

## Andrea Cooper: Using pathogens to probe the immune response

Working at the interface between pathogen and host, Andrea Cooper investigates how the immune system responds to invasion by disease-causing organisms.

When dendritic cells (DCs) patrolling the perimeter of the lung encounter the bacterial intruder *Mycobacterium tuberculosis*, they trigger a series of location-specific events that culminate in an immune attack on the bug. DCs first secrete the cytokine interleukin (IL)-12p40, which helps the cells migrate from the lung to the draining lymph node, where they present *M. tuberculosis* antigens to T cells.

Once there, DCs produce IL-12p70 and IL-23, which direct T cell priming and differentiation. Ultimately, interferon (IFN)- $\gamma$ -producing T cells are lured into the lung tissue where they do direct battle with the invaders.

Cooper's first contact with pathogens and the immune response occurred as a graduate student in Jenefer Blackwell's laboratory at the London School of Hygiene & Tropical Medicine, where she studied changes in the expression of surface molecules on *Leishmania* parasites in the guts of sand flies (1).

Later, as a postdoc in David Sacks' laboratory at the National Institutes of Health (NIH) in Maryland, Cooper investigated the T cell response to *Leishmania* antigens in patients recovering from leishmaniasis (2). Cooper next headed west to Colorado State University, where she first demonstrated the essential role of IL-12 and IFN- $\gamma$  in the control of *M. tuberculosis* (1–4). And now at the Trudeau Institute, on the shores of Saranac Lake in upstate New York, Cooper, along with her husband John Pearl and the rest of her laboratory, is parsing out how cytokines secreted by DCs and T cells help

orchestrate host immune responses against pathogens (5).

### THE PATH TO PATHOGENS

*Why did you want to become a biologist?* Do you know David Attenborough, the British broadcaster and naturalist? Well, he was kind of an inspiration for me. In fact, I wanted to go and count rock hyraxes in the savannah.

*How did you make the jump to Leishmania parasites? That's a far cry from counting small, furry mammals.*

My undergraduate project was on neuronal development in chicks, and while I was working on that I got really excited about cell biology and also the intricate interactions between hosts and pathogens. While I was finishing my undergraduate degree and preparing for final exams, I told my tutor that I was going to do a technical course and he said, "Oh, don't be silly, Andrea. You need to do your PhD!"

I got really excited as a scientist during graduate school at the London School of Hygiene & Tropical Medicine. My laboratory was working on mice, there were people doing human work, and there were also sand fly people—sand flies are the vectors of *Leishmania*. So although I wasn't really supposed to be working on sand flies, I got friendly with a guy who was doing sand fly stuff and we did some experiments together. And that was one of the papers for my thesis.

*After graduate school, you were a postdoc at the NIH in Maryland. Interesting that once you moved to the US you never went back to work in the UK.*

That's what my parents said too. I promised them I was only leaving [England] for two years, but I was drawn into the terrific resources that are available here. In Europe and the UK, scientists are a bit more constrained by funding so



Andrea Cooper and son

they're always very careful, whereas in the US we have a lot more resources.

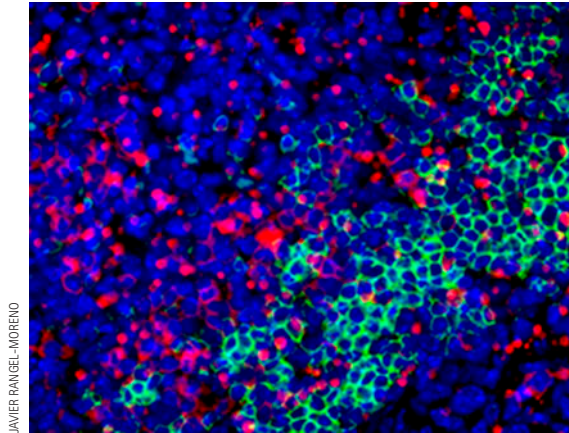
*Your next stop was Colorado State, and I see that you switched pathogens there. Shall I tell you the real story about that?*

*Sure!*

I had some hunting friends, and we went out West to do falconry in Wyoming. I really enjoyed the whole western experience and thought maybe we'd like to move out there to see what it's like. David Russell [now at Cornell University College of Veterinary Medicine] was a good friend of David Sacks, and I also knew him because he was a postdoc studying *Leishmania* when I was a graduate student in the UK. David Russell said he knew some people in Colorado who

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JAVIER RANGEL-MORENO

**T cells (red) and B cells (green) in a *Mycobacterium tuberculosis*-infected mouse lung.**

had a program in *Mycobacterium tuberculosis*, which would be a good model for me to know. And so he introduced me to Ian Orme at Colorado State. And when Ian and I met up, we decided it would be a great match. It was very fortuitous. Ian energized me to a great degree, not only about the science, but also about my career.

#### *Do you still go hunting with falcons?*

I still like to watch the birds, but it's not something that one can do as a hobby. The people who do falconry do it full-time. But I've stood next to golden eagles; I've stood next to gyrfalcons and all sorts of beautiful birds. You take them out hunting and it's a combination of bird, dog, and human. There's nothing artificial involved, no guns or anything. You simply go out and if you're lucky, you might get a sage grouse for dinner at the end of it.

#### **COUNTERING DISEASE**

*How are the interleukins you're investigating involved in the immune response to *M. tuberculosis*?*

Tuberculosis highlights why we have such a complex immune system. Since infectious disease is what the immune response is designed to counter, I think you need to probe the role of cytokines using infectious diseases or diseases developed in a vertebrate host. The IL12p40 homodimer, for instance, seems to be involved in taking immature DCs from a nonresponsive

to a responsive state in mice, allowing them to migrate in response to homeostatic chemokines. We've seen this in both tuberculosis-exposed DCs and DCs exposed to *Yersinia pestis*, which causes plague. The IL-12p70 heterodimer is required to maximize the IFN- $\gamma$  response. In the absence of IL-12p70, although we get initial control of bacterial growth, it's not very long-lived. So IL-12p70 seems to be required to maintain long-lived, maximal IFN- $\gamma$  responses within the

tissue. In the absence of IL-23, which drives the expansion of IL-17-producing T cells, we don't see a clear impact on infection for the first 100 days, but it seems that there may be an impact later, and we're working on that right now. We do know that in the absence of IL-23, you lose a substantial portion of the IL-17 response to *M. tuberculosis*.

#### *What has your laboratory learned about the immune response induced by tuberculosis vaccines?*

Vaccine-induced memory is slow to respond to aerosol delivery of *M. tuberculosis*. We think this is why vaccination works well to limit disseminated disease, but is less effective against pulmonary disease. We examined the early cellular response to aerosol infection of vaccinated mice and found that an early vaccine-dependent IL-17 response occurs in the lung, and this coincides with an accelerated local chemokine response. If this early IL-17 response is missing, then vaccine-induced memory in the form of an accelerated IFN- $\gamma$  response doesn't occur. By investigating the nature of the earliest cellular response in the lungs of vaccinated animals, we may be able to accelerate the memory response and improve vaccination protocols.

#### **SHORES OF THE SARANAC**

*You're based in Saranac Lake, which looks pretty isolated. What's it like raising a family there?*

I'm very fortunate to have a very supportive husband who's here at the institute with me. Together we've made the laboratory work very nicely. And we have a four-year-old son who just loves to do experiments. He's always drawing graphs and things like that. We have a daycare at the institute that's been a terrific environment. And we have a beach! You've done your grant submission, you've sweated through the night trying to get it done and submitted, and then you go down to the beach for either a swim or an ice skate, depending on the season. It's very, very nice.

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1. Cooper, A.M., et al. 1993. *J. Exp. Med.* 178: 2243–2247.
2. Cooper, A.M., et al. 1995. *Immunology* 84: 423–432.
3. Cooper, A.M., et al. 1997. *J. Exp. Med.* 186: 39–46.
4. Cooper, A.M., et al. 2002. *J. Immunol.* 168: 1322–1327.
5. Khader, S.A. et al. 2007. *Nat. Immunol.* 8: 369–377.



Cooper and family on Trudeau Institute's beach.