EPISODE 1 :: PROBIOTICS & THEIR DEMONSTRATED MODES OF ACTION

Featuring :: Adam Baker, PhD; Karyn Wulf, MD, MPH

TRANSCRIPT

Maura: I'm sure you've been hearing a lot lately about probiotics, and how important they can be to our overall health—especially now, at a time when immunity seems particularly important. These microscopic bacteria tend to look and behave a lot like the "good" bacteria already living in our gut. They're said to provide digestive balance, boost immune health, and keep your gut working as intended—which are all great things.

Maura: But what *are* probiotics, really? And how do they function to bring all these benefits to bear? Is a single probiotic strain enough to make a difference, or is a blend of strains a better approach? How are they made? How much is enough? And do they work better for some age groups than others? Clearly, this is a big topic, and we have a lot of ground to cover to really do it justice.

Maura: That's why we've decided to create a podcast series around probiotics, dividing the discussion into three different episodes. So today, we'll talk about probiotics and their demonstrated mode of action. In episode two, we'll address strain differences among probiotic species, along with their clinical relevance. And in our third episode, we'll discuss probiotic manufacturing and quality.

Maura: I'm Maura Bowen, podcasting for Abbott Nutrition Health Institute. I'm honored to have with me today Dr Adam Baker, Director of Science, Human Health Innovation for Christian Hansen in Hørsholm, Denmark. Also joining us today is our own Dr Karyn Wulf, Medical Director of Pediatrics here at Abbott. I'm happy to get to cohost with Dr Wulf today because she's responsible for all the great interview questions you'll hear across the next three podcast episodes. Dr Baker, Dr Wulf, welcome!

Dr Baker: Thank you so much.

Dr Wulf: Thank you, Maura.

Maura: Let's set the stage a bit by telling our listeners a little bit about yourselves and your backgrounds. Dr Baker, let's start with you.

Dr Baker: Thank you Maura. My name is Adam Baker. I am currently the Director of Science and Human Health at Christian Hansen in Denmark. I've had the hour of working at Christian Hansen for the last eight years, where really, we've been focusing on the critical role that bacteria play in the microbiome throughout the life stages. And of course, there's a particular focus on the microbiome and the developing microbiome in infants and as they're born. Going back a little further, I actually have been working on the pharmaceutical and biotech industry for over 20 years, where I've been lucky enough to be working with complex diseases and oncology, and trying to advance and understand therapies and diagnostics to support patient diagnosis and treatment in many serious diseases.

Maura: Excellent. Thank you for that. And how about you, Dr. Wulf?

Dr Wulf: So nice to be here today. Thank you for having us, Maura. And Dr Baker, we're thrilled to have you here today. I am a general pediatrician and I have been in clinical practice for 18 years and I am the Medical Director for pediatrics here at Abbott.

Maura: Thank you to you both for the helpful background. I have a few notes for our listeners before we get started today, because the Covid-19 pandemic is still our daily reality. So, we're dialing in for today's call. As I mentioned, Dr Baker is calling in from Denmark, and Dr Wulf and I are ringing in from Columbus, Ohio. So, our recording quality may sound different from what you're used to hearing. Secondly, we're going to switch up our the format we established in our first series episode so we can get a dialog going between our two experts. Dr Wulf will do the interviewing with added commentary, and Dr Baker will provide his insights.

Maura: Dr Wulf, are you ready?

Dr Wulf: Absolutely.

Maura: All right, great. Well thanks, Dr. Wulf. Take it away.

Dr Wulf: Great, Maura. Thank you so much. Dr. Baker, it's great to speak with you today. To start us off, can you tell us a little bit about how probiotic strains are selected for use in human health?

Dr Baker: Great, thank you, Dr Wulf. I'm very excited to be talking today. So yeah! I mean, how are probiotic strands selected? I think here at Christian Hansen, we're developing a whole package of information around probiotic strains before we even start to think about how we use them in human health. And part of the work that I'm doing, part of the work we're doing here at Christian Hansen is focusing as much as we can on understanding as much as we can about these probiotic strains and then delivering them into the right time, in the right place, where we start to focus on how we can use them in human health. So, some of the things we think about is we do a complete and comprehensive analysis of their genomes—these strains and their origins—and are they safe to use. These are key things we do before we even start to study how they work. Then, real fun stuff, we start to do extensive scientific data in the labs—pre-clinical data, we would call it—studying how the potential ways to provide bacteria can work in the human body. This is what we call modes of action. And based on these data, we can start to select particular strains for particular health benefits and indications. We even have an artificial gut system which I'll touch on later, which you could help to use to understand how the bacteria perform as they go through our gastrointestinal system. And finally, at the end of all of this, we also start to deliver clinical information and clinical understanding on how the strains work. And we put all of these things together. This is everything we have to think about when we start to talk about what is a probiotic strain, and how we're using it for human health.

Dr Wulf: That's fantastic. As Maura said in her introduction, there's a wide range of uses for probiotics but to focus our discussion a little bit today I really would like to focus on the pediatric space. So, are there any preclinical or clinical studies about the health benefits of probiotics in pediatric patients?

Dr Baker: Yes. The simple answer is yes. There's a lot of information, and this information is growing at a rapid rate now. Particularly now we understand more about the microbiome and the critical role of bacteria in young and first-born and even before, so we really started to understand this space. So, there's a lot of preclinical data and a lot of clinical data in the pediatric space. I think you have to be quite careful now, though, because now what we need to do is actually understand in this space and with the science of probiotics, what are we actually talking about? Which are the scientifically-described strains and how are they actually being used? It's something we're very proud of at Christian Hansen, that we can talk about how a certain probiotic strain is working in that space at that certain time in your life, doing a certain function. And that's what you have to focus on very, very much: No probiotic is the same, and they don't all do the same thing.

Dr Wulf: So, focusing our conversation even more, there have been quite a few papers published over the last 20 years looking at the use of probiotics in the NICU, and more recently some studies published by major pediatric societies talking about the use of probiotics in the pre-term population. Could you tell us a little bit more about some of the probiotics that Christian Hansen makes that can be used in the space?

Dr Baker: Yeah, I think we're actually very proud of what's been happening. There's a recent position paper from the ESPGHAN committee on nutrition and working group on probiotics and prebiotics. And they actually recommended specifically certain strains. One of them is a combination of what we'll talk about it more today maybe: the Bifidobacterium, BB-12 (*Bifidobacterium animalis* subsp. *lactis* BB-12®), Bifidobacterium infantis (*Bifidobacterium infantis* (DSM 33361) and S thermophilus TH-4® (*Streptococcus thermophilus*, TH-4®), all of these coming from Christian Hansen, which are used as a combination and have been demonstrated to be very, very effective in preterm infants in reducing certain instances of NEC. I think this also comes from the fact we have such a depth of science, a depth of understanding, and you'll hear later a depth of quality and safety from these products, and it's really being recognized by these associations.

Dr Wulf: So, you mentioned the B. infantis, the B. lactis, and the strep thermophilis as three strains Christian Hansen makes that have been recommended. Could you talk a little more about the mechanism of action of each of these strains?

Dr Baker: Yeah, I would love to. And it's fantastic that we're actually talking about the mechanism of action of strains, because all strains are different, and all strains can work in slightly different ways. We're talking about the infant gut and we're talking about the pediatric space. And we know that Bifidobacterium's genus is very important. And there are certain species within this genus that have more specialized roles in the infant gut. One of them is the infantis. And infantis has sort of been specialized to utilize in HMOs. These are the human milk oligosaccharides found in breastmilk. It's been demonstrated. We can show it. You can see it from the genome, and we can show it in the lab that the infantis strain can help colonize the developing gut as they utilize these HMO to grow. But there are other modes of action we need to think about. There are things we can consider about how we would reduce gut pathogens. The BB-12® strain—Bifidobacterium BB-12®, in the combination of three strains—has been demonstrated to do this.

Dr Baker: We can also talk about immune effects, and we'd like to consider how we can boost and support the development of the immune systems and the infant gut. And we can demonstrate again with the BB-12® strain and the TH-4®® strain in this combination, how they've actually being used and have a favorable inflammatory response, and actually is used in building a healthy immune system. So, these are the types of combinations that effect the modes of action we like to think about. Solely, they're all so important and very beneficial, but put together they can be even more beneficial.

Dr Wulf: Dr. Baker, can I pause here for a second and ask you to clarify? Sometimes use numbers and strain names interchangeably. Could you explain that system a little bit to our audience?

Dr Baker: Yeah, I'm actually trying to talk about the names of the bacteria so you can understand what form of species or strain name. So, it's a Bifidobacterium animalis (*Bifidobacterium animalis* subsp. *lactis* BB-12®) and then sometimes we've been able to give them a specific name because we have so much data and supporting data around them, so we call that Bifidobacterium animalis (*Bifidobacterium animalis* subsp. *lactis* BB-12®) , we call it the BB-12® strain.

Dr Wulf: Fabulous, thank you. Clearly there are a lot of studies about the Bifidobacterium animalis (*Bifidobacterium animalis* subsp. *lactis* BB-12®) , we've also been talking about that same strain, we call it BB-12®. What makes this particular probiotic so important?

Dr Baker: We're actually very proud of the BB-12® strain, as I'll call it from now on. It really is actually the best

documented Bifidobacteria in the world. There are many hundreds of publications but if you look closely, we can describe over 80 clinical trials that have been done with BB-12® within the infant and child space, so this is a very interesting strain. We have a mammoth amount of data available on the strain and we understand very well how we think it actually can work so we know. We know that actually by itself very, very good infant strain in the sense of what it does to support the infant microbiome. You can see more information on the Probiotics Institute, which is an educational resource we have hosted at Christian Hansen. It describes how BB-12® has been associated with many health benefits in infants and children.

Dr Wulf: So, Dr Baker, what benefits do TH-4®® and B. infantis add for infant gut health?

Dr Baker: Now that's a great question. So, we stopped to look at the B. infantis—the bifidobacterial infantis. It's been shown that certain species of Bifidobacteria are found in the infant microbiome, and the infantis is one of these. The TH-4®® strain, what we've been able to demonstrate in the lab is it really can actually start to promote beneficial immune responses. And that's really good and really important because we really know this development of the microbiome in the infant is also key with the development of the immune system. We like to see these combinations. So, this is a complimentary type of mode of action, and you can even consider it like an additive effect of having these different strains that have sort of different functionalities or characteristics present.

Dr Wulf: So, Dr Baker, in your earlier description of the work done at Christian Hansen, you say you have studies on each of the individual strains. Are there any individual clinical studies you'd like to call out for our audience to help them understand the individual strains?

Dr Baker: We can see different combinations of different individual strains being used. We're very, very lucky when we think about the BB-12® strain, the bifido animalis (*Bifidobacterium animalis* subsp. *lactis* BB-12®) , because this has so many clinical trials on it. So, there are strains there where you can start to understand how that works in combination with the TH-4®® or sometimes by itself. So, in particular I think there are some studies that we've been very, very interested in where we actually considering basically focusing on the Mohan, et al, study from 2006, but we're actually studying how BB-12®, the bifidobacterial lactis BB-12® is actually able to affect the intestinal microbiota. We've seen some very, very interesting results there.

Dr Baker: We've also been able to see how the BB-12® lactis (*Bifidobacterium animalis* subsp. *lactis* BB-12®) can actually have an effect on incidents of possible infections in very low birth-rate infants. These are the types of studies we actually use to actually give us information about how they actually sort of work together in different modes of action, building up that scientific evidence, building up the clinical evidence around strains, about how they're really working in preterm infants.

Dr Wulf: So with all of that individual data on the individual strains, what happens when probiotic strains are used together? Do you find benefit from combining certain strains?

Dr Baker: We can certainly demonstrate the way single strains work, and that's often what we do and that's certainly what I spent quite a lot of time doing in the labs with my teams. We need to understand how they work individually. And we can certainly show also (or, we want to show and are showing) in certain situations, combining strains has certain advantages. In the instance of this particular combination of the three strains we're actually showing that the infantis strain—the Bifidobacteria infantis—is able to bring its utility, is ability to grow on HMOs, so the situation, we have immune stimulatory effects of the BB-12® and the TH-4®® strain…these are different modes of action, all highly related to a healthy infant microbiome, healthy infant gut. So, bringing these multiple modes of action together is very likely and has been demonstrated with clinical trials to be beneficial.

Dr Wulf: Dr. Baker, you described several of the advantages of combining strains. Are there any clinical studies looking at this particular combination of the three probiotics strains we've been talking about today in the neonatal intensive care unit setting especially looking at outcomes like necrotizing enterocolitis or NEC?

Dr Baker: Yeah, that's it, that's a great question. And I think this is actually very important that actually with these three combinations of strains there are actually two clinical studies we focus on a lot; the Bin-Nun, et al, study from 2005, where exactly this, we were looking at 145 preterm infants, and the outcome of this trial was that actually the probiotic group had significantly lower instances of NEC and significantly less sever NEC than was seen in the placebo group. This was great finding of the study, and this was then complemented very much by the Jacobs, et al, study that was published in 2013. This was a very large multicenter double-blinded study where over 1000 preterm infants were studied. (There were actually 1099 preterm infants.) And the findings again were very positive that in the probiotic group, you had a 50% lower instance of NEC compared to the placebo group. I think this is very, very important because this also complements all the science we've been developing here at Christian Hansen of the individual strains clinically and with the mode of action science and the safety data that we use to describe how these strains work.

Dr Wulf: If we change tactics a little bit, could you talk to us a little bit about a probiotic dosing? How are the doses of probiotics or the number of colony forming units (or CFUs) decided? And along those lines, can you over- or underdoes probiotics? Should we be thinking of probiotics like drugs and thinking of a therapeutic window or do they act differently?

Dr Baker: That's a great question—a really interesting question and a challenging question. Dosing, it's a good discussion. In some respects, we have some of the answers already because we've already seen that when we use some of the doses, we're using with these three strains in clinical studies, we can actually see clinical efficacy. We can see the strains are working at that particular dose. So, at these levels we can say they are having the effects, they are reaching the part of the body, they are reaching the gut and they are doing what we'd hoped they would be able to do. But, when you start looking at the science of the strain, that is when the discussion can become interesting, because we can start to think about the mode of action and then we can start to think about how the probiotic is eliciting that effect. And that can actually help us consider what is the type of dose we would expect or foresee we would need. And if I try to allude a little more to this, if we're thinking about a sort of seeding or colonization, you're looking for a dose of the bacteria, like the infantis, where you will hope that it will get to the lower colon and it will be able to sort of colonize and grow within that colon and have it effect. So, it may not be needed to be in such a high dose to have that effect. Whereas you may need a slightly higher dose or would consider that if you're thinking about an immune stimulatory approach in the small intestine that maybe the TH-4® is eliciting or sometimes we might use another strain, then you might be considering a slightly higher dose so it can have its effect transiently in the small intestine. So, it's a great discussion, and can you overdose? It's very difficult to consider that you could overdose with these types of bacteria, but we can certainly consider how we expect the dose to work by thinking about how the strains work in what context.

Dr Wulf: So, along those lines, one of the questions that I sometimes hear from clinicians or parents is, is more better? Or can you combine probiotic products?

Dr Baker: Yes. And I think—is more better?—in certain cases, what we can say is that we can certainly like to combine probiotics, and that's thinking about having synergistic or complementary effects. So, we've demonstrated here, and we talk about it with these three strains, how they have complementary effects. So that in terms of adding more strains together can certainly be beneficial. The amounts you add of that is not quite so black and white, that you just add more and that is better. You need to have an amount added. You need to give a clinically relevant dose. And what is a clinically relevant dose? That depends on how you expect the bacteria to perform its function. And again, we have to think about each of the bacteria can perform its function in different ways. So yes, it's a slightly complicated answer but that's where we consider these things.

Maura: Wonderful insights. Thank you both for this discussion. I hope you're ready to keep talking about this topic because as you know we have two probiotic episodes to go. So: Hydrate yourselves – we'll plan to discuss strain differences next.

Maura: Meanwhile, for our listeners, both Abbott Nutrition Health Institute and Chr. Hansen have a host of educational materials on our respective websites to help you learn more about some of the concepts we discussed on today's podcast episode. Visit anhi.org today and click "RESOURCES" and then "KNOWLEDGE HUB" to find probiotic related content on neonatal health and the microbiome. And, be sure to visit the Chr. Hansen Probiotics Institute—theprobioticsinstitute.com—to learn more about how probiotic strains can benefit the microbiome across the lifecycle. (I mean it—they have a probiotic benefits video that is not just informative, but visually pretty jaw-dropping. So be sure to check that out.)

Maura: Finally, be sure to return for our next two probiotics episodes to help us continue this important discussion.

Maura: Thanks everyone. Stay healthy and safe.