**Dr. Mariam Hanna**

Hello, I'm Dr. Mariam Hanna, and this is *The Allergist*, a show that separates myth from medicine, deciphering allergies and understanding the immune system.

What if the most important immune signal in your patient isn't in their genome, but in their gut? You see a child with an inborn error of immunity, recurrent infections, inflammation that doesn't quite fit, maybe even neurocognitive changes. You optimize antimicrobials, immunoglobulin, targeted therapies, yet something still doesn't add up.

Now imagine this: the same patient, but viewed through a different lens. Not just host genetics, but a disrupted microbial ecosystem actively shaping an immune system, barrier integrity, and systemic inflammation. Well, that's what we're going to talk about in this episode.

We'll explore the microbiome as more than a bystander in IEI, as a functional readout of immune dysfunction, and potentially even as a therapeutic target. We're going beyond adding a probiotic.

To help us unpack this evolving space, I'm joined by Dr. Emilia Liana Falcone, a physician-scientist whose work sits at the intersection of microbiome science and immune dysfunction. Dr. Emilia Liana Falcone is a physician-scientist and director of the Microbiome and Mucosal Defense Research Unit at the Montreal Clinical Research Institute.

Her research focuses on how the microbiome shapes immune and neuroimmune responses, particularly in inborn errors of immunity and post-infectious conditions, identifying key mechanisms and therapeutic targets. She leads microbiome studies for the Primary Immune Deficiency Treatment Consortium, holds a Tier 2 Canada Research Chair, and was elected to the Canadian Academy of Health Scientists as an Emerging Leader.

Clinically, she's an infectious diseases physician at CHUM and working at the intersection of the microbiome science, immunology, and infectious disease—the intersection of it all—and the perfect guest to have join us today. Dr. Emilia Liana Falcone, welcome to the podcast.

**Dr. Emilia Liana Falcone**

Oh, thank you so much, Mariam, for this wonderful introduction. I should have you come around with me everywhere.

**Dr. Mariam Hanna**

I am happy to do so after learning about the cool things that you've been studying and where we are in this field. So we'll go to basics and then we'll dig deeper. When we say gut microbiome in 2026, what should clinicians actually be thinking about?

**Dr. Emilia Liana Falcone**

As a clinician in 2026, I think it has to be a lot less about who's there—the names of the specific microbial taxa—but a lot more about the host-microbe interface. For me, that's the intestinal barrier.

So while community structure matters, what's really more clinically relevant is how these microbial communities are interacting with the intestinal barrier and then, by extension, with the immune system. So it's not about really who's there, but really about what signals are being generated and how the host is then responding to them.

**Dr. Mariam Hanna**

Okay, so not who's there, but how the host is responding to them in this interaction. It's sounding like a party already. And what really makes IEI kind of a clean model to study this, to study host-microbiome interactions?

**Dr. Emilia Liana Falcone**

Ah, so, I mean, I find IEI is absolutely fascinating. But the first step here is that for the most part, these are monogenic diseases with a very clear-cut immune defect.

So we have this sort of almost like natural human experiment, if you want, where you have a clear gene that's aberrant, that leads to an immune phenotype. And now we could make a direct connection with an altered microbiome signature that's then leading to an altered ecosystem because of the impact of the inborn error of immunity at the level of, for example, the intestinal mucosa.

**Dr. Mariam Hanna**

So should we stop thinking about the microbiome as an exposure and instead start thinking about it as this, like, readout of this IEI or this immune genotype that this patient has now?

**Dr. Emilia Liana Falcone**

Yes, yes, absolutely. With a bit of a nuance, and you'll see as I explain a little more. So, you know, you have an inborn error of immunity, right? And that's going to lead to directly or indirectly some sort of impact, most likely at the level of the intestinal barrier.

In a lot of cases, especially in a disease such as, for example, chronic granulomatous disease where 50% have inflammatory bowel disease. This then alters the environment, which then will have an impact, undoubtedly, on the intestinal microbiome. Yes, who's there, but really more importantly, on what who's there is doing.

So there's sort of like at the level of the intestinal barrier, there's sort of these rules, right, that are established, you know, by the tone that's established by the immune system of the host. There's an input on what organisms are there, how they're being contained, what's going on in terms of inflammatory tone, how the barrier is behaving—is it more permissive? Is it a little bit more leaky?

And then that has an impact on the metabolic environment. So when you go and you add an inborn error of immunity into the mix, this definitely gets altered, undoubtedly will alter the microbiome signature. But then the microbiome itself is also getting feedback from external inputs like diet, medications, and infection.

In that sense, when it's getting altered, it can communicate back to the host's immune system and then further modify disease expression. So what you get is this sort of like bidirectional interaction, really, that yes, maybe it does start off with the immune deficiency altering the signature, but there's definitely a communication between host and microbe.

**Dr. Mariam Hanna**

Yeah, that bidirectionality already starts making me think of, like, is the microbiome driving the disease? Or is it the consequence of the dysfunction? Or is it both?

**Dr. Emilia Liana Falcone**

It's both, and in a sort of a sequence. So you have an inborn error of immunity, and there's initial microbiome changes, and they're a consequence of the immune dysfunction. The immune defect, it's altering the intestinal environment, and the microbiome is going to sort of shift accordingly.

But then, once that ecosystem has been established and then altered, it becomes biologically active in its own right, and could then further contribute to inflammation, and then by extension, barrier dysfunction. This probably deepens immune dysregulation, and potentially even has impacts on end organs, which will then ultimately impact disease severity.

**Dr. Mariam Hanna**

Okay, and how early does this signaling begin? Is there kind of like a window of opportunity in utero, in early infancy, in childhood? Where is this window of opportunity problem?

**Dr. Emilia Liana Falcone**

Yeah, so you just hit on a really important point. There's definitely this window of opportunity in early life, and that's super important. There's lots of fascinating research in this domain.

And we know, like from birth to about two years of age, the microbiome is really dynamic. It's very plastic, could be really influenced by different factors. But then again, so is the immune system.

So here they are both being very plastic and sort of getting educated with each other, growing together, and then, what I believe, shaping what will be the long-term immunological patterns of the host. If you introduce a specific immune defect at that stage of development, you're going to start to create an altered mucosal environment, intestinal environment, really early on. That's definitely going to have an impact on how the immune system will then develop.

So I think definitely infancy is a really important window of opportunity. It's probably not the only one. I think there's other instances in life where things change for sure, depending on the exposures of the individual.

And we know also towards the end of life, things will start to change as well, both at the level of the diversity of the microbiota and at the level of the functionality of the immune system. So again, this interaction remains very dynamic, but early life is a really important window of opportunity.

**Dr. Mariam Hanna**

Are different IEIs then effectively creating very different and distinct bacterial niches, ecological niches in the gut? And for instance, like phagocyte dysfunction or T-cell dysregulation translate into predictable microbial and then metabolic outputs?

**Dr. Emilia Liana Falcone**

Yes, I definitely think so. And I think that's really the right way to think about it in the realm of inborn errors of immunity. So if, for example, we go back to the chronic granulomatous disease, right?

So we have phagocytes; they're producing little to no reactive oxygen species. We know that renders these patients susceptible to infections, and we know it causes paradoxically a lot of inflammation. So at the level of the intestinal barrier, something very particular is happening, right?

We know that there's shifts in Th1 versus Th17 response, but there's also differences in how the barrier deals with this change in reactive oxygen species. That's going to ultimately impact things like oxygen tension at the barrier, which has an impact on how the intestinal epithelial barrier repairs itself when there's damage or its resistance to damage.

And I can also argue the point from the aspect of the microbes: if they're seeing less reactive oxygen species over time, they may adapt as well and perhaps produce more reactive oxygen species. That's sort of like one concrete example, whereas if you compare that to, say, T-cell dysfunction or even disruption of the B-cell compartment, and there maybe we'll have issues with how the microbes are being sensed or basically how they're being coated with different immune globulins.

Maybe instead of having more IgA coating, we might have more IgG coating, which down the line can trigger more intestinal inflammation, for example.

**Dr. Mariam Hanna**

And there's that bidirectionality again. Okay, we're going to go back to CGD. What are the most reproducible microbiome signatures that we see in this condition?

**Dr. Emilia Liana Falcone**

Yeah, so I would say that the most reproducible signatures, they're not really at the level of individual taxa, although we do tend to see some trends across different studies and especially when you introduce intestinal inflammation into the mix. But really what there tends to be is sort of this loss of certain protective and beneficial functions.

You know, we tend to see always that, oh, there's decreased alpha diversity in the context of different diseases, especially intestinal inflammation. But I like to look at it a lot more as a loss of certain helpful functions. And of course, you know, when you have less diversity, you might see a couple taxa that become more enriched.

But it doesn't necessarily mean that they're the causal organism. It could just be that they've had an opportunity to become enriched because you've lost certain other safety mechanisms.

**Dr. Mariam Hanna**

Okay, and how tightly does this signature kind of map to phenotypes?

**Dr. Emilia Liana Falcone**

Oh, so that maps very well. And that's where things become really interesting from a clinical perspective. So certainly, you know, we and others in different inborn errors of immunity have shown that patients with certain inborn errors of immunity, at least the ones that were studied, have distinct microbiome metabolomic signatures compared to healthy individuals.

And, you know, as much as possible, when we're doing those studies, we want to try to control for all the variables that could also be causing shifts in the microbiota. For example, exposure to antibiotics, having active intestinal inflammation, other medications as well, and so on.

But when you have your cohort of patients in an area of immunity, and then you start to see distinction between either different disease phenotypes or different degrees of disease severity, it becomes very interesting. And I think that's your first step towards some sort of function.

So we saw it, for example, in chronic granulomatous disease, where the microbiome does a really, and even the metabolomic signature, in fact, do a really good job at distinguishing patients with CGD with and without inflammatory bowel disease. We also did a study in patients with CTLA-4 deficiency.

And, you know, here we know that these patients could have lots of autoimmunity, lymphoproliferative disorders, but we also know that some patients have very little phenotypic manifestations, at least at first. Sometimes it can get worse over time, but they have the same deficiency, very little disease severity. And there again, we saw that the intestinal microbiome and metabolome could distinguish individuals with different degrees of disease severity.

**Dr. Mariam Hanna**

Okay, how does defective ROS signaling reshape the microbial metabolic environment? Sorry, that was a mouthful.

**Dr. Emilia Liana Falcone**

So what we found in CGD, and this was largely based in a mouse study, is that depending on the CGD genotype, there could be sort of different impacts at the level of the intestinal barrier. Some of these impacts were altered reactive oxygen species production by the intestinal epithelial cells, sort of in response to the phagocytic ROS.

There's also changes in mucin production. So in some cases, there was less mucin being produced. Differences in also containment of the microbes. This had a lot to do with changes in patterns we saw in IgA versus IgG and IgM coating of intestinal bacteria.

And we also saw changes in Th1 and Th17 responses at the level of the intestinal lamina propria and ultimately increased inflammasome activation both at a systemic level and locally. What we found is that there was sort of this paradoxical state where the immune deficiency predisposed to dysbiosis certainly, but it also created this certain environment at the level of the intestinal barrier that then amplified the inflammatory responses to this intestinal dysbiosis that was driven by the genotype.

So we got really, really interested actually specifically in NLRP3 inflammasome activation. And knowing that we weren't the only ones to have seen this in CGD, we really started to wonder what could be like sort of the functional link between intestinal dysbiosis and increased NLRP3 inflammasome activation, especially systemically.

That got us really into a brand new field of investigation with respect to the functional study of the intestinal microbiota. It's one that's not very studied in general, but has a lot of promise. And that was looking at the production of bacterial extracellular vesicles by the intestinal microbiota.

So we know eukaryotic and prokaryotic cells both produce extracellular vesicles. So that includes bacteria. And these vesicles are these lovely parcels that contain proteins, metabolites, nucleic acids. And we know that they interact with host cells through different mechanisms; like even a bacterial extracellular vesicle will interact with a human host cell.

So we started studying these vesicles collectively from the stool of patients, so from their microbiota. And we found that actually what we call GMEVs—gut microbiota-derived extracellular vesicles—from patients with CGD and IBD not only drove more intestinal barrier dysfunction, but they also activated more of the NLRP3 inflammasome.

And we saw that this was happening actually in a TLR4-dependent manner. So we think that these GMEVs could be, for example, a very plausible way that intestinal dysbiosis could actually get translated into a specific inflammatory pathway.

**Dr. Mariam Hanna**

It goes without saying, you don't think this is all hype. This is all epiphenomena. This is convincing to you. Is that correct?

**Dr. Emilia Liana Falcone**

Absolutely. Absolutely. Because we make it our mission to study these effects functionally.

So one of the ways through the study of these gut microbiome-derived EVs, which if we take them and we co-culture them with intestinal organoids, we could clearly look at their inflammatory impact. But also if we just give them to mice, we can recapitulate certain elements of immune dysregulation seen in certain inborn errors of immunity—in this case, in chronic granulomatous disease.

And another way we look at it, which is a little bit more commonly done, is we've also colonized germ-free mice with the microbiota from patients with CGD and healthy individuals. So we'll look systematically at microbiota from healthy individuals, patients with CGD with and without inflammatory bowel disease.

And we clearly see that a CGD mouse colonized with the microbiota from a patient with CGD and inflammatory bowel disease will have more severe colitis and will exhibit certain aspects of the immune dysregulation at the intestinal barrier. So for me, that's a great way to show causality.

**Dr. Mariam Hanna**

Excellent. Excellent. Okay. And now it's slowly time to peel you from benchside to bedside to the therapeutics.

So I'm going to bring you in a little bit, or we'll start. The ketogenic diet, that data is striking. Are we changing the microbiome, the immune system, or as we talked about earlier and a few times already, a bit of both?

**Dr. Emilia Liana Falcone**

Well, it's actually both. So in work that we recently published in *Blood*, you know, we were looking for a sort of dietary intervention that we can use to help treat CGD-IBD and ideally one that would target the NLRP3 inflammasome.

So that's where we came up with the idea of testing a ketogenic diet in these mice, which in mice, it's basically a lot of Crisco. And seriously, it's very greasy. And what we found is that definitely giving a keto diet to mice with CGD, even more so than actually wild-type mice, led to a decreased susceptibility to colitis, and this by blocking the NLRP3 inflammasome.

But we also looked at the microbiome and we found that it was clearly altered compared to mice who were on the control diet. But just to push that last part a little further, we actually took the microbiota from mice that were fed the ketogenic diet and then transferred them to germ-free mice just to see if the stool itself could transfer some of these benefits.

And it did. To a certain extent, it did protect the mice from colitis. So that did show that, you know, yes, there's a direct inhibition, but there's also a change in the microbiota that had that—increased, I would say, the protective effects at the level of the intestinal barrier.

**Dr. Mariam Hanna**

Fantastic. Bring on the Crisco. Where are we with these microbiome targeted therapies today? Like where do they stand? Prebiotics, probiotics, anything else out there?

**Dr. Emilia Liana Falcone**

Hmm. I think these approaches are generally very promising. I think in the realm of inborn errors of immunity, it's still very much in the research space in the context of, you know, carefully clinically evaluated studies.

I would say that especially, for example, in CGD, where we tend to try to modulate the microbiota in some cases with diet. So there was a study that looked at exclusive enteral nutrition, for example, which we know works very well in pediatric Crohn's disease. There's also some studies underway looking at fecal microbiota transplantation in CGD and also in a couple of other inborn errors of immunity.

So I think we're sort of there. I think that our work in mice probably brought forward maybe ketogenic diet, if not necessarily as a definitive treatment for CGD-IBD, maybe just something that can serve as an adjunct, like sort of improve maybe or prime better immune responses to certain immune modulators. That's an aspect that we think is really fascinating, a really good potential space for microbially-based interventions in the realm of inborn errors of immunity.

**Dr. Mariam Hanna**

Okay, fair enough. And if you had to prioritize one research gap that would actually change clinical practice—I know I keep telling you I want something at the bedside—what would it be right now?

**Dr. Emilia Liana Falcone**

I think we really need an actionable biomarker where we could link immune genotype with phenotype and microbial function. And again, I think with that, I want to reiterate that I feel like the future of treatments in the realm of inborn error of immunity could very well be this combo of a sort of immune modulator with some form of microbial modulation, whether that be with a metabolite like a postbiotic, whether that be with a dietary intervention, it might be with fecal microbiota transplantation, or even who knows, maybe a GMEV.

You never know, you know, but something that I feel could prime for better responses to treatments and maybe then lead to less intense treatments and perhaps reduce toxicity in the same line of thinking with that.

**Dr. Mariam Hanna**

You heard it here first. Calling all researchers: get your gears going here. All right, time to wrap up and ask today's immunologist, Dr. Emilia Liana Falcone, for her top three key messages to impart to patients and physicians on today's topic, microbiome in IEI. Dr. Falcone, over to you.

**Dr. Emilia Liana Falcone**

All right, so in IEI, the microbiome is often a functional readout of immune genotype and not just an external exposure. I think that's really important. The second point is the real signal in microbiome research comes from mechanism, linking microbes to barrier physiology, to immune pathways and metabolism.

And finally, the future is precision combination therapy, where we compare microbiome-directed approaches with immune modulators.

**Dr. Mariam Hanna**

That's perfect. Thank you, Dr. Falcone, for joining us today on today's episode of *The Allergist*. Thank you.

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Thanks for listening. Sincerely, *The Allergist*.