

BIOMEDICAL RESEARCH

Immunology Uncaged

An immunologist argues that to move beyond mice and galvanize clinical research, his field needs its own version of the Human Genome Project

With a routine blood test, your doctor can ascertain how well your metabolism handles lipids and whether you are vulnerable to heart disease. But don't expect to get a test that reveals whether your immune system is working normally or whether you are at risk for, say, autoimmune diseases. The reason: Researchers still can't define what's normal for the immune system, says Mark Davis, an immunologist at Stanford University in Palo Alto, California. Cardiologists can specify healthy levels of LDL, HDL, and triglycerides, but immunologists can't do the same for cytokines, key chemical messengers that trigger immune cells to mature, divide, attack, or perform other actions.

Researchers' reliance on mice deserves some of the blame for this ignorance, says Davis. No mouse-phobe, he keeps 400 cages of the rodents for studies of how T cells recognize pathogen molecules. But mice, says Davis, make a "lousy model" for the human immune system. The human and mouse lineages diverged some 65 million years ago, and the rodent's immune system has adapted to safeguard a small, short-lived animal that scurries around with its nose in the dirt.

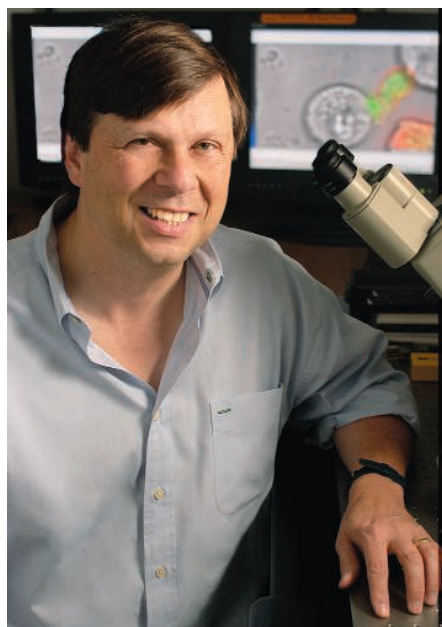
However, nobody has cataloged the differences, and as a result, inconsistencies between human and mouse immunity often leave patients in the lurch, Davis says: "Hundreds of clinical trials have been based on curing mice, but almost none led to clinical treatments." Take the case of myelin basic protein (MBP). Injecting MBP into mice causes a condition similar to multiple sclerosis, which can be prevented by doses of proteins that blunt the immune reaction to MBP. But clinical trials of these protective proteins were stopped because they made some people with multiple sclerosis worse.

Failures like that have spurred Davis to call for immunology to go big science in a very human way. If enough labs combine efforts to analyze the thousands of blood samples drawn in the United States or around the world every day, a so-called Human Immunology Project could quickly amass and scrutinize data from large numbers of healthy and sick people, Davis says. Within 5 to 10 years, he predicts, "we could have the first crude benchmarks of immune function." Davis doesn't know what these benchmarks

will be—perhaps the levels of particular cytokines or the abundances of certain types of T cells—but he says researchers will probably settle on five or six variables that reflect overall immune status in people, the equivalents of LDL, HDL, and triglyceride levels.

Davis is far from the first to point out the "mouse" problem in immunology. "Studies on mice are very elegant and beautiful, but they aren't reflecting the needs of the [human] population," says Jacques Banchereau, head of the Baylor Institute for Immunological Research in Dallas, Texas.

Hoping to address this problem, Davis over 2 years ago helped to found Stanford's Human Immune Monitoring Center. HIMC analyzes blood samples mainly from Stanford clinical research labs but also from some biotech and pharmaceutical companies, says Director Holden Maecker. The center can measure levels of 50 cytokines, run microarrays to nail down gene activity, and gauge the abundance of more than 30 varieties of white blood cells using flow cytometry, a technology for counting and sifting cells. The researchers receive their results, but HIMC also stockpiles the data. Within a year or two, says Maecker, the center should have enough measurements from multiple studies to start nailing down



Back to basics. Stanford's Mark Davis wants immunologists to pay more attention to human immunity.

what's normal for the immune system.

The U.S. National Heart, Lung and Blood Institute in Bethesda, Maryland, has established a similar facility, the Center for Human Immunology, Autoimmunity and Inflammation. The center, says Director Neal Young, provides access to technology, such as the latest flow-cytometry and gene-sequencing machines, that researchers at the National Institutes of Health (NIH) might not be able to afford or have the expertise to use. Many of these studies—a current one tracks the effects of the H1N1 flu vaccine on 200 NIH employees—will be "just looking," Young says, and will accrue large amounts of basic immune data, which the center plans to make public.

Projects like these are a start, says Davis, but a concerted effort is needed. Large-scale projects are not only cheaper because of economies of scale, but they will also use standard procedures that yield comparable results. Moreover, squeezing the most information from blood samples will require an assortment of experts—from clinicians to bioinformatics virtuosos—who aren't available to every lab.

Banchereau is supportive of Davis's call. So is Ralph Steinman of Rockefeller University in New York City, who suggests that such a project could benefit one of his areas of interest: vaccines. "The truth is that to push vaccine science—say, for HIV or cancer—will require a major effort in human immunology."

Davis's push for more basic research on human immunity has also impressed people who control the scientific purse strings. He's received grants for such work from the Howard Hughes Medical Institute and the Bill and Melinda Gates Foundation. And last year the U.S. National Institute of Allergy and Infectious Diseases announced that it would spend \$100 million over five years on "human immune profiling research centers" that will track how our immune system responds to jolts such as vaccination and infection. The first grants are due to be awarded in May.

A human immunology project would require more research like this—and more money. Although Davis hasn't submitted a formal proposal, he suspects that the bill would be in the hundreds of millions of dollars, much less than the \$4.3 billion (in today's dollars) that the U.S. government spent on the Human Genome Project. Even some of the biggest fans of Davis's idea wonder, however, if such a project is affordable given the current economic climate. But unless we attempt to understand how our own immune system works, "we won't realize the health benefits of immunology," Davis says. "It's not a sustainable strategy to stay focused on mice."

—MITCH LESLIE