Dr. Jill

Your Functional Medicine Expert®

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#102: Dr. Jill interviews Bob Miller on Genetics of Platelet Activation and the RANTES Pathway

Dr. Jill 0:13

Hello, everybody! You are in for a special treat today. I know you hear me say that a lot, but today is extra special because we're going to go down some really fascinating pathways. Bob is going to share some of the latest research on RANTES and platelet activation. You know Bob from some of my other interviews. I will actually formally introduce him once again in just a minute or two.

Dr. Jill 0:34

But first some housekeeping. If you want more information, you can visit my website, jillcarnahan.com. We literally have 10 years of almost weekly articles. So, loads and loads and loads of information. They're all free for you to read, peruse, and share with your friends, family, or, if you're a physician, with your patients. Sometimes I get other doctors who say, "Can I use your blogs as handouts?" I don't mind that you share those. I love it; I love the information. For me, just like Bob today, I know one of our passions in life is bringing great information. We actually get a thrill out of studying and learning. So we're the weirdos; we're the nerds. I was the nerd in my class that really loved to read and study and learn. So here you are, two nerds today going on platelet activation. I'm super excited.

Dr. Jill 1:19

If you want products—sometimes we talk about products and services—you can find all of those at drjillhealth.com. As you well know, we have over a hundred episodes on YouTube. You can subscribe there, and actually, if you do, that would help me out. Give me a review. Or you can find us on audio anywhere you listen to podcasts—Stitcher, iTunes, and Spotify—you name it. You can find all of our episodes there.

Dr. Jill 1:43

We'll try to make this friendly for those listening, Bob, if there's some slide. We're going to do slides, which I know you all love to see, but we'll try to read a few little details, so if you're just listening by audio and not seeing the video, you'll maybe be able to follow along as well.

Dr. Jill 1:56

Now, just a warning: We're going to dive deep; we like to go deep into the physiology. So don't worry if it's over your head; there will be some takeaway points. Bob is so good at bringing about the basics. I know a lot of other doctors, practitioners, and healthcare professionals listen to us on this podcast. So for those of you who want to go deep, you're going to go deep today.

Dr. Jill 2:16

So, let me introduce my friend Bob. I have to tell you a funny story. You may have heard me say this before. But one day, I was texting Bob, getting ready for our interview. I just audio-texted like we do, and it said, "Hey babe, when are we getting on?" So then, the last time we had a conference—I sometimes get the honor of introducing Bob—I told the whole audience, "Babe; his nickname is babe." So, hey, babe! Good morning, and it's great to see you today. Then the whole audience at the conference—I think you got a lot of "hey, babe!" Right Bob?

Bob Miller 2:46

I did.

Dr. Jill 2:49

So we love to joke and laugh about that. That was very funny, and the name has stuck a little bit. So sometimes that's how Siri goes. Anyway, without further ado, Bob Miller is a traditional naturopath specializing in the field of genetic-specific nutrition. He has earned his naturopathic degree at Trinity School of Natural Health and is board certified through the ANMA. In '93, he opened Tree of Life Practice and served as a traditional naturopath for 25 years. For the past several years, he has been exclusively engaged with nutritional genetic variants and related research, specializing in nutritional support for those with chronic Lyme disease, and as we'll talk about today, many other chronic infections and toxic triggers.

Dr. Jill 3:30

Bob, I just want to say that I always love having you on because it stimulates my learning; I learn new things. We go back and forth, and often we'd be like, "Oh, I'm seeing this in practice. Do you think this relates?" So literally, in real-time, I feel like we're often making great discoveries. I feel like one of the things you're leading us with is your background and pathways. You can really pull these together. You've got a team of researchers doing a lot of the work as well. I just love how you pulled this together.

Dr. Jill 3:56

If any of you know about research, I just talked to a patient the other day who had a mold litigation case, and he was talking about how in the legal system he is trying to prove that his daughter was sick from mold. And it's almost impossible because what happens is that the standard of care in medicine right now is 20 years old. So what we're doing in medicine right now as the standard is very, very old as far as the research. What you and I are doing, and what we love to do, is pushing the envelope, getting the research out there. What happens is, just like I talked about to my patient, he brought up all kinds of studies about toxicity and health. And he could prove it because the research was up-to-date with what he was seeing in his daughter. But when he came to the court of law, he was trying to prove: What does medicine say?

Dr. Jill 4:38

Sadly, while I love allopathic medicine, what medicine says is very delayed. So the research right now, in 20 or 30 years, might be the standard of care. What I love about framing this conversation is that we are on the cutting, bleeding edge of: What does the data show about pathways? And we're actually saying, "Could this be part of the issue?" We're not saying that we have a for-sure drug or supplement that's been studied for 20 years, but we're saying, "Looking at these pathways, this makes sense, and this may be contributing." And I love being on the cutting edge because what I see, Bob, and I know you do too, are miracles because we're pushing the envelope and doing things that we feel are very safe with patients—[things] that might be brand new. We're making a difference.

Dr. Jill 5:19

I love being here with you because I know some of the information, especially today, is going to be on the cutting edge for these complex chronic conditions. We've been seeing infections and toxins for decades. I've been doing this for 20 years. This is not new. But the pandemic has really accentuated the need for lenses to view infections and toxins. Especially because this pandemic/infection affected so many, many more people than maybe Lyme disease, all of a sudden, we're seeing on a new level, the patients who need our help. So, without further ado, I'm going to let you share your screen and dive right in.

Dr. Jill 5:55

Oh, sorry! One more thing, because I pulled an article. I was reading this last week, and I talked to one of my friends. We had a game night the other night, and the talk

was on blood viscosity. Can you imagine? At Dr. Jill's house, game night is all about: What else is new in the world? So this article was talking about how the thickness of the blood has a lot to do with morbidity and mortality—meaning: Cause of illness and death, and symptoms. We know that there's an effect with COVID on this, and we've known for decades that there's an effect with other viruses, other infections, and toxins. And today we're specifically talking about the RANTES pathway and platelet activation. This all has to do with the thickness of your blood. And if you don't think that's relevant, think again, because we're going to show you some amazing evidence.

Dr. Jill 06:38

I read in this article—this was profound—that over the age of 60, our blood viscosity, regardless of infection or toxin, exponentially increases. That's part of the increased risk of stroke, heart attack, and all these [other] things. So, I feel like in my expertise right now, this area of learning is going to be one of the most profound things that change how I practice medicine. So, go ahead and show us your slides, Bob, and let's dive right in.

Bob Miller 07:06

Okay, let's get to it, and thank you for that introduction. It is always so much fun to be here with you, Dr. Jill. I am so excited to present this because it's mind-boggling, what we're going to look at. And, of course, you always mention that this is educational information only; we're not practicing medicine or telling anyone how to diagnose or treat any disease.

Bob Miller 07:28

I think people have seen this slide before, but I plugged it in again—the "Platelet Activation," "The Three-D Chess Game Played Underwater"—because there are so many factors that play together with this. So, we're going to be talking today about platelet activation and aggregation. So, I found this cool little chart. So let's talk first about what platelets are—what a miracle they are. They float around in our blood, and they are just kind of there. If we ever get a cut or a wound, they go from a resting platelet, they get activated, and then they become aggregated, where they clot. They're your friends because they keep you from bleeding to death or losing all your blood.

Bob Miller 08:11

So, Dr. Jill, in every interview we've done here, we've talked about how many of the things we're talking about are helpful unless they're excessive. That theme just keeps coming up for us. And the same way with your blood clotting—without this,

with the least little cut, you'll bleed to death. [If it's] excessive [on the other hand], that's where you get the blood clots, and then you're more prone to heart attacks and strokes.

Dr. Jill 08:35

Bob, just on that line, what I'm seeing in clinical practice, I'm actually starting to test patients for coagulation deficits in the blood—a huge panel. What's interesting in most of them who have issues [is that] they have not only bleeding issues but clotting issues, both at the same time. So, this is very relevant because it's the Goldilocks [scenario]. You can have some severe issues and you can actually be [both] hypercoagulable and hypercoagulable, meaning you can clog easily but also bleed easily at the same time—there are different pathways.

Bob Miller 09:02

Interesting! All right, here's some blood clot 101. I think most people know this, but [I'll mention it] just in case they don't. It's a mass of blood that forms when platelets, proteins, and cells stick together. And then, as we said, your body forms a blood clot to stop the bleeding. Then, your body usually breaks [it] down and removes the clot. But sometimes they form where they shouldn't, your body makes too many, or the blood clots don't break down like they should. This can cause health problems for us. They can form and travel to the blood vessels in the limbs, lungs, brain, heart, and kidneys. [They can cause] deep vein thrombosis—I'm sure people have heard about that. Pulmonary embolism—it's another problem. Or they can affect ischemic stroke, heart attack, kidney problems, kidney failure, and pregnancy-related problems.

Bob Miller 09:51

Here's an article. We always like to say that everything we talk about is [based on] peer-reviewed studies. This talks about arterial hyper-coagulability as a cause of stroke in adults. Now, this I found very fascinating: The "deadly type of stroke increasing among younger and middle-aged adults." This was just published, as you can see here, on February 4th of this year. This was in the American Heart Association journal, Stroke. It said, "New cases of debilitating and often deadly type of stroke that causes bleeding in the brain have been increasing in the U.S., growing at an even faster rate among younger to middle-aged adults than older ones… an 11% increase over the past decade." Again, it was just published in the journal. So something is going on that is causing this to occur.

Bob Miller 10:43

I'll be honest; this is an area we're just starting to research. Until I started digging into this, I had no idea that platelets carried serotonin. Fascinating! "Platelets transport serotonin at a high concentration in dense granules and release it upon activation. Besides the clotting, serotonin influences a variety of immune functions." Fascinating! "Serotonin levels are elevated in autoimmune diseases such as asthma, RA (rheumatoid arthritis), and during tissue regeneration after ischemia. Specific antagonism of serotonin receptors appears to improve survival after a heart attack or sepsis." And they're saying, in conclusion, "targeting immune modulatory effects of platelet serotonin may provide novel therapeutic options for common health problems."

Bob Miller 11:37

So, I was really stunned by this—that your platelets carry serotonin. We don't quite yet understand the relationship between that and serotonin in the brain, it's very complex. I just had a conversation recently with a psychiatrist who said it's now believed that the SSRIs are somehow impacting this and helping it in some ways. So it's absolutely fascinating!

Dr. Jill 12:00

Bob, I have a comment on that because fluvoxamine, which has been used at times for long COVID—I won't go into the details of that—but I looked at several articles and it has to do with the heme oxygenase, which you'll talk about today, I'm sure. And these have to be heme oxygenase agonists, I believe. I may be saying that wrong. But there's a correlation, especially with that particular SSRI and heme oxygenase. So, let's make a note, and when we talk about that later, it may come into play.

Bob Miller 12:30

Yes, absolutely! Now, platelets do not synthesize serotonin, but they acquire it from specialized cells in the GI tract. However, the serotonin secreted from platelets may have a role in platelet aggregation and therefore clot formation. And serotonin may have vasoconstrictive properties. I used to always think of serotonin as the happy thing for the brain, but it's much more than that. Elevated plasma levels of serotonin have been found in hypertension and thrombosis. So there's a lot to learn on this. We could probably do a half-hour to 45-minute talk on that someday, but for right now we're just hitting the highlights here.

Bob Miller 13:09

Now, here's what we're going to talk about today. So [I'll repeat] that old adage: "We're going to tell you what we're going to tell you, then tell you, then tell you what we told you." So, this is a map, and just for those who are new to this, these purple ovals are enzymes. Your DNA makes the enzymes. We can have what are called genetic mutations, or SNPs, where that enzyme is most of the time underactive but sometimes overactive. What a miracle we are! Here's an enzyme called TNF-α (tumor necrosis factor) and this is the first time we've spoken about this in our many interviews. I think this is, what, number eight or nine?—I believe, Dr. Jill.

Dr. Jill 13:55

Yes, if you want to listen to any of those, they're all on YouTube. We've got some great ones!

Bob Miller 14:00

So, tumor necrosis factor kicks in perhaps when we have some mycotoxins or clostridium, even Bartonella, and any source of lipopolysaccharides—gram-negative bacteria. They stimulate tumor necrosis factor. Is that a good thing? Sure—if anybody's listened to us before, you know what the next sentence is—unless it's overactive. Interestingly, you can have a genetic mutation on TNF-α that makes it over-respond.

Bob Miller 14:33

I know we've spoken before about the HFE gene. When this is mutated, we can absorb a little bit more iron. When people get two copies of this, many times they have what's called hemochromatosis. But it is very common in the English, Irish, and Ashkenazi Jewish [populations] to have one copy of this, which causes you to absorb a little bit more iron and that also stimulates tumor necrosis factor-alpha. What we've been clinically observing in our health coaching is that when people have an upregulation of TNF-α and the HFE, many times these folks have lots of inflammation that no one can seem to resolve.

Dr. Jill 15:14

Bob, I know this well because I'm a carrier. I just want to mention, for those of you listening, that this is something you can ask your doctor to test. You can test for iron and do iron studies. I always recommend that. I test that in all my patients, just to check if there's an iron excess in the blood. But you can also ask for the hemochromatosis gene. It's a very easy test to perform—insurance may or may not cover it—and it will tell you if you're a carrier. And, of course, Bob, your genetics

will do the same. But if someone just wants to ask a regular doctor, hemochromatosis genetics are not difficult to order.

Bob Miller 15:45

Absolutely. It's very common in the English and the Irish. There's a funny story behind that. The reason the Irish came to America was because of potato famines. So, by natural selection, the women who had this gene absorbed more iron. That made them healthy enough to have babies during times of famine. Isn't that fascinating? So that stimulates NF-kappa B, which is another inflammatory enzyme. That stimulates NOX and NADPH oxidase. We did a whole recording on this.

Bob Miller 16:16

I'm going to talk a little bit about SIRT1 (Sirtuin 1), which calms these guys down. We did a whole show on Interleukin 6 (IL-6), and how that stimulates it. Now, something that's being talked about quite a bit is mast cells. Mast cells are white blood cells. Again, they're our friends. They're there to help us if we have an infection. But I'm sure anyone who's paying attention to the health situation now is constantly hearing about mast cell activation, where the mast cells are becoming excessive. When they become excessive, that's when they can be harmful. Dr. Jill, in your work, what percentage of your patients do you think have excess mast cell production?

Dr. Jill 17:01

Yes, Bob, I was going to comment because this is becoming a bigger and bigger issue. Now I see mostly complex chronic patients who have lime or mold or some other infectious load or chronic fatigue. I would say at least 50%, maybe [even] upwards of 70%, have mast cell issues as part of their clinical picture.

Bob Miller 17:20

Sure, and when you started, it was probably not seen very much at all.

Dr. Jill 17:24

No. In fact, I'll just tell you, 20 years ago, in medical school, we were taught about mastocytosis, which is a blood cell disorder in the bone marrow [that is] almost like a proliferative, pre-cancerous type of condition. That's considered a zebra, which means it's really rare. And we didn't even get taught about mast cell activation, which is more of a normal number of mast cells that are overactive. Now we know that environmental triggers, toxins, infections, etc.—some things we'll talk about

today—are triggers for those mast cells. The fact that I'm seeing more and more and more of that tells me our load of infections and toxins is getting really high in the environment.

Bob Miller 18:00

Absolutely. I should also mention that mercury induces NF-kappa B, COX2, and iNOS, and glyphosate stimulates NF-kappa B—that's a roundup. Then, of course, the mast cells make histamine. By the way, we did a whole show on histamine.

Bob Miller 18:17

Now, this is new information here, Dr. Jill. I would advise everybody to really watch the video we did on iNOS. We actually called it 'the Carnahan reaction,' where the iNOS enzyme, which makes a lot of nitric oxide to kill pathogens, gets upregulated. It gets upregulated when we have a virus, bacteria, or fungus, which is a good thing unless it is overactive.

Bob Miller 18:44

INOS inhibits eNOS—that's endothelial nitric oxide, which is circulatory. If anyone's ever heard of Raynaud's, that's where you have cold hands and feet or just circulatory problems in general. Many times, we don't have endothelial nitric oxide because the iNOS inhibits the eNOS. As we'll talk about later, there are genetic mutations that cause iNOS to be upregulated. We'll get to that later.

Dr. Jill 19:13

Bob, maybe if people didn't hear, I'll just do one minute or 30 seconds here. My story, which Bob helped me figure out, was that I always called Chaetomium, one of the molds that I had been exposed to in the past, the 'narcoleptic mold,' because when I'd get exposed to this mold, I'd literally pass out. I'd have to lie down; my blood pressure would be 85/55[mmHg]. I couldn't sustain an upright position.

Dr. Jill 19:36

I talked to Bob one day, and we were trying to figure out what might be going on, and he looked at my genetics. I happened to have a very rare combination of upregulated iNOS2. So, what was happening for me was massive vasodilation, almost like if you're in septic shock, where your circulation opens so wide that you can't get pressure to the brain when you're upright. So, we kind of figured that out, and thus the name.

Dr. Jill 19:59

I wanted to mention that at the same time with those symptoms, sometimes I would actually have cold hands or feet or achy legs, which indicated that iNOS3 was being downregulated, so it all made sense when we talked about it.

Bob Miller 20:11

Absolutely. I'm so glad we found that for you. As we said, that's why we call it 'the Carnahan reaction.' I have a couple of slides to explain it when we get there.

Bob Miller 20:21

Aluminum, mercury, uranium, plastics—I think someday we're going to look back and see a big 'oops!' over all the plastics in the way they're getting down into microparticles—electromagnetic fields, high fructose corn syrup, gluten, and glyphosate all stimulate the iNOS enzyme. I think some people are probably having an 'aha!' moment at this point because look at what iNOS does: It activates platelets, and eNOS will calm it down. So, remember that slide where we showed you how the platelets get activated. Then they create something called RANTES, and that's the next slide we're going to go over. So hold on to that term here—RANTES. That's really the crux of what we're talking about here today.

Bob Miller 21:08

So, that iNOS stimulates the platelets. On the other hand, when tumor necrosis factor gets upregulated, it will stimulate an enzyme called COX2. COX2 will cause the body to take arachidonic acid, which is one of the fats, and pull it out of the cell membrane and go down a pathway where it stimulates something called thromboxane A2. And once again, it stimulates and activates the platelets.

Bob Miller 21:42

Also, you'll notice up here: Peroxide and peroxynitrite. I think way earlier we did a video on peroxynitrite. We talked about EMF. The calmodium comes from EMF. Lipopolysaccharides[LPS], histamine, and mTOR—all of those stimulate the phospholipase A2 enzyme to pull out this arachidonic acid. So here's pathway number two which can stimulate platelets and RANTES.

Bob Miller 22:11

Now, pathway number three—we did a video where we talked about the Holmes Cycle on Interleukin 6. Again, interleukin 6 is a cytokine; it's our friend unless it's overactive. So you can have genetic mutations in IL-6 or you can have multiple

environmental factors that stimulate IL-6. I encourage you to watch our video on that. It stimulates superoxide. More mast cells, more histamine. Histamine stimulates RANTES; RANTES stimulates mast cells. We've got a little bit of a—

Dr. Jill 22:48

Vicious cycle, Bob—I'd call that—right?

Bob Miller 22:54

Absolutely. Then Superoxide, mast cells, and histamine stimulate what's called the renin-angiotensin system, where we make angiotensin II. That'll cause aldosterone, which can cause high blood pressure. But angiotensin II stimulates RANTES.

Bob Miller 23:17

Then finally, we all know the benefits of omega-3 fatty acids. Your fish oils—they're your good fats. And then you have your bad fats. There are enzymes called fatty acid desaturases and ELOVL2 that end up making something called protectins and resolvins, and they will inhibit that activation of the platelets.

Bob Miller 23:42

Now, we have slides and peer-reviewed studies. But, that is basically what we're going to tell you today; how environmental toxins combined with genetic weakness can cause this pathway to be upregulated. We can also have multiple things that can cause this pathway to be upregulated. And here in our clinic, we've been doing a lot of measuring of the Omega-3s. Also, here's a urine test that you can [use to] measure the thromboxane A2. Are you finding that? I'm sure you do look at some folks' Omega-3s and arachidonic acid. Finding those out of balance just a bit?

Dr. Jill 24:20

Yes. Thanks, I was going to mention that because, again, if you're listening, [it has] a practical application. You can get omega testing through Genova Diagnostics through Great Plains. And thromboxane A2, Bob, where can that be tested through the urine? Do you know what lab?

Bob Miller 24:36

Yes, we can maybe put that in one of the links. And I think people can go there on their own if they want. We'll put that in the link.

Dr. Jill 24:44

Yes, because if you haven't I'm going—I'm so sorry, Bob, go ahead. It's called what?

Bob Miller 24:50

It's called the chronic inflammation test.

Dr. Jill 24:53

Yes, we'll get the link. That way, we don't have to worry about it. So hang tight; we'll be sure and link those. But you can ask your doctor. You may need a functional doctor who understands this. But even Quest and Labcorp have omega panels, so this is not something that's outside the reach of a normal physician to order for you. And I was going to mention those protectins and resolvins, would that include SPMs and DHA? Okay.

Bob Miller 25:17

Yes, SPMs. Yes. There are two companies that make them, and they're getting quite a bit of attention in the functional medicine world—and we'll get to this. If this pathway doesn't work, you can just jump right down here and take the protectins and resolvins to calm things down.

Dr. Jill 25:32

I have seen that to be very powerful in either post-COVID or long COVID, and in myself. Now, of course, it makes sense why. So, SPMs. I'll put links to some of those brands in the chat here or if you're listening anywhere else as well.

Bob Miller 25:49

Sure, and if anyone would like this chart to study it, just go to www.nutrigeneticresearch.org/research —> 'Download'. We don't ask for your email; there's no charge, and there's no catch. You can download the pdf if you'd like to dig into this.

Bob Miller 26:04

All right! Now we're going to talk about RANTES. What an interesting name: "Regulated on Activation, Normal T Cell Expressed and Secreted." Wow, that's quite the name here! It's also called 'CCL5.' It's a pro-inflammatory mediator of the cytokine (CC) chemokine family. Here's the key point: It regulates the mobilization and survival of immune-inflammatory cells from the bloodstream into tissues and

other areas of injury and infection. Can that be a good thing? Sure. When it's excessive, can it be a bad thing? Of course. So here they're saying, "Sustained production… is associated with several detrimental effects, such as" heart disease, "liver disease, and viral infection… Treatments that interfere with RANTES are associated with improved outcomes."

Bob Miller 26:54

Now, there are many things that will stimulate RANTES. For our discussion today, we're looking at the platelets because the activated platelets stimulate the RANTES. As we said, look what RANTES stimulate; histamine secretion by mast cells, IgE and IgG production by lymphocytes, and activation and proliferation of the natural killer cells. It recruits T cells, macrophages, eosinophils, and basophils to sites of inflammation. Again, it's necessary for our survival but harmful in excess.

Bob Miller 27:28

Now, we're going to just go through these slides pretty quickly. We're not going to read them in any detail, but just so people understand what some medical literature says [regarding] what's related to RANTES. And, by the way, Dr. Jill, I think we're just scratching the surface. I just keyed [in on] a few things and found some things and I'm sure there's a whole lot more. For the liver, it mediates hepatic injury and promotes fibrosis. So, if somebody's got liver disease going on, RANTES in excess can be a problem.

Bob Miller 28:01

Autism spectrum disorder—in a study of young autistic patients, RANTES and other chemokines were shown to be higher when compared with typically developing children. And of course, the key word here is 'hypothesis.' [It's hypothesized] that altered chemokine levels are involved in autism spectrum disorder. I think it'd be inappropriate to say, "Yes, this is the issue." But it's probably one of the contributing factors. So, they're saying chemokine plasma levels could be potential biomarkers for autism.

Bob Miller 28:33

[RANTES and Inflammation]: [RANTES plays] a fundamental role in histamine and serotonin generation and cell function. This study was on eczema, and the RANTES played a role in the ongoing chronic inflammation of atopic eczema and reflected the severity of the disease. Heart disease. Chemokines, like RANTES, control the recruitment of leukocytes within the vascular wall, [which is] essential in the development of plaque formation. They did a little study. They took something that

knocked down RANTES and was shown to reduce the progression of heart disease. So, this study is saying, keyword, 'potentially' new therapeutic strategy.

Bob Miller 29:16

Inflammatory bowel disease; Crohn's disease. So, as you know, Dr. Jill, that's something that you were trying to figure out why you were struggling with it. And they're saying here that the frequency of the RANTES was greatest in severely inflamed tissue. And they were saying, significant redundancy in the generation of these [chemotactic] signals in chronic inflammation. It was infrequent in normal colon. So it appears to be higher in inflammatory bowel disease.

Bob Miller 29:49

Now, this is interesting, you spoke about COVID. In 10 terminally-ill critical COVID-19 patients, profound elevations of interleukin-6 and RANTES [were found]. This was like a trial. This [leronlimab] blocks the RANTES going into the receptor sites. They noticed a significant decrease in the COVID plasma virus after using that drug. So there is research going on, and there is a doctor, Dr. Bruce Patterson, who put out a paper. It's still not peer-reviewed yet; it's in preprint. But he's saying that COVID is really a RANTES disease. It's probably a little more complex than that, but it clearly seems to be elevated in people with COVID.

Bob Miller 30:39

Children with RSV infections have increased CCL5 protein levels in both the upper and lower airway secretions, and it correlates positively with the disease severity. Here, we're talking about prostate cancer. The RANTES seems to be elevated in prostate cancer as well. And here's just a little chart that shows we have obesity and too much adipose tissue. And then we get inflammation, heart disease, liver issues, and beta cell degeneration in the pancreas—RANTES being one of the players that causes all of that.

Bob Miller 31:18

Now, what are some things that stimulate RANTES? So what we're saying is that the platelets function as the cells that promote immunity and inflammation, but they do stimulate RANTES. So, if our platelets get too activated, they will stimulate RANTES. Lyme disease—this is one area that we'd like to study. I'm hoping to be able to get lots of people with Lyme disease to measure their RANTES. But they discovered that borrelia appears to be a strong inducer of those chemokines. As we know, some people get Lyme disease and they don't even know they have it. Others do one round of antibiotics, and they're fine. And others, for years, are dealing with all

the massive inflammation. They see the best doctors, they get the best antibiotics, they do all the herbal things, and they still continue to struggle. Those are the chronic Lyme individuals. One of the things we need to research is how much the stimulation of RANTES may be a factor. We don't know yet, but that's an area of research that we need to look at.

Bob Miller 32:35

RANTES stimulation is also related to NF-kappa B. The strength of RANTES has been shown to be highly dependent on the pre-existence of NF-kappa B. Also, iron has been shown to serve as a direct agonist, which means it stimulates NF-kappa B, tumor necrosis factor-alpha promoter activity, and the release of the TNF-α protein. So, once again, that iron in excess kicks this all off. And again, just clinically observing those who have mycotoxins, Lyme, upregulation of TNF-α, and over-absorption of iron, [they] are the ones that are just debilitated by their Lyme disease. I'm sure you see that as well. Some people have Lyme, and they're doing okay, and other people are really in seriously bad shape.

Dr. Jill 33:31

Yes, Bob. I couldn't agree more. And I've been watching that iron connection for a while, and I haven't always known all the pathways. I just know, gosh, if you have a carrier state or full-blown hemochromatosis, you're going to struggle more with inflammation and infections.

Bob Miller 33:45

Here we're just saying once again, mast cells produce histamine, and then the histamine enhances the production of RANTES. So we're just showing the literature that shows how the mast cells create histamine; the histamine then stimulates the RANTES. Interesting correlation. Until we dug into the literature, we had no idea these were connected.

Bob Miller 34:11

So, here again, mycotoxins or sources of lipopolysaccharides stimulate tumor necrosis factor and begin this cascade: Clostridia, Bartonella, lipopolysaccharides, mercury, and glyphosate. These [SNPs here] are some of the genetic mutations. The tumor necrosis factor mutation is a gain of function; HFE is a gain of function. And we're going to be talking about the sirtuins [which are] lowered function and IL-6 [which is] gain a function. So, the more environmental factors you have combined with genetic mutations, [the greater the] potential for this thing to take off and then, as we said, eventually stimulate the inducible nitric oxide synthase.

Bob Miller 34:58

Now we're going to talk a little bit about tumor necrosis factor, and down here is the RS number that, when it is mutated, causes it to have a gain of function. TNF-α is an inflammatory cytokine produced during acute inflammation and is responsible for a diverse range of signaling events within the cells, leading to necrosis or apoptosis. Is that a good thing? Sure, unless it's overactive. Increased TNF-α, along with other genetic and epigenetic factors, stimulates PLA-2. That's the one that brings out the arachidonic acid, which then stimulates thromboxane A2, thus leading to platelet activation and increased RANTES. On the other hand, NF-kappa B plays a variety of evolutionary roles.

Bob Miller 35:47

Cytokines belonging to the TNF family induce genes regulating inflammation, cell survival, and proliferation, primarily through activation of NF-kappa B. So, TNF-α stimulates NF-kB. And what we're finding is that when individuals have a homozygous variant here, these are individuals that are so inflamed—they're going from one clinic to another trying to find help—and they're not being very successful because this TNF-α is upregulated; it's over-responding.

Bob Miller 36:25

In response to lipopolysaccharides due to your gram-negative sepsis, the monocytes are triggered to produce large quantities of TNF-α. Several studies have identified the pathways that are activated by lipopolysaccharide, including NF-kappa B. So when you're exposed to these LPS, both of these get upregulated, and they're saying the concentration of RANTES has been shown to increase due to the addition of the TNF-α and the lipopolysaccharides [LPS]. So you can see how this thing just feeds upon itself.

Bob Miller 37:01

Now, we're going to talk about mold. This is a mold test. Ochratoxin—this many times comes from water-damaged buildings. It's very, very common. This is gliotoxin. Here's the peer-reviewed study. Ochratoxin is a natural fungal secondary metabolite and it triggers significant modulation of interleukin-2 (IL-2) and tumor necrosis factor-alpha (TNF-α). So, Dr. Jill, how common do you see mold toxicity in the people who come to you who are just really struggling and coming to you because they can't get help elsewhere?

Dr. Jill 37:35

Yes. So, Bob, this is a huge thing because a lot of people come—they might know that they have a diagnosis of borrelia, which is Lyme or Bartonella or some other gut issues. First of all, I'm always asking questions about mold, but if they're not getting better on what should be helpful, I always ask and test for mold because what I found is that many times that's the factor in their environment that's weakening their immune system and creating additional inflammation that has not been addressed. So I would say that very frequently, mold is this hidden factor that they don't know about that's [causing them to be at a] standstill with their health.

Bob Miller 38:09

Absolutely, it's rampant. Now, there are a couple of nutrients that inhibit TNF-α—there are probably going to be more, but we scoured the literature—black cumin, curcumin, quercetin, and milk thistle. All of those will calm down TNF-α.

Bob Miller 38:30

Now, SIRT1, I'm finding this to be very, very important. It's part of the sirtuins. And if you study longevity, one of the things they're looking at is the SIRT1s and how to preserve their activity. We're going to talk more about the SIRT1s. For right now, we're going to talk about how they inhibit NADPH oxidase and NF-kappa B. It's one of the most well-studied sirtuins. [It has] a significant role in development [and is often considered] a marker of cell senescence—when the cells die. It decreases during aging, likely due to NAD+ deficiency. Decreased levels are found in the aging liver.

Bob Miller 39:11

SIRT1 plays a critical role in MAO-A—I have another chart for this—AMPK, regulation of FOXO, a very important antioxidant called superoxide dismutase [SOD], then endothelial nitric oxide (NOS3) that we spoke about inhibits NOX, NF-kappa B, IGF-1, and mTOR, which stands for mammalian target of rapamycin, the growth of new cells. Is that important? Sure. When it's excessive, it creates problems because it inhibits what's called autophagy, the cleaning of the cells.

Bob Miller 39:49

We should probably spend more time on this, but high fructose corn syrup inhibits SIRT1. We've all known that these artificial sweeteners probably aren't that good for us, but when I learned that they inhibit SIRT1, it was like, "Oh my goodness, that's a big deal!"

Bob Miller 40:06

Resveratrol, quercetin, and caloric restriction may activate SIRT1 activity; that's your intermittent fasting. So, when we deprive the body of nutrients for a little while, mTOR, which is the growth of new cells, [essentially] says: "Hmm, I don't have any nutrients. Okay, janitors, come out and do your job." And then that supports SIRT1. And again, just observing in our health coaching, when people have mutations in SIRT1, particularly homozygous, they're really struggling.

Bob Miller 40:39

I'm not going to read all of this. This is way too much. But this just illustrates all of the ways that SIRT1 is helpful to us, and perhaps we can put a link to the slides or maybe a link to this if somebody really wants to read it. But we're not going to just go through and read all of this. But, the bottom line is that SIRT1 is really important for your long-term health.

Dr. Jill 41:03

And Bob, if I can just put it into layman's terms real quick because you did a great job of explaining mTOR and autophagy, but I want you, listeners, to understand that mTOR is stimulated by growth hormone and by peptides. A lot of bodybuilders use anabolic steroids, even testosterone or anything like that. There are a lot of people out there using these kinds of things to decrease body fat, increase muscle mass, and get into great shape. That's basically pushing the creation of new cells and new muscle—all good. But if you don't have autophagy—autophagy, as Bob said, is the cleanup that helps prevent cancer cells—we have cells all the time that are going rogue which could be causing rapid division. Anything in that realm will cause a proneness to cancer, so we need both.

Dr. Jill 41:51

We saw with COVID, people with higher testosterone on anabolic steroids, any of those realms that were pushing mTOR, had worse outcomes. In fact, some of the treatments were for the suppression of testosterone. So, I just wonder if that was related to SIRT1. And then you mentioned corn syrup. And, obviously, the standard American diet with lots of fast food and high fructose corn syrup, we know, metabolically, if people had metabolic syndrome, diabetes, or obesity, they also fared worse with COVID. Those two things make me wonder if it was related to the SIRT1 genetics here.

Bob Miller 42:23

Yes, I believe so. I've wondered the same thing. There is some literature out there that says that COVID uses mTOR for replication because mTOR replicates and is sort of like a copy machine. It doesn't matter what you put on the glass, it'll copy it—healthy cell, cancer cell, and possibly COVID. I observed that as well. Sometimes you'd hear about these young men who were dying while somebody 78 years old survived. And it's like, "Well, what's going on there?" I mean, there are many components to it, but that may be a factor.

Bob Miller 42:55

Now, I really like this slide. SIRT1 supports eNOS—remember, we talked about that earlier; endothelial nitric oxide—the healthy blood flow. It supports superoxide dismutase, a very important antioxidant, inhibits NF-kappa B—look at this one—inhibits mTOR, and supports MAOA, which is a clearing of histamine. High fructose corn syrup inhibits; resveratrol helps. And your nitrates also seem to support SIRT1—that's like your arugula and beets and things like that. So here's the RS number: RS12778366. When it's mutated, that's when SIRT1 activity may not be as robust as it should be. I would have to say that I put that on my top ten list of SNPs that may have an impact on us from a functional standpoint.

Bob Miller 44:00

We also spoke about how mast cells become overreactive and are likely present in 9%–14% of the population. And we're just mentioning here that there are enzymes called KIT. There are a couple of mutations in the KIT enzymes—there are too many to list—that will actually cause the mast cells to be trigger happy, [in other words], respond too quickly.

Bob Miller 44:22

Most people know some of this, but we'll just review it a little bit. When the mast cells get activated, we make more histamine or interleukins. It stimulates tumor necrosis factor-α. Probably on my chart, I ought to have a line going from the mast cells back to the tumor necrosis factor in another feedback loop.

Bob Miller 44:44

Now let's talk about histamine. By the way, Dr. Jill and I did a long interview on histamine. Here are the cliff notes. They can be stimulated by allergens or high-histamine foods, and when we make histamine, we need cortisol to degrade it. The body makes something called diamine oxidase. There are enzymes called

histamine N-methyltransferase, MAO-A, and glucuronidation, all of which clear histamine. One of the most common things we see in our health coaching is that people have genetic mutations in these enzylmes. They don't degrade enough histamine.

Bob Miller 45:24

And then there's another one called histidine decarboxylase that actually takes an amino acid called histidine and turns it into histamine. We're looking through the literature, but there are some that are considered pathological, and we're just hypothesizing that they're gain of function, but we're not quite sure. But whenever we see mutations in HDC, many times these folks have high levels of histamine, even confirmed by blood work. What percentage of the folks you see, Dr. Jill, do you think have a histamine problem as one of the things they're dealing with?

Dr. Jill 45:59

Yes, Bob, just like mast cell activation and all the things that it produces, this is one thing, but it's very, very common. And one thing I was thinking as you were talking is that I think it's related to our load. I think that's why things are getting worse because of our environmental toxic load. You've just talked about all kinds of triggers in the environment that can do this, and what it is doing is revealing these deficits in genetics that maybe were there, but when the load was low, no one noticed. Now that we have more toxins, more chemicals, more glyphosate, more high fructose corn syrup, more stress, more lack of sleep—and I could go on—all of these things affect our ability to deal with the environment. So I think it's exponentially increasing.

Bob Miller 46:38

Absolutely. Yes, for sure. Now here's a peer-reviewed study: "Histamine stimulates iNOS expression". When we did our talk on 'the Carnahan reaction,' we didn't have this piece of information. We didn't know that histamine stimulates iNOS as well. We've had this slide before, but in this chain of events, we're just saying histamine enhances the production of RANTES. So I really encourage you to watch this video. It's your [episode] # 34, where we talked about histamine. That's all we spoke about in that whole talk—45 minutes on histamine. So we got into the histamine foods, the DAO enzyme—a lot of details. So if somebody wants to learn, look up # 34. That was a fun interview, Dr. Jill.

Dr. Jill 47:29

They've all been fun. I love it; you're right.

Bob Miller 47:32

Now we're going to talk about nitric oxide, the miracle molecule. [The year] 1998 won a Nobel prize for three scientists for the benefit of nitric oxide. It's an incredibly simple molecule—nitrogen and oxygen—however, it's one of the most significant molecules in the body and critical to your well-being. It acts as a vasodilator. It causes the blood vessels to expand, including, reducing blood pressure flow of nutrients to the muscles, and improving the efficiency with which wastes are removed from the muscles and organs. If we don't have good blood flow to the liver [inaudible] they're going to struggle. It stimulates the brain. It helps men with erectile function and impotence—that's why they take Viagra and Cialis to help with nitric oxide. [It] increases energy, supports wound healing, and supports the immune system. It influences every body organ, including the lungs, liver, kidneys, stomach, genitals, and, of course, the heart.

Bob Miller 48:29

Again, I'm not going to read this; there are way too many things to just sit here and read. But this just illustrates the importance of nitric oxide.

Bob Miller 48:42

Now, iNOS. So what we were talking about with all those benefits is endothelial nitric oxide. It helps circulation. There's another enzyme called iNOS—inducible nitric oxide. What does it do? It kills viruses, bacteria, and pathogens. Is that a good thing? Sure—unless it's overactive. How many times have I said that now, Dr. Jill, 8-10 times already?

Dr. Jill 49:05

I love it. Bob, what's so great about this is that our body was created to fight infections and take care of toxins. Some people get all worried and they're like: "Oh my gosh, I'm toxic with mold. What am I going to do?" Well, guess what? If you get yourself out of the environment, even without supplements, you would probably slowly detox because your body's created [to do that]. What we're talking about is when the load is too heavy, the infection is too great, our stress is too high, or as you mentioned—and you're the expert in this realm—the genetic mutations that make our particular pathway mutated and excessive. So really, these aren't bad things. Too much or too little can be an issue.

Bob Miller 49:43

Absolutely. Back to Goldilocks and the Three Bears. So, iNOS generates very high amounts of nitric oxide to fight. Total elimination is shown to increase infections. I mean, we wouldn't survive if we didn't have iNOS to kill the pathogens. On the other hand, excessive [iNOS] has been associated with many health concerns. It's linked to tissue damage and organ dysfunction.

Bob Miller 50:07

Now, this is a chart that we may have had when we did our video on iNOS. Again, I would encourage you to watch that video. But here are the cliff notes. We sort of alluded to this before: eNOS is your endothelial nitric oxide; iNOS, the inducible nitric oxide, helps with circulation and kills pathogens. When you've got histamine or many other things that stimulate this… You can see it here. Here's the list—aluminum, mercury, uranium, plastics, ethanol, EMF, high fructose corn syrup, gluten, chlorine, fluoride, roundup, high homocysteine, iron overload—[these things] stimulate the iNOS, inhibit eNOS. There's a substance called BH4—tetrahydrobiopterin—that's needed to do this. If iNOS keeps running too hard, we'll run out of BH4. That's called NOS uncoupling, which we'll talk about a little bit later. But while we're on the map, I want to show you that when we run out of BH4, we make superoxide free radicals. And what we're going to show you in a little while is that superoxide stimulates the PLA2 enzyme to make more RANTES. There's a lot that can go wrong here.

Bob Miller 51:33

We're not going into it today, but there are pathways where we make BH4—some of it beginning with the citric acid cycle. Then there's also the folate that comes in here. But when BH4 gets depleted—BH4 is needed to turn tryptophan into serotonin, tyrosine into L-DOPA—if this gets severe enough, you're going to have tremors and real severity; potential Parkinson's; and [the conversion of] phenylalanine into tyrosine. So I can't tell you how many people's moods have been boosted when we give them something as simple as royal jelly—they can handle it—and that boosts the BH4 and they start making their serotonin.

Bob 52:16

Now, this is what we call 'the Carnahan reaction,' and we're going to show you that in just a moment here. But firstly: iNOS activation and platelet secretion; iNOS activation influences platelet secretion; iNOS knock-out mice have prolonged bleeding time. So, in other words, if you don't have the platelets activating, you're going to bleed to death. But in excess, that's when you get the clots. When we did

our recording, Dr. Jill, on iNOS, we didn't know that the iNOS actually activates the platelets as well.

Bob Miller 52:56

This is now talking about the eNOS. The activity level of eNOS enzymes was significantly lower in patients' platelets with coronary thrombosis. So here they're saying this data was consistent with the reduction of the expression levels of eNOS in patients with thrombosis. So iNOS causes platelet activation; eNOS eases the burden. So that's why the eNOS-iNOS balance is so important.

Bob Miller 53:29

Here's a peer-reviewed study published back in 2021. PubMed has a medical journal called "Nitric Oxide" and they're talking about [the effects of] COVID on eNOS and iNOS activity. This simplifies it. This is a chart from a peer-reviewed study that appeared in a medical journal. As we create more iNOS in an effort to kill the virus, this is where we can get severe inflammation as it pushes down eNOS—we get blood clots. This is possibly why COVID is causing higher levels of blood clots and strokes.

Dr. Jill 54:08

Bob, if you have just a second, I want to share something really interesting. I haven't even shown this to you yet. I think I can share just one picture and then explain it really quickly. Something happened to me about a year and a half ago—because you know that I'm the guinea pig. Can you see that picture, for one second, of my leg on top of the screen there?—if it's coming through. There it goes.

Bob Miller 54:28

Is it coming through? Okay.

Dr. Jill 54:29

There. And I'll take this off so we can go back to your slides. So this is my leg a year and a half ago, and I want to tell you a real quick story that I think relates to this. I—all of a sudden out of the blue—got a very high fever [of] 104.5. I've never had that high of a fever in my life. I suspected COVID. I did not test positive, but we know that sometimes there can be errors in that, and I just stayed home and isolated. So after one test, I just assumed [I may have had COVID]. Within 24 hours, I developed a blood clot and cellulitis. This is a picture of my leg. I've literally never shared that before. I go back to your screen.

Dr. Jill 55:01

I wanted to show you because I believe I probably had COVID—we don't know for sure. But if that's correct, we know I already have a platelet issue with genetics, and then we all also know I clearly have a 'Carnahan reaction,' which is this increase in iNOS. I believe at that time, whether it was COVID or another virus, it triggered a clot, which triggered cellulitis. And that was my leg. I needed IV antibiotics to get well from that.

Dr. Jill 55:24

Fortunately, I recovered very quickly and no problem. But that's a picture of what can happen with this activation. I believe this is absolutely related to this iNOS pathway and platelet activation. I wanted to show you in real life. I've literally experienced this. I should have probably been hospitalized. Fortunately, I had connections and was able to get home IV antibiotics. But one of my friends was like: "Jill, you really need to take this seriously. Your leg could… " And I do remember—this is a funny story—lying in bed with an almost 105-degree temperature, and my thought was: "Huh, I wonder at what temperature my brain will melt." So this is just a story to show people that this is real and that it can happen. And again, it's not fear, but I'm the guinea pig. So I got to experience that and understand the iNOS pathway on a new level.

Bob Miller 56:14

Wow. That's incredible, Dr. Jill. I'm sorry you went through that. But like you said, that probably gave you some insight now that you're going to be able to help other people when you see that happening.

Bob Miller 56:25

So I'm not going to read these, but these are all the things that stimulate iNOS. So we're wondering why we're seeing more conditions today than we did before. When I was born, there was very little BPA, very little aluminum, and we weren't exposed to cell phones. I don't think mold and mycotoxins were as bad. We certainly didn't have high fructose corn syrup when I was a youngster; we didn't have glyphosate. So all of these things, cumulatively, I believe, are having an impact on all of us. But anybody who has a genetic weakness gets hit harder—that proverbial canary in the mine.

Bob Miller 57:05

Mercury is a stimulator of NF-kappa B. I'm sure, Dr. Jill, you probably check for heavy metals sometimes, and now you probably see a fair amount of people with mercury toxicity.

Dr. Jill 57:16

I do. Especially dentists, unfortunately.

Bob Miller 57:21

Absolutely. Here is glyphosate. This is the Great Plains glyphosate test. You can see this poor person was just pinning the needle. It inhibits SOD, catalase, glutathione peroxidase, as well as reduced glutathione. And look at this, [it] promoted the expression of NF-kappa B, iNOS, and tumor necrosis factor-alpha.

Bob Miller 57:48

So in this study, they didn't measure RANTES, but I think it's not hard to interpolate that if these are high, the RANTES is going to be high as well. Stephanie Seneff does a lot of talks on this. So if you just google her name on YouTube, you can find great talks from her. Have you ever had her as a guest or anyone speak about glyphosate in your videos?

Dr. Jill 58:08

I have not, Bob, but that's a great idea. I know Stephanie well. I love her research. I'm going to ask her to be on, so stay tuned. We'll have her on.

Bob Miller 58:17

Absolutely. She'll be glad to talk about glyphosate. There are a couple of enzymes. I mean, there are more than just this one. But there is an enzyme called PON1, and these are the ones that are evidence-based. And just, again, clinically observing, when we see a lot of 2s on here and the people live in a farming community and we measure their glyphosate, it's usually extraordinarily high. So PON1 is related to clearing glyphosate. There are others as well. So here it is again: "Histamine stimulates smooth muscle cells to increase iNOS expression." I just checked the other day, and it's still the most watched video on your YouTube [channel] where we spoke about interleukin 6. We went on for an hour and 51 minutes.

Dr. Jill 59:09

That was a great one—so awesome!

Bob Miller 59:12

Yes. So [episode] number 42. It's interesting. We spoke about peroxynitrite, histamine, 'the Carnahan reaction,' IL-6, and the Holme cycle, and all of a sudden it's like they're tying together into this. It's just rather astonishing how it all comes together.

Dr. Jill 59:36

You know, Bob, I love that you said that. I want to emphasize that we've just been going along learning and these pathways are amazing, but we did not expect for it all this to—like you said, today is really the accumulation of all of this—come together. I'm first of all amazed at your work—I want to say that publicly; we so appreciate it—but secondly, how it all really, really makes sense, doesn't it?

Bob Miller 59:59

Absolutely. I was blown away when we were talking about those things separately, and it's like, "Oh my gosh, they all work together to create this RANTES."

Bob Miller 1:00:10

So we kind of alluded to this before, but this is just another quick slide. When you have enough BH4, the eNOS makes nitric oxide; if we run out of BH4, we make superoxide. I'm going to show this very soon: Superoxide stimulates PLA2.

Bob Miller 1:00:27

Now, there are gain of function mutations in the iNOS enzymes. That means it's overactive, and then that'll create more superoxide. So here are the common functional iNOS polymorphisms—the RS2779249. When this is mutated, the good one is the C and the bad one is the A. So if you are CA, that means you have one mutation. If you have an AA, you have two mutations; 4.73x increased iNOS expression when you had this genetic mutation.

Bob Miller 1:01:06

Here's another one. RS2297518—the good one is G, the risk is A. And you can see here that the double A (AA) only occurs in 3.9% of the population. It's related to early onset Crohn's disease, ulcerative colitis, inflammatory bowel disease, and increased nitrosative stress, meaning it's making peroxynitrite and oxidative stress in the gut.

Bob Miller 1:01:35

Here is the infamous 'Carnahan reaction.' Dr. Jill is very brave. She allows us to put her genome on the internet. Here's that NOS2 that's upregulated. This '2' means that mother and father gave her a mutation. The other one—that's upregulation—mother and father gave her the mutation. So that's why we're calling it 'the Carnahan reaction.'

Bob Miller 1:02:04

Here is what can cause that to happen. Again, these things were mentioned before. The genetics could be [from] the NOS2 being gained. I'm not talking about it today, but there's actually a NOS3—lack of function—if we don't make enough superoxide dismutase. SIRT-1, as we spoke about, supports the production of superoxide dismutase and helps eNOS. DHFR and QDPR help recycle your BH2 to BH4 and the MTHFR A1298 is also involved with making enough BH4. So if you want to get more details on 'the Carnahan reaction,' watch the video on iNOS. We went through it in detail. So I'm hoping, Dr. Jill, 100 years from now they're still talking about 'the Carnahan reaction.'

Dr. Jill 1:02:57

All for the greater good.

Bob Miller 1:02:59

Absolutely. Now, pathway #2. There's an enzyme called phospholipase A2 (PLA2). What this one does is take arachidonic acid from the cell membrane—that's one of the fats—and pulls it out. I think I'll do a little expansion here. You can see that superoxide, peroxynitrite—I would encourage you to watch our video on EMF because we get too much calmodium—lipopolysaccharides, histamine, and mTOR all stimulate PLA2. The adrenal glands make cortical steroids. Ginkgo biloba as an herb, curcumin, and CDP-choline all inhibit PLA2. What can happen is that when we have any of these environmental factors, they'll stimulate the PLA2 to bring the arachidonic acid out. Then the tumor necrosis factor can also stimulate the COX1 and COX2 enzymes, and we go down a pathway where we stimulate the TXA enzyme and make thromboxane A2.

Bob Miller 1:04:18

Now, we don't do this in our software yet, but when we come out with our new chip, we want to make sure we have all the PLA2 enzymes because there might be some that are activated. We want to look at COX1 and COX2.

Bob Miller 1:04:31

This was an interesting one because this guy takes these inflammatory things and moves them over to make prostacyclin, which is actually vasodilative and inhibits platelet aggregation. Now one of the things that's interesting is that aspirin and NSAIDs will actually encourage going over this direction. That's why some people take aspirin—although it's now said not to because of bleeding. But just to show the action, aspirin will block coming down here to make the thromboxane A2, and again, activate the platelets and stimulate the RANTES.

Bob Miller 1:05:12

We're not going to get into it today, but interestingly, collagen, epinephrine, iNOS, and angiotensin II stimulate the platelets. But I find it interesting that collagen plays a role in that. We need to dig into that just a little bit more.

Bob Miller 1:05:30

So here is the importance of the adrenal glands to make cortisol. The adrenal glands also knock down histamine. So this is an important pathway. And that's why you spoke earlier about doing those blood tests to see where your arachidonic acid is—our arachidonic acid to EPA. Those are all important markers to look at because that will be pro-inflammatory.

Bob Miller 1:05:55

So here's a little information on that PLA2—phospholipase A2. It liberates arachidonic acid, and then that arachidonic acid makes prostaglandins and leukotrienes. When rat platelets are incubated with phospholipase A2, thromboxane A2-like activity and prostaglandins are formed. Again, it's pro-inflammatory. Right now, there aren't any tests for PLA2. I know Great Plains used to have it, but they couldn't get the regent. And I've talked to them and said, "You guys have got to get that back," because it's so important to look at this PLA2.

Bob Miller 1:06:38

All right, here's a quick overview. This came from the Great Plains website—Bill Shaw. By the way, Bill Shaw was a pioneer. I mean, he was talking about PLA2 a long time ago. "When experiencing infections, PLA2 can break down the phospholipids

of the membranes of bacteria, fungus, and parasites." So I sound like a recording here. Is it a good thing? Yes. "However, inflammation… often becomes excessive" and then "the same phospholipase that attacks infectious agents may attack the cell membranes… damaging or killing those cells." "The most common free fatty acid produced" by this "is arachidonic acid, which can increase the production of… mediators of inflammation"—which we spoke about—[such as] "prostaglandins and leukotrienes."

Bob Miller 1:07:25

"Superoxide anions could stimulate phospholipase A2." We've spoken about this many times, particularly how EMF is making more superoxide if we don't take our oxidized glutathione back to the reduced superoxide. And if you remember when we spoke about the NOS uncoupling, what do we make? Superoxide. So I believe superoxide is public enemy number one. Again, superoxide is helpful. It kills pathogens, but in excess, it's a problem. So the products of this phospholipase A2 are membrane-damaging agents and may be responsible for mitochondrial damage during oxidative stress.

Bob Miller 1:08:10

Here we're saying that a study of intestinal cells has shown that TNF-α potentiates the release of arachidonic acid. So the more you have that TNF-α being upregulated by environmental factors or genetic upregulation, the more you're going to take that phospholipase A2 to stimulate the arachidonic acid release.

Bob Miller 1:08:38

Now we're going to talk a little bit about thromboxane A2—this can be measured—stimulating the platelets and creating RANTES. However, these activated platelets can also stimulate something called sCD40L. We're going to get into that just a little bit. But before we do, there's a lot of talk about how the Mediterranean diet has a lot of health benefits. Oleanolic acid comes from olive oil. That may stimulate this PGI2 enzyme to shunt this inflammatory thing over to prostacyclin, which is vasodilative and also inhibits platelet aggregation. So it's absolutely fascinating how we've been talking about the Mediterranean diet—the olive oil. We now know the pathway that that can move through. So I was blown away by that one, Dr. Jill.

Dr. Jill 1:09:36

Yes, unbelievable, and I love olive oil. It's good for us. I see this often with these pathways. We do a lot of testing [with regards to] micronutrients and things. I see a surprising number of people who are deficient in oleanolic acid.

Bob Miller 1:09:51

Absolutely. So if that's the case, a little bit of olive oil might certainly be beneficial. Okay, here's the thromboxane A2. Prostaglandin counterbalances the thrombotic and vasoconstrictive properties of TxA2. This balance can become dysregulated in pathological and physiological situations. Increased activity of thromboxane A2 could be associated with myocardial infarction, stroke, arteriosclerosis, bronchial asthma, pulmonary hypertension, kidney injury, hepatic injury, allergies, angiogenesis, and the growth of cancer cells. When activation of thromboxane A2 is uncontrolled, there could be pathological consequences.

Bob Miller 1:10:42

I'm not going to read all of this, but the bottom line here is that activated platelets also express sCD40L. Now we're going to get into that. But first, serotonin is transported by the platelets and released upon activation. This induces constriction of injured blood vessels and enhances platelet aggregation to minimize blood loss. Interestingly, platelets contain high amounts of serotonin. And a dysfunction of the serotonin system is involved in the development of several behavioral disorders. This is just hypothetical, so we're not making any statements here, but it may be involved in depression, anxiety disorders, and self-aggressive disturbances.

Bob Miller 1:11:31

The platelets are able to take up dopamine and express various dopamine receptors, which could make them an interesting tool to study the underlying mechanisms of schizophrenia. There are lots to learn here. We're just in the very beginning stages of understanding this. The platelets store large amounts of serotonin that they release during the thrombus formation, and that [is what] creates the clots. But what I found interesting: It induces hydrogen peroxide—H2O2—and if you have an overabsorption of iron and you don't clear your hydrogen peroxide, you get hydroxyl radicals that are very pro-inflammatory.

Bob Miller 1:12:14

All right, sCD40L. Activated platelets are the major source of sCD40L, which has been implicated in platelet and leukocyte activation. And this sCD40L is involved in inflammation and vascular diseases. So here are the activated platelets stimulating the sCD40L.

Bob Miller 1:12:36

Now, this is interesting: "High early sCD40L levels in trauma patients reflect tissue injury, shock, coagulopathy, and adrenal activation and predict mortality... sCD40L may be involved in trauma-induced endothelial damage" and blood clotting.

Bob Miller 1:12:57

Now here's a chart. When we get the activated platelets, sCD40L is activated, which increases VEGF—we'll talk about that a little bit—and encourages the growth of tumors. So that's why it's so important that we don't have this elevated. I'm sure, Dr. Jill, you measure VEGF on occasion.

Dr. Jill 1:13:19

Yes. I was going to say, Bob, there's some new [insight] with Dr. Patterson's research. We can now measure sCD40L with special labs as well. So, literally, we're doing panels to look at all of these things now. They're not easily accessible as far as lab requests go, but they are available to be tested.

Bob Miller 1:13:36

Absolutely. I'm excited to hear you're doing that because I think we're going to find that long-haul COVID and possibly even chronic Lyme disease have increased RANTES and sCD40L. I've been talking to the folks at iLabs about that. Hopefully, we can do some research.

Bob Miller 1:13:55

So these myeloid-derived suppressor cells are relatively newly defined; they suppress immune responses. There's a role for this in solid tumors. It's been extensively characterized as pro-tumor. In intensive clinical studies, circulating and infiltrating MDSCs at the tumor site were associated with a poor prognosis in patients with solid tumors. In a study of breast cancer patients, the overall survival of preoperative patients with MDSC levels greater than 1% [of total PBMCs] with stage 4 disease was significantly shorter compared to people who had [levels] lower than 1%. So what they're saying in this study is that MDSC levels could work as a good prognostic indicator, especially in those with advanced breast cancer.

Bob Miller 1:14:46

VEGF—that is the growth of new blood vessels. Is that important? Sure. But what happens when someone gets cancer? They need those new blood vessels for it to grow. So they're saying the inhibition of VEGF-induced angiogenesis significantly inhibits tumor growth. Angiogenesis is the growth of new blood vessels.

Dr. Jill 1:15:12

You know what else, Bob? I'm seeing, as you mentioned, mold can either decrease or increase VEGF, but also Bartonella, which you mentioned, as an LPS inducer. I see abnormally high VEGF with Bartonella as well.

Bob Miller 1:15:27

Absolutely. These are exciting things that are happening here.

Bob Miller 1:15:32

We did a whole video on this. We called it the Holmes cycle, where—let me just zoom in here a little bit—multiple endogenous mediators like histamine, dopamine, and angiotensin II. All of these will stimulate interleukin-6. Mold and mycotoxins, Lyme disease, lipopolysaccharides, and EMF [all] stimulate interleukin-6. When interleukin-6 gets stimulated, we get superoxide through NOX, mast cells, and histamine. By the way, we talked about heme oxygenase; it calms down the mast cells. Then histamine stimulates RANTES.

Bob Miller 1:16:17

Now, as we talked about in that video, superoxide, mast cells, and histamine stimulate the REN and angiotensin system. That will stimulate angiotensin I and angiotensin II. And the literature is there: Angiotensin II stimulates RANTES. So this is where we spoke at length in that long interview about the importance of IL-6. Again, it's our friend, unless it's overactive. So yet another third way that we can make too much RANTES.

Bob Miller 1:16:56

I'm not going to read this. These are the SNPs, the genetic mutations that could be involved when they're mutated, that would allow this to be more proactive.

Bob Miller 1:17:08

We showed this before, but again, because this makes the histamine, the mast cells create the histamine, and the histamine enhances the production of RANTES. [A

study of] mast cells showcased the mast cells as an additional renin source. So interestingly, mast cells can stimulate that renin-angiotensin system. It's going to make more interleukin-6 and just keep things moving around. So mast cells could be targeted along with renin-angiotensin system inhibitors to manage angiotensin II dysfunctions. The angiotensin II [inaudible] aldosterone, which causes you to hold onto sodium and excrete potassium—that's related to blood pressure and edema.

Bob Miller 1:17:57

Histamine and renin—histamine has been shown to stimulate the release of renin, and superoxide activates the renin as well. So that's just backing up what we talked about. Here's the peer-reviewed study. I'm not going to read it, but the bottom line is that you get this feedback loop when you have superoxide, mast cells, and histamine, and it just feeds upon itself—an inflammatory cascade. When we did this video, we had no idea that angiotensin II stimulated RANTES. And again, I'm not going to read this, but this is the Holmes hypothesis that is related to toxic environmental factors creating these inflammatory agents, depleting our NADPH, and stimulating the renin-angiotensin system in that positive feedback loop of inflammation. So again, if someone is interested, watch our video # 42.

Dr. Jill 1:19:02

And Bob, if you're listening here—wherever you're listening—I will include these links, so don't worry about finding them. I'll make sure they're included.

Bob Miller 1:19:12

Oh, good. Yes, when I grabbed this, there were 2,900 people who watched it on YouTube—that's amazing!

Dr. Jill 1:19:17

And, Bob, I just looked; it's over 3,000 now.

Bob Miller 1:19:24

Wow, okay. All right, here's the one on the NOX pathways where we explain that Holmes cycle.

Bob Miller 1:19:32

All right, now we're going to wrap up with the omega-3s: Resolvins and protectins. So a meta-analysis revealed an association between your polyunsaturated fatty acid supplementation and a reduction in platelet aggregation. High-risk patients with cardiovascular disease or diabetes could benefit from omega-3 therapy. This is fascinating. Again, it's a peer-reviewed study. Both EPA and DHA—these are the parts of your fish oils when you take them—get incorporated into platelet phospholipids at the expense of arachidonic acid, which may help reduce platelet aggregation via a reduction in the arachidonic acid-derived platelet-aggregating/pro-coagulant metabolites. EPA competes with AA for that COX enzyme, reducing its action on arachidonic acid, and it reduces the formation of that thromboxane A2. EPA/DHA also get incorporated into neutrophils and red blood cells at the expense of linoleic acid and arachidonic acid. It decreases whole blood viscosity and increases red blood cell flexibility, thus likely reducing the risk of thrombosis.

Bob Miller 1:20:57

Now, what happens is they go through a couple of steps, and I'm going to show you a chart here in a couple of moments where we make what are called protectins and resolvins, and they're associated with various beneficial effects and the prevention of various diseases. They modulate the immune system, which is helpful for autoimmune [diseases], rheumatoid arthritis, cardiovascular [diseases], Alzheimer's, type 2 diabetes, and cancer. This is an interesting little chart here. When you get a tissue injury, you get acute inflammation. The lipoxins, resolvins, and protectins complete resolution. If not, you'll get abscesses, scars, and chronic inflammation from the prostaglandins and leukotrienes. So that's why these are so important to resolve—complete resolution when we have the resolvins. And that looks like a duplicate slide.

Bob Miller 1:21:58

So now here's arachidonic acid, and it shows on this chart the different pathways. We want to map this all out genetically and epigenetically. But you can see the arachidonic acid comes down and makes acute inflammation and chronic inflammation. Interestingly, there are a couple of pathways that we haven't identified yet. This might be a future show to talk about how we can get that arachidonic acid to come down to actually help [with] the resolution of inflammation. So arachidonic acid isn't all bad. But your EPA and DHA go down these pathways, and here's where you make their resolvins and protectins. The standard American diets that I think you alluded to earlier were much heavier in the omega-6s and the things that will create the arachidonic acid versus—

Dr. Jill 1:22:51

Yes, seed oil. It's so practical, if you're listening. Seed oils, I would really avoid. Those are going to be sources—canola oil—all these oils that can become rancid and can produce more arachidonic acid. You want the omega-3s, which are in your wild salmon and your fish, and the bottom line is that you should probably be taking fish oil. And I like—especially if you have this inflammatory pathway—higher DHA and with SPMs. I actually put a link on this site to Mega Omega. There are other ones, but that one happens to have both EPA and DHA, and SPMs—all in one.

Bob Miller 1:23:24

Wow. Very impressive. Okay. This resolvin E1 is generated during the resolution of inflammation in the human vasculature. And a study has shown new potent agonist-specific antiplatelet actions. Now, this is a little confusing. Agonist means it helps the antiplatelet actions. These actions could underscore some of the beneficial actions of the EPA in humans.

Bob Miller 1:23:50

I really like this chart. So here are your omega-6s. From a genetic standpoint, we are finding that there are enzymes called FADS—fatty acid desaturases. They're involved with taking your omega-6s to FADS2 down through to make arachidonic acid. But this is interesting: Omega-6s may use up the available FADS2s. So when we consume our FADS2s, they have to go through multiple steps.

Bob Miller 1:24:22

This is a new one that we've just added, ELOVL2—I'm finding it to be very significant. This is what takes your EPA [and turns it] into DHA so we can make the protectins and resolvins. What we're observing [is that] when people have a lot of mutations in their FADS1 and FADS2, they have unresolved inflammation. They just can't seem to get to the bottom of why they're in their mid-40s, and they hurt all over. Part of it could be that they're not getting down to these protectins and resolvins, because they will inhibit the platelet aggregation and the RANTES. So we have this on our computers. We show this to folks all the time: Why it's important that we get those omega-3s, but more importantly that we get down through this way, and if we don't, we may need to use those protectins and resolvins to just bypass the weakness here.

Dr. Jill 1:25:16

And Bob, I want to tell you something really interesting. I showed you all my leg when it was severely cellulitic and probably from platelet aggregation. I did not know this pathway, but I'm pretty intuitive. I didn't at the time know why I just knew they were anti-inflammatory. I took four times the recommended dose of SPMs. Those are the resolvins that you're talking about. I took very high doses of these, and it really, really helped. And it's no wonder; you're showing me the pathway for that.

Bob Miller 1:25:42

Yes. So here are the studies showing—this was just published back in 2017—FADS and ELOVL2 may have a role in the differences in omega-3 requirements. So what we're finding is that the more ELOVL2 mutations [there are], the more there's a higher need for DHA. And here are FADS1 and FADS2. So this one over here means mutation. You can see this person had a mutation in every one of the FADS1, and they had mutations in most of the FADS2.

Bob Miller 1:26:15

The people that are really struggling—we see them every once in a while—homozygous, or both parents gave them a mutation straight down through. Those are the folks that are really struggling with getting their EPA turned into DHA and making their protectins and resolvins. I would have to put this on my top 10 list of important genetic things to be aware of because we find that it really is involved with those who are struggling.

Bob Miller 1:26:45

Here's a peer-reviewed study. "Our results suggest"—if somebody wants to look it up, it's RS953413—it regulates your polyunsaturated fatty acids "by altering ELOVL2 expression" through the FOXA genes. And again, we're finding that, when combined with tumor necrosis factor, folks are in a lot of inflammation.

Bob Miller 1:27:12

Here's a study: "Clinical studies in humans shows that marine omega-3s provide anti-platelets effects. Three grams of omega-3 polyunsaturated fatty acids for four weeks lowered fibrinogen, thrombin, and factor V levels." We've talked about this before; it's the expense of arachidonic acid. EPA also competes with arachidonic acid for the COX enzymes, reducing its action on AA. If we remember, the COX enzymes are the ones that bring it down and make thromboxane A2. So they're

saying EPA both directly and indirectly reduces the formation of arachidonic acid—thromboxane A2. That activates the platelets.

Bob Miller 1:27:57

Now here, there are all kinds of tests out there; this one just happened to come from Omega Quant. This was a middle-aged lady who got COVID and was doing very poorly—this was post-COVID. But here's her omega-3 index. It should be at 8%-12%; [hers was at] 3.5%. Then here's the ratio of omega-6s to omega-3s. It should be 3.1 to 5.1—[hers is] off the chart [at] 11.9. Arachidonic acid to EPA should be 2.5 to 11.1—[hers is] 35.1, again off the chart. In my opinion, it's important that people know where this is. So talk to your physician, whoever that is, and see if you can see where these are because it's more important than we ever realized.

Dr. Jill 1:28:53

And as I mentioned earlier, Bob, these are now available in your regular labs. So this is not a functional cash lab; you can get it through Quest or Labcorp or Boston Heart or some of these other labs—it's available.

Bob Miller 1:29:05

Yes. Then here is the test for thromboxane. It's the same individual. The thromboxane should be less than 141— [141] is a little high, [421 or less is] moderately high, and way too high [is above] 421—[hers was at] 643. No wonder this person was struggling in this case study. This is the same person who had that arachidonic acid. The arachidonic acid was stimulating the thromboxane A2 and creating massive inflammation, fatigue, and lots of histamine.

Bob Miller 1:29:42

All right, so what's a potential action plan? This is a really short list. But there are a couple of practical things you can do: Make sure you're in a mold-free environment; clear mold if an issue; if you work with a functional medicine doctor, see if you have some mold inside you; if there's real concern, see a functional medicine person for heavy metals and glyphosate; check for Lyme, clostridia, and lipopolysaccharides; consider eliminating high fructose corn syrup, especially with the SIRT-1 mutations; a low histamine diet if histamine is an issue; check what we just talked about here, and maybe consider checking the thromboxane A2; As Dr. Jill mentioned, they're not easy to get, but you can measure RANTES, sCD40L, VEGF, TNF-α, IL-6, [etc.] Dr. Jill, are you doing what are considered the long-haul panels? Is that what you're doing?

Dr. Jill 1:30:37

That's exactly what I'm doing, correct.

Bob Miller 1:30:41

And then you can do your genomic resource test if you want to see if there are any mutations that may worsen the situation.

Bob Miller 1:30:50

So that's it, other than just a brief commercial for health professionals. If you're a health professional and you'd like to look at all this, we have a genetic test called Your Functional Genomics. The software analyzes everything for you and puts it together. We also have online education. If you're a health professional and you want to try the certification course, here's where you go: nutrigeneticresearch.talentlms.com, and you can save $100 by using the coupon code DRJill. It's not for everyone, and it's not for the faint of heart, but for somebody who really wants to dig in and study, it's a good resource for you.

Bob Miller 1:31:31

Anyone who wants to contact our clinic, www.tolhealth.com, there's our phone number: 717-733-2003. The software, if you're a health professional and you want to try a free trial, there's the website: functionalgenomicanalysis.com. Yvonne Lucchese and Chrissy Bannon are your helpers. We have a whole line of nutrients that support the function: freedomtoformulate.com. So we just went through probably a three-day course in an hour or an hour and a half, but there it is.

Dr. Jill 1:32:06

Bob, it's always so fun. For those of you who stayed with us the whole time, [which] a lot of you did, I hope you enjoyed it. I know someone commented: "I'm glued to my seat." So I know that this is not for everyone, but for those of you who enjoy the pathways and understanding…

Dr. Jill 1:32:20

And I would just encourage you if you're a patient who's listening and you're overwhelmed by this—that's okay. Sometimes we're overwhelmed too. But get a functional doctor. You can do the testing with Bob's companies that he just put up there with your doctor. And there are lots and lots of solutions out there. A lot of

the stuff we're talking about we see in clinical practice. We don't yet have hundreds of thousands of people in randomized controlled trials, but this is where science starts. We ask the questions, we look at pathways, and we make hypotheses, and that's where you're on the leading edge, and I couldn't be more honored to be here with you. So thank you again for sharing.

Bob Miller 1:32:58

Well, thank you for allowing us the platform here to bring this out, because if it wasn't for you, we'd be sitting here having fun by ourselves and not sharing it with anyone. So I really appreciate your openness to bring this out. You're a pioneer yourself in the work you're doing. And hopefully 'the Carnahan reaction' will be well known and help a lot of people.

Dr. Jill 1:33:18

If I can go through something to help people, I'm all good with it, like my leg and everything else. So thank you all for listening today. We will be back again, so stay tuned.