Shane Crotty: Exploring immune memory

Virologist and published author Shane Crotty sees immune memory as the key to making a better vaccine.

What will Shane Crotty do next? Currently an assistant professor at the University of California, San Diego and an associate member of the La Jolla Institute for Allergy & Immunology (LIAI), he's accomplished a lot in very little time. As a double major in biology and writing at MIT, Crotty began a biography of the Nobel prize-winning molecular biologist David Baltimore to fulfill his writing thesis requirement. This culminated with the 2001 publication of *Ahead of the Curve* while Crotty was a graduate student in Raul Andino's laboratory at the University of California, San Francisco (1). While he was there, he also determined that the antiviral drug ribavirin works by inducing lethal mutations in RNA virus genomes (2).

Now, Crotty's laboratory at LIAI focuses on immunological memory and the immune response to vaccines and infectious diseases. Recently, they discovered that one key to a long-lasting immune response is T cell expression of the protein SAP (SLAM-associated protein), which is needed to help B cells become long-lived plasma cells or memory cells (3, 4). On a more practical level, he and his laboratory figured out that one reason the smallpox vaccine elicits such a strong protective antibody response is because it presents multiple antigenic targets to the immune system (5, 6). With that knowledge, they produced a mélange of monoclonal antibodies for the National Institutes of Health to treat smallpox in the event of a bioterrorist attack.

"SAP is central to immunological memory, and so therefore it should be central to vaccine design."

ATTAINING VACCINE GREATNESS

What is it that makes a really good vaccine really good?

There are about 25 licensed vaccines, and 23 of them clearly work because of protective antibody responses. The smallpox vaccine is in that category. One reason the smallpox vaccine is such a good vaccine is that it drives protective antibody responses to several different targets on the virus. A diverse response is better than a magic bullet, or a single response. And this will probably also apply to large pathogens like bacteria and parasites, which have hundreds of surface antigens. Based on the smallpox vaccine model, being able to make responses to multiple antigens is probably the way to get really good protective immunity in a population.

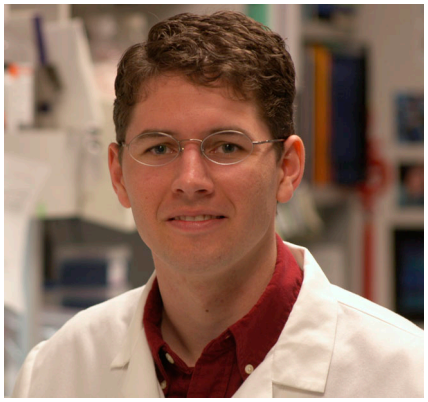
Do all vaccines work the same way?

All vaccines are predicated on immunological memory. And almost all good antibody responses and memory antibody responses are dependent on $CD4^+$ T cell help. So what is it about T cells that controls the B cell response? SAP knockout mice can make an acute response, but they have no antibody memory, no B cell memory, and it's because of a problem with their $CD4^+$ T cells. There are humans with defects in the SAP gene, and they have the same problem.

We know that SAP is central to immunological memory, and so therefore it should be central to vaccine design. This has led us to interest in follicular helper $CD4^+$ T cells, which are specialized to help B cells. We're trying to understand this T cell subset and how SAP does or doesn't relate to it. How do you really get T cells to help B cells so that you get good germinal centers and then a good memory response? We think it comes from the follicular helper $CD4^+$ T cells. We've been working on it since I started my laboratory five years ago, and now it's certainly a hot area.

SCOUT, AUTHOR, SCIENTIST

You listed the Eagle Scouts among your honors on your website. Do you ever get to use the skills that you learned as an Eagle Scout now that you're grown up?



Shane Crotty

I do think that it's really useful for developing leadership skills, because you have to be able to organize groups of people, whether you're just doing projects or whatever.

Is it useful for laboratory management?

Yeah, I actually think so! Laboratory management is one of those tough things to learn. There aren't that many ways to learn how to be a boss.

Do you think that working on* Ahead of the Curve *influenced your decision to work on viruses and the immune response?

It did, but it was an inadvertent thing. I majored in biology and writing at MIT. So writing was a real part of what I was doing at the time. I did a biography of David Baltimore as my writing thesis. I wanted to write science for nonscientists, and it's very easy for that to end up being boring. Focusing on a given individual is a great way to make it more exciting. Then in grad school I took a class on virology because I realized that it would make sense to know more about it for the writing I was doing. So I took this virology class and I was hooked.

Was it simple to combine writing and research?

That was challenging. I tried to do both at the same time, and I couldn't.

Text and Interview by Kira Heller
kiraceae@gmail.com

At an article level, I think it's totally possible to write and do science at the same time. At a book level, it's just impossible, in my opinion, if the book is a single entity. It just takes too long to wrap your head around the whole project, keep styles consistent, and remember what you were dealing with 50 pages ago. So I tried to do both for a while, and then finally I took two months off, and later another month off, where I just didn't go to the laboratory at all.

Did your research have anything to do with the book?

Raul Andino, my graduate advisor, had been in David Baltimore's laboratory. I was actually quite interested in avoiding Baltimore connections initially, because I really considered the writing and the science separate. I wasn't a Baltimore groupie. But it turned out there were basically two virologists at UCSF, and one of them told me his laboratory was full, and the other was Raul. So it's just sort of the way it played out.

Are you working on any writing projects right now?

I'm not. I consider it off and on, but running a laboratory is more than a full-time job, so it's just not practical. And definitely a book isn't practical because it takes a huge amount of time. So, no, it's pretty much all paper writing.

What do you do for fun when you're not in the laboratory?

Play with my kids. My daughter was born six months before I started my laboratory, and my son was born two years later. So it's been a very busy five years.

BIODEFENSE STRATEGIES

Are any of the discoveries you've made about the immune response to the smallpox vaccine being put to practical use?

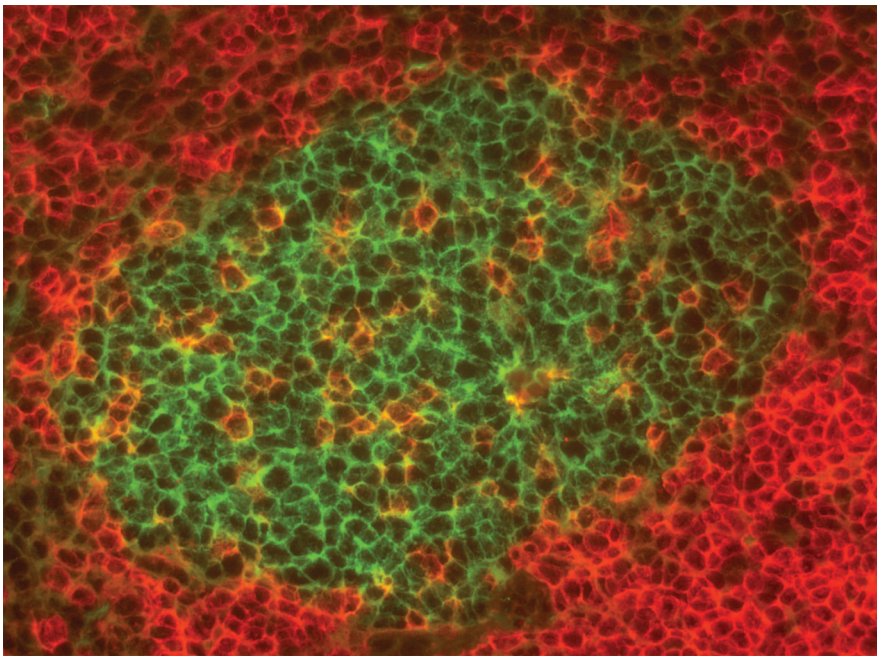
In terms of vaccine design, it's just too early. Most of the things we've been publishing have just been in the past couple of years. But there is an interest in having a cure for smallpox and monkeypox from a bioterrorism perspective. There's a vaccine stockpile, but it would also be nice to have a cure if smallpox did show up. There were clinical trials back in the 1960s where they took antibodies from one person and transferred them into people who were exposed to smallpox, and it had about a 75% cure rate. Now that we know the key antibody targets for smallpox, we've made fully human monoclonal antibodies to them. We've got an NIH grant to do this because we've already shown in mice that these monoclonals protect against poxvirus infection. So, we recently manufactured a big batch of protective monoclonal antibodies. You know, it's a bizarre project. We're working hard to make something that we hope never actually gets used.

If you were given unlimited money from the government for immunology research, what would you spend it on?

I suppose if it were up to me, I would put more emphasis and money in the area of vaccine immunology, particularly on studying it as a component of human immunology. I'm certainly not the only person saying that. Mark Davis had an opinion piece in *Immunity* in December that said what a lot of people have been saying and thinking, myself included, which is that mice are great, but we've really got to know human immunology a lot better. In theory, we've got techniques and ways to do this, but the experiments are expensive, and it's tough to get grants funded because the experiments aren't as clever and fun as all the things you can do in mice. But they're hugely important. I definitely think that we need more emphasis on human immunology, and that is frequently constrained by money.

"We're working hard to make something that we hope never actually gets used."

1. Crotty, S. 2001. Ahead of the Curve. University of California Press, Berkeley. 270 pp.
2. Crotty, S., et al. 2000. *Nat. Med.* 6:1375–1379.
3. Crotty, S., et al. 2003. *Nature.* 421:282–287.
4. Cannons, J.L., et al. 2006. *J. Exp. Med.* 203:1551–1565.
5. Benhnia, M.R., et al. 2008. *J. Virol.* 82:3751–3768.
6. Sette, A., et al. 2008. *Immunity.* 28:847–858.



SHANE CROTTY

B cells (green) interacting with CD4⁺ T cells (red) in the germinal center.