

Dana Philpott: Exploring the land of NOD

Scientist and mom Dana Philpott has dedicated her career to figuring out how mammalian NOD-like receptors detect invading pathogens and help prevent autoimmune disorders such as Crohn's disease.

While a postdoc in Philippe Sansonetti's laboratory at the Pasteur Institute in Paris, Philpott and her colleagues made the surprising discovery that the toll-like receptors, which initiate inflammation in response to bacterial lipopolysaccharides and other pathogen-derived molecules, were not the only pathogen-sensing receptors in town. Along with Gabriel Nuñez at the University of Michigan, they had found a second set of bacterial detectors in the cytosol, which they dubbed nucleotide-binding oligomerization domain (NOD)-like receptors. NOD1 and 2 respond to specific bacterial peptidoglycan motifs by activating the JNK and NF- κ B signaling pathways (1). NOD2 turned out to be a sensor of muramyl dipeptide (MDP), a cell wall component of gram-positive and -negative bacteria

that is found in many adjuvant preparations. The group later found that a mutation in NOD2, commonly found in Crohn's disease patients, abrogates the immune response to MDP, suggesting that NOD2's ability to detect this ligand helps prevent the development of this autoimmune disease (2).

PATHOGENS IN PARIS

You spent nine years in Paris, first as a postdoc and then as a group leader. What brought you there, and what made you decide to stay?

I did my PhD in Toronto on host-pathogen interactions. So, when I decided to do a postdoc, I was looking for a laboratory where I could continue that work, and I really wanted to go to Europe. If you ask anybody in the world who are the top people working in host-pathogen interactions, they would say Philippe Sansonetti and Pascale Cossart, who are both at the Pasteur Institute. So I asked Philippe Sansonetti if it would be possible to do a postdoc in his laboratory.

He said, "Yes, but I have a two-year waiting list." So I waited for two years. I finished my PhD and worked as a postdoc at McMaster University [in Ontario] with Dr. Mary Perdue. Then I got some funding and went to Philippe's laboratory, and it was great. I loved it.

Once we made the initial discovery about NOD proteins and had a paper, I was lucky enough to be chosen by the Pasteur Institute for one of their first independent group leader positions. It was actually the first time they had done this in France. Usually as a young scientist you join a senior scientist's laboratory, develop your group within the bigger laboratory, and then someday you can break away. But this was the first time they actually offered young group leader positions—it offered complete independence to the young scientist.



Dana Philpott and Stephen Girardin

What were you looking for when you discovered the NOD proteins?

We were looking for a receptor that would respond to bacterial infection. We got interested in NOD because there's a family of these proteins in plants that do very similar things. When a plant cell gets infected, it can detect pathogens that come into the cytosol—what's called the hypersensitivity response. We thought there might be something similar going on in mammalian cells because we could see that these proteins could be activated after an intracellular bacterial infection. So now we know that NODs are expressed by a number of different organisms; even sea urchins have similar proteins. It's a huge evolutionarily conserved family.

Going back a little further, I see that you took three years off between getting your bachelor's degree and starting your PhD. What did you do?

I worked as a technician in Calgary for a lovely man named Decker Butzner,

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After becoming a group leader at the Pasteur Institute in 2002, Philpott continued to explore the role of NOD-like receptors in initiating innate and adaptive immune responses to a variety of bacterial pathogens, such as *Helicobacter pylori* and *Listeria monocytogenes* (3, 4). In 2006, she and her partner—and frequent collaborator—Stephen Girardin moved to the University of Toronto, where they continue to investigate the

who is a pediatric gastroenterologist. He showed me what research could be like. We did intestinal physiology, so I have a good basis in the intestine, which really makes an impact on my work now.

Is that where you became interested in host–pathogen interactions?

Exactly. From the basic studies we were doing on physiology, I wanted to look at

how bacteria interacted with the intestine, and I did my PhD with another pediatric gastroenterologist, Phil Sherman, who was working on enteropathogenic *E. coli*, which causes diarrhea.

What is it with you and the pediatric gastroenterologists?

I know! My first student was a pediatric gastroenterologist, and now I

have a pediatric gastroenterologist fellow in my laboratory. It's a funny connection, but it's great. It's nice to have the medical people around. They have a way of looking at questions differently.

NOD AND AUTOIMMUNITY

How do NOD2 mutations contribute to Crohn's disease?

About 30% of Crohn's disease patients have a mutation in NOD2. The mutation was discovered in 2001, and it was the first susceptibility gene that was linked to Crohn's. It caused a huge uproar in the community. Everybody and their dog wanted to work on it, but we had a head start because we'd already been working on the pathway a little bit. We discovered the ligand for NOD2 in 2003, along with Gabriel Nuñez. But its role in the pathogenesis of the disease is still unclear.

What is your hypothesis?

Since NOD-like receptors were first discovered as innate immune detectors

of microbes, the first idea that everyone had was that they play a role in host defense, which I think makes sense. They're there to detect any bacteria that might come into the host and they initiate an inflammatory response to get rid of that pathogen. But people are now coming around to the idea that instead of their major role being in host defense, they probably play more of a role in homeostasis—especially in the context of the intestine, where gut epithelial cells are in constant contact with huge masses of bacteria and different microbes. We think NOD2, in particular, may play a role in making immune cells in the mucosa of the intestine more tolerant to the bacterial flora.

Rather than being a true defense molecule (although it might play that role as well), under normal conditions NOD2 is probably providing homeostatic signals to maintain the gut environment in a state that's tolerant of its flora.

So immune cells in the intestines of Crohn's patients are overreacting to bacterial exposure, and that causes inflammation?

Yes. It's clear that bacterial flora play a key role in the disease. A number of studies in animal models and in humans have found that [Crohn's] is absolutely flora driven. We don't know if it's a specific bacteria, but if you house mice that have the tendency to develop colitis in germ-free conditions, they don't develop the disease. And if you put them back in conventional facilities where there are bacteria and microbes, then they immediately get the disease.

If we could somehow give Crohn's disease patients with a mutation in NOD2 a signal that is normally driven by the protein, then we could go around the NOD2 block. So what we're working on at the moment is to define the factors that are produced after NOD2 is triggered. And if we could give those factors to Crohn's patients exogenously, it could help to tolerize their immune cells. It's kind of pie in the sky stuff, but it keeps me coming to work.

And when you're not at work, what are you doing?

Running after the kids on a daily basis. Stephen and I have a five-year-old daughter and a two-and-a-half-year-old son. I think we're pretty good role models for other scientists who want to have kids. They see us working nine to five, and never working on weekends. They don't notice that from eight to midnight, Stephen and I are often working away, but I wouldn't trade it for anything. I'm happy to work those kinds of hours; at least we can spend the time as a family.

Do you have any advice for young female scientists who are concerned about having time for a family one day?

We recently had a lunch with our colleagues in the immunology department, and we were talking about women and science. And I asked the men, "Has anyone ever asked you how you balance your family life and your work life?" They said, "No, never had that question." But I have women students coming in and asking me, "Can I do this academic life? Can I handle both kids and work?" You have to be lucky and you have to have a very supportive partner, but you can do it. And you don't have to work 18 hours a day. You just have to be very efficient when you're at work. That's my advice to women students. Do it!

"About 30% of Crohn's disease patients have a mutation in NOD2."

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