Why immunology research needs a more human focus

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Mark Davis. Credit: Stanford University Medical Center

Vaccinology—once a hit-and-miss matter of injecting a killed or severely weakened pathogen into a patient's arm and hoping for the best—has undergone major advances with the advent of analytical technologies that permit direct measurements of human beings' responses to experimental and licensed vaccines.

Mark Davis, Ph.D., a professor of microbiology and immunology and the director of the Stanford Institute for Immunity, Transplantation and Infection, has contributed to these improvements in several ways. First, he has spent his career studying the immune system's complexities and activities. Davis, the Burt and Marion Avery Family Professor and a Howard Hughes Medical Institute investigator, is widely credited with advancing scientists' understanding of T cells, a class of immune cells whose individualized receptors allow them to recognize parts of particular pathogens and tumors and either destroy them directly or report their presence to the immune system's central headquarters. Second, Davis and his group have pioneered methods for identifying individual human T cells' characteristics, accelerating discovery in vaccinology. Third, he long ago began calling for a shift in the field's experimental focus from mice to humans.

Davis weighed in on how these efforts have influenced immunology.

1. In 2008 you proposed, in an essay in the journal *Immunity*, that immunologists should turn their research focus from mice—at the time the experimental model of practically everyone in the field—to humans. Why did you make that suggestion?

Like almost all of the biological sciences, in immunology almost everything we know comes from the experiments we are able to do. You can ask the most terrific questions, but if you don't have a way to answer them, you can't go any further. You're often just treading water until the right technology comes along to get at one of these problems.

I thought immunologists were falling into the classical trap that many successful fields, institutions and companies fall into: They want to keep doing what made them successful previously. It often blinds them to warning signs that things are not so great, or to new emerging opportunities they should take advantage of. I saw this mentality holding

back the field.

Inbred mice were perfect for what we needed to learn about basic immunology, making it one of the most successful specialties in modern biology. But the idea took hold that mice could be the key to understanding human diseases—you just had to create a mouse model of a particular disease and study it with the great tools we have for mouse work, and this would lead to major advances in treating and curing those diseases in human beings.

While these efforts generated tons of data and insights into aspects of some diseases, only rarely were they leading to actual treatments. I'm a strong believer in paying close attention to the results of your experiments. In this case, the results were telling me these mouse models of disease were a start, but we were missing something important to understanding human diseases.

The logical thing was to start looking carefully at human diseases directly, by drawing blood from people—a relatively noninvasive procedure, which they were often undergoing routinely anyway—and using our new tool sets to assess thousands of different variables in blood (like proteins, genes or cell types) whose numbers, activation levels and interactions might help us figure out what we had been missing.

2. How did that go over?

I knew I was asking for trouble. And, indeed, the basic immunology community was shocked and annoyed. Many prominent immunologists who'd spent their entire careers developing mouse models of human diseases thought I was trashing their life's work. Scientists are like most people: They like to do what they know how to do and will resist change.

I wasn't that popular in the mouse world for a while. But the audience I

was hoping to reach were young people just starting who didn't have a large investment in a mouse model and might read what I wrote and think about doing some human work.

3. What ultimately came of your proposal?

The biggest problem with what I was proposing back in 2008 was that we really didn't have good technologies or strategies to get high-quality human data. But about a month after that essay came out, the National Institute for Allergies and Infectious Diseases decided to make it the basis of a new $100 million grants program. Since then, the movement that I and others started for studying immunity in humans has really blossomed.

For much of the past 15 years we've been developing tools to get the kind of high-quality, in-depth human data we needed. The funding we've received from NIAID and numerous other sources has led to, among many other things, a muscular expansion of Stanford's then-fledgling Human Immune Monitoring Center, now a world-class powerhouse for "systems immunology": the integrated use of multiple batteries of the most advanced immunological assays on human blood and tissue samples, performed at large scale. There's a flood of work now in that vein.

The development of technologies that can be applied to human beings—many of which were pioneered here at Stanford Medicine—has led to more and more discoveries. This has been wonderful to see.

One of our recent studies, using a technology we developed for pinpointing just which part of which pathogen a specific T cell binds to and responds to, allowed us to show that people who've been exposed to various harmless coronaviruses, which typically cause no more than a common cold, are less likely to develop severe cases of COVID-19 if

they get infected.

Another study by our group unearthed subsets of T cells that act like military police. They protect the body from autoimmunity after the immune system, mustering all the troops it can to fight off an infection, has activated other immune cells with the capacity to attack our own tissues. Prior to the infection, those dangerous immune cells had been, effectively, under house arrest. Once the infection is under control, these specialized T cells round those renegade immune cells up and put them back in handcuffs and leg irons again. If it weren't for that, infections might well trigger autoimmunity in many of us.

4. What are the big, unanswered issues in immunology today?

While we've learned a tremendous amount about the basic workings of the immune system in the past 50 or so years, we don't know why many vaccines (fortunately not the pandemic ones) fail, or why the immune system fails to control cancerous cells or why autoimmune diseases persist once they get started. There's a ton of things we need to understand better to deal effectively with these important problems.

5. You were recently elected president of the Association of American Immunologists. What new directions do you hope to promote?

Being president gives me a platform to encourage members to think more about human immunology and tell people how to do it, since it's such unfamiliar territory still for most immunologists. But this is a very broad field. You never know where the breakthroughs will come from. All the different areas have potential value.

But the main mission of the association is to support our members in doing their best science, not to impose my own preferences on anyone else. I completely embrace a push by our previous president, Cornell University professor Gary Koretsky, MD, for the association to become more of a public institution.

We've seen an explosion of misinformation about vaccination during this pandemic, which has cost thousands of people their lives and even more their health. We want to be a trusted, independent source of good science for public health issues related to immunology, like vaccines. We've never done this, so there will be a learning curve, but it's the right thing to do, and we're going to try.

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