David Masopust: Tracking tapirs, T cells, and other David Masopusts

Masopust recognizes the vital role that memory T cells play in defending us against chronic infection. Now, an older generation of immunologists is recognizing him.

What a year for David Masopust. The 36-year-old microbiologist won the NIH Director's New Innovator Award in September, shortly after winning the American Society for Microbiology ICAAC Young Investigator Award and the Beckman Foundation Young Investigator Award. Lymphocytes hadn't even crossed his mind 15 years ago. But after some soul searching and tapir tracking in Costa Rica, Masopust began to hone in on immunology, eventually joining Leo Lefrancois' laboratory at the University of Connecticut. There, he charted the migratory patterns of memory T cell populations in peripheral tissues after infection (1). He then delved deeper into the nature of immunological memory in Rafi Ahmed's laboratory at Emory University in Georgia before moving to his current position as Assistant Professor at the University of Minnesota.

"What if every CD8+ T cell in your entire body was specific for HIV?"

Memory T cell endurance can determine whether or not repeated exposure to a pathogen results in calamity. Masopust is trying to figure out what makes virus-specific $CD8^+$ T cells tire or malfunction, and in doing so he's helped discover ways to reverse T cell exhaustion (2). Masopust's portfolio is filled with studies on memory T cell responses after vaccination and mucosal infection (3, 4). And although he's not the type to say it himself, his body of work on $CD8^+$ T cells will undoubtedly contribute to the next wave of vaccination strategies.

What are tapirs and how did you find them?

[Laughing] Tapirs are large mammals. Some people describe them as a cross between a pig and an elephant because they have a semi-prehensile snout that can uproot small trees. Actually, they're related to rhinos and weigh 300 pounds easy.

I used to help a field biologist track tagged tapirs with radiotelemetry. Basically, I'd go out alone in the jungle in the middle of the night, triangulate two signals, interpolate those directions, and get an idea of where a collared tapir was. It involved crossing a river in a rowboat with holes in it—sharks and caimans all around.

Did anything scary ever happen?

Once I was charged by a tapir while I was sort of snoozing against a fallen tree. One tapir had been chasing another out of its territory. After the smaller tapir leaped into the water, the bigger one turned its eyes toward me and seemed to say, "Why don't you get out of here, too." I escaped, but it was intimidating! I really felt out of my element in the jungle. Nothing bad happened to me, but a guy I worked with was mauled by a puma one night.

Did your tapir-tracking experience inspire you to become an immunologist?

Not really. After I graduated college, I just felt that I needed to investigate what made me happy, so I went to Central America and took on a variety of random jobs down there.

How did you move from tapir tracking to graduate school?

It had to do with a wedding. I was beginning to feel that field research wasn't for me, and then I suddenly had to leave Costa Rica because my stepsister was getting married in the US. I read Laurie Garrett's book, *The Coming Plague*, which really got me interested in infectious disease. Then I met Leo Lefrancois, and his laboratory ultimately became a great fit for me.

THE FUTURE OF MEMORY

Did you imagine you'd be so successful?

I went to graduate school thinking that I'd be lucky if I got a degree at the end. If I had thought about it more, maybe I wouldn't have done it, because this is a tough career path. But I didn't think about it, and therefore I wasn't afraid to fail.

David Masopust

What do you think is a hot area of immunology for young investigators to enter now?

I think the field needs to really start considering the pathogenesis of organisms. People should also investigate how the quantity and quality of memory T cells are regulated, how they relate to protection against real-world infections, and how they can be manipulated or exploited. I think a lot of the focus right now is on dissecting why some effector T cells become memory cells, and I'm afraid that the point can get lost. The point is learning how to protect a host against real-world infections.

What are you doing to get closer to actual problems in humans?

Although we've been doing reductionist experiments in small animal models, instead of just ending every paper by stating the implications for vaccines and blah, blah, blah, we've been trying to test

Text and Interview by Amy Maxmen
amaxmen@rockefeller.edu

our assumptions. For example, rather than suggesting that CD8$^+$ T cells can prevent chronic HIV infections, we are trying to test that directly. What if every CD8$^+$ T cell in your entire body was specific for HIV? What would happen then? I'm a fan of bold, extreme questions. And even though this experiment [with SIV in primates] won't give us a vaccine, it could at least tell us that it's possible to prevent this infection with memory CTL [cytotoxic T lymphocytes].

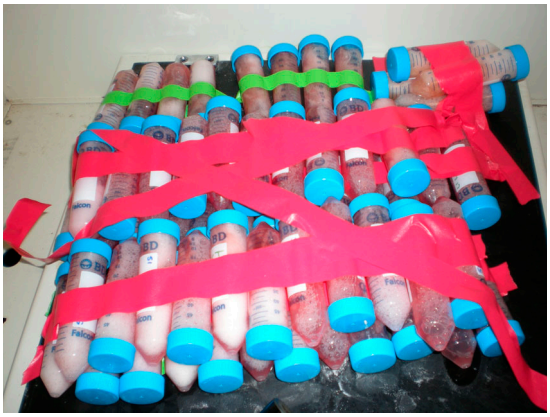
What topic do you think will win the next Nobel Prize in Physiology and Medicine?
I'm hesitant to guess about prizes in general, but I think the next Nobel awarded to immunology will go to a technique that can turn on a protective immune response or turn off a destructive response. That's the Holy Grail of adaptive immunity. Or it will be awarded for a preventative HIV vaccine. In general, I'm hopeful about vaccine development.

BOY IN A BUBBLE

Do you worry that people in the vaccine field rely too heavily on model systems?
Yeah, I worry a little bit. There's a culture of safety first, and that's reasonable because you don't want to endanger human beings. But too much safety constrains what one thinks is possible. I think that's why some approaches that have not succeeded are often repeated with minor refinements. Part of the problem is that there's a limited pool of money, and a lot of what is funded tends to fall into a narrow range of acceptable risk. I think people expect a degree of novelty, but they also want a certainty that whatever you're doing is going to work. And that's troubling because it forces people to do safe science, and science shouldn't be safe. Well, some of it should be safe, but some should push the envelope.

If smallpox was a problem today, and you were proposing the current cowpox vaccine, one has to wonder if you could ever get far enough in your research to demonstrate effectiveness.

You've helped discover a way to revive exhausted CD8$^+$ T cells with antibodies that block the interaction of the inhibitory PD-1 receptor and its ligand. Are you sure exhaustion should be blocked therapeutically?
I may be in the minority here, but I'm skeptical. Exhaustion happens for a reason. It's an evolved response, which means it may have to do with the longevity of the host. Let's say the liver cells in your body were infected with a virus and your immune system went about killing all of them, then you'd no longer have a liver. So even if you got rid of the infection, you'd be in trouble. I think one has to be careful with these kinds of therapies, particularly when they are blunt and target every exhausted cell. The saving grace with the PD-1 blockade therapy may be that it's not very effective by itself. If it were combined with something that focused on an antigen of interest, like in therapeutic vaccination, it would be more appealing to me. Still, you're playing a dangerous game.


Memory CD8$^+$ T cells can be isolated from various organs in LCMV-immune mice.

You helped overturn the dogma that the size of the memory T cell compartment was fixed. What's the implication of this result and why hadn't this been recognized before?
I think it means we can be far bolder in terms of generating a CD8$^+$ T cell vaccine (5). There are also academic issues to explore about the maintenance and longevity of effector memory CD8$^+$ T cells. We have clues now that some types of memory T cells aren't playing by the same rules as traditional memory T cells. Part of why this hadn't been recognized before was because of the way experiments had been designed. You take a laboratory mouse that's lived a pristine life in a cage and then give it one infection and study that response. But that approach doesn't capture the complexity of the real world. People talk about how humans and mice are so divergent, but immunological experience can be vastly different within a species. If you catch a mouse in a barn and look at the fingerprint of its immune response, it's night and day compared with a laboratory mouse. That's actually a fun little side project we're doing in the laboratory—catching mice in a barn and looking at their immune systems. I got tired of studying these laboratory mice, these boys in a bubble. What happens if they eat Taco Bell scraps and get *Salmonella* and breathe city air?

So you track mice, too?
Luckily it's much easier than tracking tapirs.

Are you familiar with David Masopust of the Masopust Polka Band in Oklahoma?
I am aware of him. I found him by "Googling" my name. Actually, my father called him once to say hi because my father is also named David Masopust.

"What happens if [lab mice] eat Taco Bell scraps and get *Salmonella* and breathe city air?"

What did he say?
Nothing. He wasn't excited, or at least not as excited as my father was. I toyed with the idea of asking the David Masopust Polka Band to play at my wedding, but I changed my mind. I don't think my friends are down for polka.

1. Masopust, D. 2001. *Science.* 291:2413–2417.
2. Barber, D.L. 2006. *Nature.* 439:682–687.
3. Lefrancois, L. 1999. *J. Exp. Med.* 190:1275–1284.
4. Miller, J.D., et al. 2008. *Immunity.* 28:710–722.
5. Vezys, V., et al. 2009. *Nature.* 457:196–199.