patterson 43:55
It's a good question. Patients come in with lists of those agents. My first question is: How's that going? But you know what? All kidding aside, we've looked at some of these agents with our panel. We have a non-subjective means to test anything and everything for its anti-inflammatory activity that would contribute to improvement in the pathology. It's hard to say. I typically tell patients: "Don't stop. You don't have to stop." It's neither here nor there. But the only one I talk about is turmeric, because turmeric, for some reason, increases blood levels of maraviroc.

Dr. Jill 44:50
Interesting. So that's a nice synergistic effect. That makes wonderful sense. One other question that I know people are thinking [about]—because we talked about mast cell activation and it's obviously connected—is this because we get cytokine activation, mast cells are part of our immune system and they're becoming activated and prostaglandins and histamine are part of this? Can you correlate how that fits in at all, if anything, with the whole idea of mast cell activation?

Dr. Bruce Patterson 45:15
Having been in long COVID [research] for so long and [seeing] some of the early theories, mast cell activation was one of them. People took various agents. They weren't that effective. To me, if there was a lot of mast cell activation, I'd see elevated interleukin 13 in everybody.

Dr. Jill 45:41
And you did say that just with long Lyme, that was one of the patterns with… Was it IFN-γ and interleukin [inaudible]?

Dr. Bruce Patterson 45:49
[inaudible]

Dr. Jill 45:50
Okay. Maybe in that particular subset, there's more mast cells than not. Fascinating. What is the future? You and your lab are doing some incredible work. This is a game-changer for those of us out in the field practicing medicine. What do you see for the future? What things are going to be coming out? What's next?

Dr. Bruce Patterson 46:12
We've had so much good news, especially in this last quarter of the year. Number one, we're seeing broad reimbursement [inaudible]. That makes us extremely happy. Now it's not just a long COVID test. Originally, we were coding it as long COVID. But the fact is, now that we have the new algorithms to detect chronic Lyme and have suggestions for ME/CFS, I presented at this meeting about a month ago that there may be five different immunotypes based on cytokine profiles that we discovered for ME/CFS. There may be five flavors at a minimum, immunologically. We all know that it's very heterogeneous. We don't know what the underlying cause is. But we're starting to map that out on an immune profile level so that we can use

targeted therapy and ME/CFS, which are independent of a virus, bacteria, or whatever could be causing it.

Dr. Jill 47:27
That's exciting because I think sometimes the toxic load and infectious burden, which I'm dealing with on this level, [make] it so hard to determine exactly what. But if we can go straight to the immune system and say, "This is what's happening," and we know what to target, it does matter but it almost doesn't matter what the original cause was.

Dr. Bruce Patterson 47:42
Right. I tell that to people frequently. At the end of the day, my initial thoughts are, "I don't care what's causing this, because the immune abnormalities are causing your symptoms, and I'm going to take care of those." So coming up at the end of the year is reimbursement for the test, which is very, very exciting. The fact that we now have these patterns that separate and define long COVID, Lyme, ME/CFS, and even fibromyalgia is all very exciting so that we can treat them because they are treated differently. Then, most importantly, great work by my team at IncellDx in getting our trial design for maraviroc and statins and long COVID. [With] all of that written up, all the additional information, all of it's been submitted to the FDA. We're excited that 2024 will get our trial underway and hopefully, at some point, get approval. The good news is they're already approved drugs, so it's a different pathway where we're looking at efficacy as a major focus. It's going to be an exciting year. It's all been springboarded by the use of this diagnostic in chronic inflammation. It's resulted in great patient outcomes. And that's the thing that gets me.

Dr. Bruce Patterson 49:32
I've gotten letters, calls, and everything. This one girl, who is 12 years old, wrote me a letter on colored paper with colored pencils: "Thank you, Dr. Patterson, for making me better." You get one of those and you're like, "Okay, all that work" that for me started in the late 80s in viruses "was all worth it."

Dr. Jill 50:00
I love that! And that's such a great way to end here because, truly, that's why you and I do what we do—to see the patient's faces and see a change in their health. That's the reason I get up every day and I know for you too. And it's a long road sometimes. But I just want to say that I've been in this role for a long time in my

little, tiny window of functional medicine as an MD, but I see the value. And to me, not only this conversation, this podcast, and all the work that you do are profound. This is a game-changer. If you're listening, you just listened to history being made, and it's going to continue for you if you stay tuned to the studies that Bruce Patterson's work and group are putting out.

Dr. Jill 50:40
I just want to say, on behalf of all physicians out there like me, thank you truly because this is the kind of game changer and these are kind of those pivotal moments, like when the cell danger response came out and we understood that and some of these things are always game changers. Thank you. Thank you. Thank you for your work. Where can people find your work, your information, and the lab? Give us some websites, places, and resources where they can find you. And we'll list these if you're listening or you're driving. We'll list them everywhere this podcast is shown.

Dr. Bruce Patterson 51:07
www.CovidLongHaulers.com is the best place to get a hold of us or me. It's a functional website. We're about to launch a physicians' link so they can order the test directly for their patients. That's where all of our publications, talks, etc. reside. Of course, if you search on YouTube with my name and long COVID, you'll probably find just about everything we've ever talked about.

Dr. Jill 51:48
Thank you, as always. We're recording around the holidays so thank you as always. Once again, here you are, taking time very close to the holidays to share this great information. Truly, from the bottom of my heart, thank you for your work. Thank you for your intelligence, genius, and curiosity. I hope I can continue to support the work that you're doing.

Dr. Bruce Patterson 52:06
Thank you.