Ron Germain: Towards a grand unified theory

As data floods in, Germain works overtime to decipher which immunological information matters and how it can be applied to saving lives.

At 15, Ron Germain cared for white mice kept on a ping-pong table in his basement. "You couldn't just buy inbred mice at the pet store," he recalls, "but I had a connection." With his C57BL/6 and A/J strains, he attempted to cure graft-versus-host disease with thymic transplants. His mother would supplement these experiments by driving him to Rockefeller University, where the young Germain snuck into seminars on immunology. And so it is little surprise that he's since risen through the ranks of T cell immunology, first at Harvard Medical School and later at the National Institutes of Health (NIH). He's helped elucidate the expression, structure, and function of MHC class II molecules, the cell biology of antigen processing, and the molecular basis of T cell recognition (1). Currently, he and his team peer into the dynamics of immune cell movement using two-photon microscopy, and construct mathematical models of T cell signaling and activation (2–4).

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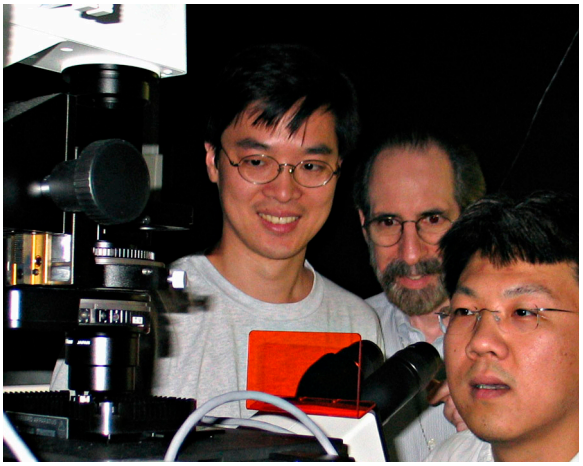
In 2006, Germain spearheaded a systems immunology program at the National Institute of Allergy and Infectious Diseases (NIAID), which included the development of software to build and test complex models. More recently he's helped establish the Center for Human Immunology (CHI) at the NIH, an interdisciplinary effort with the goal of translating analyses of the human immune system into therapies for immune-mediated diseases.

What strikes me about your papers, particularly one called "The Art of the Probable" (5), is your attention to overriding concepts and emergent properties in the immune system.

It's true, I'm a conceptual person. I'm not so interested in ferreting out every little detail. I want to understand how things work in the larger sense. In my papers, I don't tend to report five new transgenics, three knockouts, and 82,000 blots. That's just not how I do science because getting data doesn't necessarily give you important answers. Sometimes I'm afraid we've failed to pay attention to how the immune system actually works. Too many things are described in these very black-and-white, linear ways—you do this and you get that. But that's not biological reality. And that was the point of "The Art of the Probable"—that there's more to things, like fluctuating cells states and bi-stable conditions.



Ron Germain (center) at the two-photon microscope with Alex Huang (left) and Hai Qi.

How will immunologists handle the flood of raw data spewing forth from technological advances?

Part of the trick will be to figure out what data we need. Data space is infinite, and trying to fill that space up won't give you the key. People need to come to grips with the fact that you need to make the right measurements and combine them in ways that let us better understand complex systems. A major goal of ours is to create models that predict how a cell or organism behaves if perturbed, and to do this, we need particular kinds of information.

Don't you need to generate data before building a model?

When people say this, I point out two things. First of all, as you rigorously define a process in order to model it, you find gaps in your knowledge that you'd otherwise forget about when you're not thinking discreetly. And second, if you build a very good model and make predictions with it, it can begin to tell you about behaviors you didn't expect that then lead to new experimental avenues of research.

SCIENCE'S NEXT TOP MODEL

How can a systems biology approach make inroads into vaccine research?

In vaccine research, you need to combine several different types of measurements. People are just beginning to get a feel for how to accomplish this. For example, some investigators are doing extensive array and SNP [single nucleotide polymorphism] analyses to look at expression levels and quantitative trait loci, and then link these back to phenotype.

I'm very interested in such approaches because I think that seeing how the larger system behaves is an important goal. The whole concept behind the CHI is to see if we can collect the right types of data at the right density to better model and better understand the human immune system.

What is happening at the CHI?

The first thing that's exciting is the level of inter-institute cooperation in the scientific arena. People from multiple institutes are getting together and trying to do things that none of us could do in our individual laboratories. The people involved are donating their time and energy to try to get this to happen because we all believe this is important.

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The good news also is that there are a number of other places outside of the NIH gearing up to do very similar things. We're all making efforts to adopt common operating procedures, measurement styles, and data deposition approaches so that we can build a large database of qualified findings. At the NIH, we've gotten a bit of a head start in creating the normal human immunome.

What's a normal human immunome?
It's a multi-omic characterization of the state of the human immune system. It's a database we're building based on results from expression arrays, highly multiplex flow cytometry and cytokine assays, genetic analyses, and functional studies. We're working on this internally across many institutes, we are seeking collaborations with companies, and we're in touch with external investigators nationally and internationally.

Right now we're looking at how the normal human immunome is perturbed by flu vaccines in nearly 200 individuals. We get two prevaccination bleeds and then we do a series of early and late post-vaccine bleeds. We hope to get about 17,000 different sub-phenotype possibilities from the flow analyses and 60–100 cytokine measurements on every one of the samples. We'll keep material on reserve for later to do SNP chips, HLA typing, and eventually sequencing if it becomes cheap enough. The idea is to then put this all together in a very deep analysis.

What might it tell us?
Far more than what we know now. You can't do experiments in people the way you do them in animals. But there are ethical manipulations of the human immune system that go on all of the time, whether it's vaccination or whether it's treatments for rheumatoid arthritis or other immune-related diseases. And so our goal is to measure the state of the normal immune system and the system as it gets perturbed by things like vaccines, infections, or therapies. As this database grows we can begin to relate it to genotype as well. It's an ongoing goal.

With this project we're taking the benefits that have come from decades of investment in basic research and putting time and energy into a larger effort that aims to better understand the human immune system. Ultimately, we want to use that information to rapidly improve health. In the flu project there are more than 20 investigators from different institutes helping to get this started and there hasn't been a single discussion about authorship. It's just a feeling that we should do this, we're going to do this, and we'll figure out publications later.

FATHOMING COMPLEXITY

What's holding up vaccine development for neglected diseases?
It's simply unclear how to make vaccines for many diseases. It's been doable to make vaccines against diseases that you are robustly immune to if you survive the initial infection. However, vaccines against infectious agents that don't give you natural immunity are difficult to make, neglected or not. And this goes back to this fundamental issue of not understanding the human immune response well enough. I think that's one of the wake-up calls that's come out of the HIV experience, which is that we don't know exactly what we need to do. And in some cases, even when you know what you want, it's not easy to get it to happen.

Can advances in adjuvants help?
I think everybody has figured out that you need the right adjuvants. But the "dirty little secret" is that people don't understand what makes for a good adjuvant for certain things versus others. And then there is a safety issue. One thing that is a struggle—and I've been on a number of panels this year looking at this—is that there are adjuvants permitted for use in Europe that are not permitted for use in the US. For example, an adjuvant for the flu vaccine allows you to reduce the dose by one third to one tenth in terms of total amount of antigen. And even at a lower dose, that adjuvant gives you a higher response more rapidly after a single booster or injection. But the question that still comes up is whether there has been enough post-use tracking to be sure there are no untoward effects in terms of say, autoimmunity. And that's almost unanswerable in short-term trials because in very large populations you will find a certain number of autoimmune events that occur after getting vaccinated because statistically, some people will have autoimmune events.

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The next question is what is the risk–benefit ratio? If there are diseases that have high morbidity, which you can only prevent with adjuvants in vaccines, then a slight risk compared with doing nothing at all is still a huge benefit. You have to look at that balance. The question is how to get the data to know what that balance is. It's all very, very complicated. Hopefully, the CHI will help.

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2. Stoll, S., et al. 2002. *Science.* 296:1873–1876.
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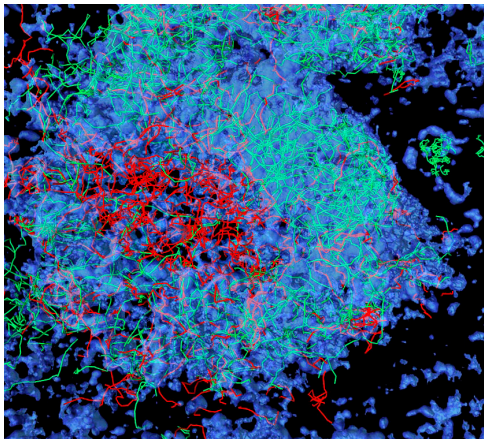

The migration patterns of transgenic T cells (tracks in red and green) in follicles (blue) can be mapped with intravital two-photon microscopy.