Dana Philpott's Cutting-Edge Research of Host-Microbiome Interactions in Inflammatory Bowel Disease

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Dr. Dana Philpott

After completing her undergraduate degree in cellular, molecular and microbial biology at the University of Calgary, Dr. Dana Philpott went on to complete graduate school at the University of Toronto. Her graduate work involved studying enterohemorrhagic and enteropathogenic *E. coli* under the supervision of Dr. Philip Sherman in the Department of Molecular and Medical Genetics. Dr. Philpott then went on to complete a Postdoctoral Fellowship at the Institut Pasteur in Paris, France with Dr. Philippe Sansonetti. From there, Dr. Philpott was appointed a Group Leader at the Institut Pasteur. Today, Dr. Philpott is an Associate Professor at the University of Toronto in the Department of Immunology. Dr. Philpott's research talents have been widely recognized in the form of a number of prestigious distinctions and awards. These include the Marie Curie Research Training Grant, the CIHR Post-Doctoral Fellowship Award, the EMBO Young Investigator Award and, most recently, the 2011 CIHR New Investigator Award. Dr. Philpott brings to the field of immunology research her strong background in microbiology and a passion for understanding the molecular and cellular basis of both innate and adaptive immunity in bacterial infection and auto-immune disease. Dr. Philpott is featured in this edition of the UTMJ alongside her colleague, Dr. Ken Croitoru. Together they have won a 15-million dollar Canadian Foundation for Innovation (CFI) Leading Edge fund which they have used to establish the University of Toronto Host-Microbiome Research Network (HMRN).

UTMJ: Could you describe how you first became interested in research, and your journey to becoming a gut-centric immunologist?

DP: I guess my decision to go into research was when I was doing my Bachelor of Science in Calgary and I didn't know what the heck to do after I got my degree. In those days, I didn't really know that this life existed; you weren't really exposed to research in those days, I think, as much as you are now. So I decided to take a job as a technician after my Bachelor's degree. I was doing medical research for someone at the University of Calgary, working on GI physiology questions and I just really enjoyed it! I loved it and I had such good mentors there, and they really pushed me to do graduate school. They said "Get out of here, you've got to do graduate school!" So, I decided to go to the University of Toronto. I came here and did my PhD with Phil Sherman at SickKids and we worked on microbe-host interactions in the context of diarrheal diseases. We were looking at the bacteria that causes Hamburger disease 'O157:H7', an enteropathogenic *E. coli*, and examining the mechanisms of how these bacteria cause the host to respond. I decided I wanted to continue in research, so when I decided to do my post-doc, I thought: Okay, there's this fellow at Stanford University, he's like the biggest guy in cell microbiology …. But, then there was a guy at the Institut Pasteur in Paris who was also one of the big names in this field…I decided to go to Paris.

UTMJ: Do you speak French?

DP: I do…not perfectly. *[Laughs]*

UTMJ: It must have been good enough to get by as a Postdoc.

DP: *[Laughs]* Exactly, I was good enough. I didn't know any French when I got there. Yeah, it was really hard, actually. We had lab meetings in French that were very difficult…

UTMJ: Wow. That was really brave of you. It must have been scary…

DP: I was just stupid, actually. *[Laughs]* I went in with very closed eyes. That was probably good or else I probably wouldn't have gone if I had known how difficult it was. I would've been like, 'No I don't wanna do this' *[Laughs]* …. Yeah, so I did my Postdoc there and again had amazing mentors, and I was able to get a permanent position at the Institut Pasteur as a group leader after 4 years of postdoctoral work. I stayed there for another 5 years with my own independent lab, which was really nice and then my husband [Dr. Stephen Girardin] and I decided to look [for work] in Canada, and came back to Toronto. Both of us were offered positions here; he's in Laboratory Medicine and Pathobiology and I got Immunology. I always say that I'm a microbiologist but we study the host response to bacterial infections, so, in that way I'm an immunologist, but not the pure kind of immunology that goes on down the hall from me. *[Laughs]* Which is good, it's a learning experience, right?

UTMJ: It seems like it would be valuable to bring a different perspective to things

DP: Yeah! I think [it's] really nice here that, you know, my immunology friends here have taught me so much and then I bring in the microbial angle. Everyone thought as an immunologist that [microbes] just throw LPS [lipopolysaccharide, an endotoxin]. Some people didn't even know what LPS was…they only knew it comes from gram-negative bacteria, but they didn't really understand what that meant. I bring in more the bacterial perspective, I think.

UTMJ: You do a lot of work in collaboration with other groups, both focused on basic and clinical gut immunology, but is there a question that you're most interested in answering through your research? How do you set out to answer that question?

DP: I've always had an interest in gastrointestinal physiology since I was doing my technician work, and now I think it's really bloomed into this interest in Crohn's disease. For me, that is really…you know [with] all of my research, we do things that are not directly related to Crohn's, but I always try to bring it back into the idea of 'how does this effect gastrointestinal inflammation?' Overall, we're trying to understand how the innate immune system contributes to the pathogenesis of this disease. That's really my mission statement, I guess: to understand Nod-Like Receptors and their implication in disease pathogenesis. So we have that angle, and we also have the microbial angle. We're looking at the microbiota and how different components of the microbiota can either be protective or contribute to the inflammation that we see in Crohn's disease. Most of my work is animal-based and we use a lot of animal models in colitis and intestinal inflammation in general. So, weaving this kind of idea of the host response as well as how the microbial signals contribute to the pathogenesis of disease – [that is my research focus].

UTMJ: I understand your research is primarily basic, but you're also somehow involved with the GEM project, a large clinical study lead by Dr. Croitoru*. What is your role in that and how does the work you two do feed back and forth?
**Editor's Note: An interview with Dr. Croitoru is also featured in this issue.*

DP: Yeah, I'm not directly involved…but their findings certainly influence the work that we do in the lab; I think that's the biggest thing. Ken [Croitoru] and I are good friends, so I know a lot of what that project is bringing in and also from his basic research, too. We do a lot of projects that are together. We share a graduate student, Ashleigh Goethel; she does research in both my lab and his lab that is related. She's really the person that brought together the idea of the Nod-Like Receptors and the microbiota and how this relates to what they're seeing in the GEM project.

UTMJ: So, you've been able to take some of the data from the GEM project and look at it in your lab?

DP: Definitely, I mean it definitely influences what we've been doing with animal models. They've been looking at…did you talk to him?

UTMJ: We did…he said to ask you about Nod-2.

DP: Yeah, the work he's done in patients has really influenced what we do because, as he was saying, they were trying to see if the genetic defect seen in the Nod-2 gene [that has been] associated with Crohn's disease somehow influences how the microbiota organizes itself in the gut. So far, they haven't seen a genetic influence on the microbiota as such in this disease context (although, there could be other diseases where you could see a difference), and it's exactly what we mirrored in the animal model. So we used an animal model of Nod-2 deficiency to model what they see with patients, and we saw that the structure of the microbiota does not differ between normal mice and these mice deficient for Nod-2. So for us – and again his work has influenced us and I think the field – really it says that it's not the genetics *per se* [directly influencing the gut mucosa]. It's more [that] if you have the genetics, the inflammation itself is what modifies the microbiota. His work is really suggesting that, and our work in mice mirrors that.

UTMJ: Interesting. Conversely, have findings from your lab influenced [the GEM] project? Is there some sort of information flow in that direction?

DP: For sure. One of the new areas of research in our field that is coming out (and we're just starting to do this) is that you can grow primary human intestinal cells *in vitro*. So, you take stem cells from the intestine of humans, of patients, or normal people, and you can culture these in vitro and they actually grow into what we call a 'mini-gut'. It's actually very weird, but it's amazing. So they form this little spheroid thing that has crypts sticking out of it like a little flower, like a daisy, and it reconstitutes all the cells within the epithelium: the enterocytes that absorb nutrients and water, these Paneth cells which are important in microbial defense. It's the colon or the small intestine…you can grow either piece. But the nice thing for us is that it reconstitutes the total cells that are within the intestine. So then what we're doing with Ken and also Mark Silverberg (who he works with a lot too) and also in collaboration with my husband [Stephen Girardin], is we're taking patients who have a certain gentotype – they can have the Nod-2 mutation or another muta-

tion seen in Crohn's disease – and we can grow these cells *in vitro* and then we can try to see if they have some defects that we are already seeing in our animal model. This way, we can really study in the context of the disease what a given mutation does to the epithelial cells, how it affects their organization, and how it affects the different cell populations, such as Paneth cells, goblet cells, etc. You can really focus on these *in vitro*, so [this method] is going to open up so many different avenues for us in terms of our research. It is really an exciting time for us!

UTMJ: It sounds incredible!

DP: It's really nice. Moving forward with patients, the hope is that we can bank stem cells from all the patients that come in, and then in the future we'll be able to test different drugs on these intestinal epithelial cells. Some people say that we can maybe correct the defect; you can use these systems of gene editing to fix the mutation and actually transplant these cells back into the patient. This is where the future is going and there are people, such as this man in the Netherlands, actually trying to fix cells in vitro and transplant them back to the patients.

UTMJ: Does that mean that you are interested in developing therapeutic interventions, or are you more interested in defining the disease and understanding the microbiology and immunology behind it?

DP: I guess I'm really interested in understanding the disease pathogenesis, but I think we're at this point now where we can perhaps go forward with a few ideas of how to look at treatment differently. So, we're developing a certain assay right now, which I think is really exciting, in collaboration with Vertex Pharmaceuticals, and the idea will be to do a high throughput screen to try to correct this particular defect. For me, I want to be involved in the cure process as well. I think that would be exciting, so I think the development of this assay could, again, suggest different ways of treating Crohn's disease that we haven't thought about. Like, right now Crohn's disease is all about dampening the inflammation, not getting to the root of the issue, so I hope with the kind of research that we're doing and perhaps with this new screen, we'll be able to reverse the actual defect rather than just dampen [inflammation] by giving patients steroids or anti-TNF, which is one of the big treatments in Crohn's. [This assay will] really get to the heart of the defect that's involved in Crohn's. We'll see.

UTMJ: You guys have this huge research network that requires a lot of interdisciplinary expertise. What is it about IBD, the immune system or the microbiome that makes that approach to research necessary?

DP: I think the complexity of the microbiota…I mean there's, you know, maybe a thousand or more species within our gut and [we question whether] there is a possibility that we could maybe target one of those organisms, get rid of them and then influence our health. I think that's really the exciting area now, and I think it's something that's really tangible to the public as well. That's why I think it has really taken off because, you know, you tell people that aren't in science what you're doing and they automatically know about the microbiota. They ask me all the time "Probiotics, what do you think?" or "Should I take antibiotics because I know it's going to wipe out my gut microbiota. What should I do?" So I think it's the complexity of the microorganisms, and we also still don't know what constitutes health in terms of the microbiota; we have no idea. We know some general features of dysbiosis and disease but we don't know if that's causative yet. [As] I was mentioning with the bacteria in Crohn's patients, there's no change at baseline, but we have inflammation that changes the microorganisms. So we don't know anything yet about causation, and [we wonder if there is] an organism that's actually pushing the disease…

UTMJ: That's something that Dr. Croitoru mentioned. He said that if there is such an organism, it probably disappears by the time the patient arrives or that it is not well defined.

DP: Exactly, we can't find it. It's too low-abundance within the huge populations in the gut mucosa. And, I guess on top of the complexity of the organisms [involved] is the complexity of the products they produce. So there's a lot of interest right now into the different products produced by this class of bacteria: short-chain fatty acids for example. We're working on one called uracil and how that influences the host. So, it's the bacteria, it's their metabolites, it's their cross-talk. Maybe in the presence of one bacteria, an organism doesn't make a certain metabolite, but when there's another population it will start making something else and then that might affect your gut. So it might not actually be the bacteria, but it could be something else that's influencing it to produce a given metabolite so … there's a thousand different possibilities …

UTMJ: It sounds like you guys need a lot of computational power to sort this out…

DP: Oh yeah, and mathematical models. I think there's an interest in trying to develop mathematical models to try to understand all of these different complexities, but I think when you're talking about 1000 organisms, all the metabolites they produce, all the relationships they have with each other … it's beyond my comprehension.

UTMJ: So basically, it's the complexity and also all of the different levels of host-microbiome interactions that makes this area so hard to sort out and that requires so many perspectives.

DP: Yes, exactly!

UTMJ: Before we wrap up, is there an innovation that you're most excited to see develop over the next 10 years, or perhaps a methodology that you're really excited to work with?

DP: I like both of those options actually… *[Laughs]*

UTMJ: You can answer them both!

DP: Like I was mentioning, I think the development of this ability to edit stem cells and [use them in] transplantation… I think that has some huge potential in the future. I mean, there are these kids that have these horrible gut disease that need intestinal transplants at birth and this fellow in the Netherlands is working on a way to try to repair those intestines using the patients' own stem cells. So that's a really nice idea, right? You don't have to worry about any rejection … although you do have to worry a little bit about gene editing and whether you can get rid of the vectors to make sure you don't get cancer later on. All of these things are a bit of a worry, but I think that's the real excitement in the field of gastroenterology right now, is the potential of these stem cells and how we can use them to cure diseases. And then on the other side, I also like the microbiota part. I think it's going to be amazing to see in the future how we can modify the microbiota. I'm on this team grant – it's not me, but a group here – working on phages, which are viruses that infect bacteria, and using pieces of the phage to try to target specific bacteria within the microbiota. Which is going to be amazing. Rather than antibiotics, you're going be able to take what is like the tail fibre of the phage and poke a hole in only that species of bacteria and get rid of it. That's where they're trying to move forward in terms of modifying the microbiota. I think that's the big thing: modifying the microbiota and [figuring out] ways we can do that. Do we know what a healthy microbiota is? I don't know, but this ability to get rid of single species will be huge for us to try to understand their contribution to overall health and disease. And then, the other side of the stem cell work is mind-boggling; I love that.

UTMJ: It seems like in the next couple of years there is going to be a lot of amazing research and innovation happening in your field. It's exciting.

DP: Yes…and I think the amazing thing too is my students, my Postdocs, because those guys are the ones who come up with a lot of these ideas; I should also mention them. They're the one's that really push the research!

UTMJ: I saw on the door to your lab it says 'Dana's Troops'! This seems like a fun place to do science.

DP: *[Laughs]* Yes! They're great! I think that's the nice thing about being a researcher, when you have people working with you that are amazing and bring the ideas [and] who are so excited about research, too. That's really fun.