Fiona Powrie: Gut diplomacy

Fiona Powrie seeks to regain the peace that's been disrupted in patients with inflammatory bowel disease.

The immune system's quieter side went unnoticed for some time, while inflammation-inducing proteins soaked up all the attention. Fiona Powrie stepped in just after the concept of inflammation-reducing "suppressor" cells had emerged. In Don Mason's laboratory at the MRC Cellular Immunology Unit in Oxford, Powrie and her colleagues lent the vaguely described cells definition, by showing that one set of $CD4^+$ T cells protected rats from death induced by injecting another set of T cells (1).

Two decades later, these protective regulatory T cells, now defined by expression of the transcription factor Foxp3, have stolen center stage. And Powrie has been watching them perform one of their most vital tasks: hushing inflammatory responses to food, as well as commensal and other nonthreatening microbes in the gut (2). She helped demonstrate that regulatory T cells in the intestines have the same qualities as those that quell inflammation in response to self-antigens (3). In Bob Coffman's laboratory at the DNAX Research Institute in California, she and her colleagues revealed that regulatory T cells act through the antiinflammatory cytokines interleukin (IL)-10 and transforming growth factor (TGF)-β to counter inflammation driven by tumor necrosis factor (TNF)– and interferon (IFN)-γ–producing effector T cells in mouse models of colitis (4, 5). As chair of the new Translational Gastroenterology Unit at the University of Oxford, Powrie will be working with clinicians to facilitate the application of what she knows about gut homeostasis to patients who've lost it.

"The intestines are really the Wild West of the immune system."

Did your parents influence your decision to become a scientist?
In a way, yes. But not from their own study. My father was in the financial world and my mother was a nurse. But my mother was very ill throughout my childhood with an immune-mediated disease. And that influenced my interest in understanding the immune system and the devastating consequences that problems with that system could have.

Was there a particular moment when you thought, wow, regulatory T cells are cool?
I can remember a time when I was working on my PhD with Don Mason. We were trying to understand the functions of T cell subsets, and we discovered that one subset of T cells led to a fatal disease in the animals and the other subset of T cells inhibited that disease. It was such a striking life-or-death issue that it influenced the rest of my career.

Why did you focus on the intestines?
The intestines are really the Wild West of the immune system. It's the least understood part and it's in close proximity to a huge number of bacteria. There are actually more foreign cells in your body than your own cells, so the immune system must learn to live peacefully with this beneficial commensal flora. A breakdown of that relationship can cause disease.

BENCH TO BEDSIDE

At DNAX, were you constantly aware that the ultimate goal was a product?
Sure, DNAX was part of Schering-Plough and the aim was to translate basic immunology research into new treatments for diseases. I was personally involved with the development of recombinant IL-10 that moved into clinical trials. But in those days, DNAX still operated like a research institute and people pursued huge, fundamental questions related to the theme of immunology.

Do you still keep the pipeline in mind?
Absolutely. I think one of the things that DNAX did was give me exposure to how one might apply their work in the clinical setting. I think the transition from basic science into applied research is important. In fact, we are now developing a new Translational Gastroenterology Unit in Oxford in which laboratories for basic science research in model systems will sit right next to the Gastroenterology Clinic. It's a fairly novel setup for translational medicine as I will head this new academic gastroenterology effort even though I'm not a clinician.


Fiona Powrie

How do you see the basic and clinical research sides interacting?
This is a real challenge and has not always been successful in the past. A real issue is communication—both clinicians and scientists need to feel that they are a valued part of a team effort. Having the basic laboratories so close to the clinic means that scientists and clinicians can talk to each other and share ideas. I mean, that's what makes science so fun, really. If you didn't tell people what you did, what would be the point of doing it?

I think people will communicate though. I work with a fabulous set of clinicians who are very willing to listen to what's coming out of the basic science research and think about how we can apply it to the clinical setting. Now we'll

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be able to take the pathways that we've identified in model systems and actually ask if this is what we see in inflammatory bowel disease patients. For example, we would like to identify subsets of patients that might be more suited for one treatment versus another, rather than applying a treatment across the board.

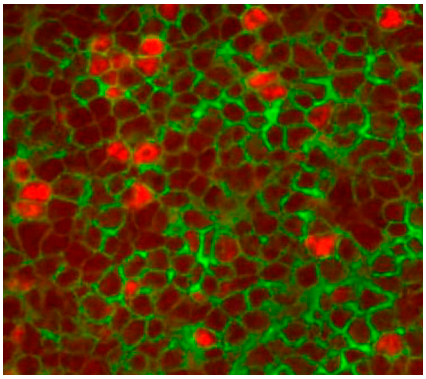
What went wrong in the immunomodulatory drug trial that tested the CD28 superagonist antibody TGN-1412?
Well, there were unanticipated results in humans that were not obvious from the studies that had been performed in primates. It turned out to be a more potent stimulus than expected and the effects were profound. Of course, the trial has led to a lot of caution in terms of injecting things that we would consider to be agonistic or activating antibodies. And it made us aware that when you cross species, it's not always possible to predict function because of different receptors and so on. One has to be extremely cautious when moving experimental treatments into humans. At the same time we do need to move forward with novel therapies. It's a balance.

What do you predict about the next wave of immunomodulatory drugs?
Anti-TNF treatments already work fabulously in some patients with inflammatory diseases. But some patients don't respond. I think one of the ideas that has emerged from our work and others is that it may not be sufficient to simply take away inflammatory drivers; you need to reset the balance. And that's where regulatory pathways are important. I think we will advance the field by learning how to manipulate these populations of cells. It's hard to think that cell-based therapies will be widely acceptable in terms of their costs. But there should be ways to administer agents that promote regulatory T cell responses in situ. This could be useful for inhibiting autoimmune and inflammatory disease, allergy, and graft rejection.

CHEWABLE TREATMENTS

Does our diet affect intestinal inflammation?
Diet absolutely plays into it. I mean, one of the treatments for inflammatory bowel disease is changing your diet. There are certain foods that potentially influence the intestinal bacteria. And we know that components of our diet have a very important role in influencing immune function. But pinning down definitive molecules and pathways is challenging. Still, there has been some progress. There's a lot of interest in the effect that vitamin A has on influencing immune function at the moment. Also, when researchers have knocked out short chain fatty acid receptors in mice, they've shown that it influences intestinal homeostasis.

What do you think about the probiotics industry?
I think it's an interesting area. There is evidence that for retaining remission in inflammatory bowel disease, probiotics can help. However, the data about whether probiotics can treat a flare isn't as convincing. Precisely how probiotics, or prebiotics, are working and what immune cells they interface with is not understood. I do think it's an important area for the food industry to explore, so that one can design nutritional components that are enhanced over the ones we have. I mean, you can put things into the gut. That's so much easier than getting something into joints or into the brain. So this is an area that we can easily manipulate, but we need to understand more about it. One approach is to administer bacteria that produce molecules that restore immune homeostasis. This concept is being used in Phase III clinical trials now, with a probiotic bacteria that can deliver an antiinflammatory type cytokine called IL-10. By ingesting this probiotic bacteria, you can deliver, in a targeted fashion, something that is good for intestinal homeostasis. These bacteria are equipped with suicide genes so that the organisms don't become a potential hazard.



Foxp3⁺ (red) and CD4⁺ (green) regulatory T cells inhabit the spleen.

If you switched your focus, what would you turn to?
If I had to do it again, I might look into inherited immune diseases. For example, I'd look at individuals who are susceptible to bacterial infections that run in the family. Investigators have been able to actually go in and identify the pathways that are altered. And that has provided a lot of insight into immunity and host-susceptibility. Another fascinating area is understanding how tissues shape the immune response. If we're going to develop therapies for diseases, we want to be able to target that action to particular organs, and understanding the interaction between the stroma of an organ and immune cells may provide novel pathways for organ-specific targeting in various diseases. There are lots of things I'd do … and actually, I might yet.

"It may not be sufficient to simply take away inflammatory drivers; you need to reset the balance."

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