

Mouse trap? Stanford immunologist calls for more research on humans, not mice

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The fabled laboratory mouse — from which we have learned so much about how the immune system works — can teach us only so much about how we humans get sick and what to do about it, says a leading researcher at the Stanford University School of Medicine.

The time has come for immunologists to start weaning themselves from experimental rodents and to embark on a bold, industrial-scale assault on the causes and treatment of specifically human disease, writes immunologist Mark Davis, PhD, in an essay to be published Dec. 19 in *Immunity*. Davis, director of the Stanford Institute for Immunity, Transplantation and Infection, proposes that the current mouse-centered, small-laboratory approach be supplemented by a broad, industrial-scale "systems biology" approach akin to the one that unraveled the human genome.

"We seem to be in a state of denial, where there is so much invested in the mouse model that it seems almost unthinkable to look elsewhere," Davis, the Burton and Marion Avery Family Professor and professor of microbiology and immunology, writes in the essay.

Over the past several decades, the little mouse has proven immensely helpful in generating a fundamental understanding of how the mammalian immune system works, Davis said in an interview. "The mouse has been incredibly valuable," he added. "That's part of the problem."

Experimental manipulations that are commonplace with lab mice, such as genetically engineering them to express a foreign protein or to be deficient in the expression of one of their own, would be unthinkable in a human. Because experimental mice can be used to get quick answers, Davis argues, researchers look to the mouse to tell them everything. "In humans it often takes years to find out anything. There are a lot more regulatory, financial and ethical hurdles," he said.

But when it comes to adapting therapeutic interventions that seem to cure all kinds of infectious disease, cancers and autoimmune conditions in mice for use in human beings, the record is not so good. The vast majority of clinical trials designed to test these interventions in people end in failure.

"Mice are lousy models for clinical studies," Davis asserts in his essay.

There are probably some good reasons for this, said Davis. For starters, mice are rodents, separated from humans by some 65 million years of evolutionary divergence from our common ancestor.

That's not all. While it takes about 20 years for a person to reach sexual maturity, a mouse gets there in three months. The roughly 100 years during which the furry, diminutive animals have been domesticated and bred in labs are, therefore, the mouse equivalent of 8,000 human years, during which they have been inbred and kept relatively disease-free. They would never survive in the wild, said Davis.

Meanwhile, the past 8,000 years have seen humans crowded into cities, he said. "We've been selected by urbanization, with plagues such as the bubonic plague and smallpox that routinely killed huge numbers of people, and modern scourges like HIV and malaria that still infect and kill millions each year. Most humans are infected with six different herpes viruses, and who knows what else. And while we're suffering

away, getting colds and flu, the mice are living in the lap of luxury in miniature condominiums, with special filters on the cage tops to keep bad things out." They're in such pristine shape, Davis notes drily, that researchers have to induce facsimiles of human disease in them. These conditions may or may not accurately mirror ours.

"We can't depend on the mouse for all the answers, because in some cases it's not giving us the right answers," Davis said. "But think about what we can do with people. People come to hospitals, get vaccinations, give blood and tissue samples for routine lab tests and clinical trials. We're not learning nearly as much as we could from these samples. As with the recent history of human genetics, we could be much bolder."

The Human Genome Project, which has radically accelerated the pace of human genetics, was conducted as a large industrial operation carried out mainly in a small number of large centers, including one at Stanford. In a spirited debate attending that project's initial conception, many academics objected strenuously on the basis that doing the same thing over and over isn't a good way to train students and researchers, said Davis. But, he added, "The Human Genome Project didn't destroy the small lab. It complemented it."

In his Immunity essay, Davis writes: "Although the small academic labs as we know and love them are great for innovation and out-of-the-box thinking, some problems in biology, particularly those that involve a great deal of repetitive assays and data collection, are much better suited to a larger-scale organization and execution. The data are both more uniform and considerably cheaper."

Davis sees the need for a national or even international infrastructure to capture information from blood and tissue samples. A local template is Stanford's Human Immune Monitoring Core, run by Davis' colleague David Hirschberg. Affiliated investigators send human samples to this

facility, where copious assays of cell types and immune secretions in blood and tissues extract data about experimental subjects' immune status, in a relatively short time. "This information goes back to the principal investigators, but it also gets captured in a database we're developing," Davis said.

The creation of high-throughput assays that could quickly and cheaply measure vast numbers of immunologic variables (many of them first elucidated in the mouse) in a standardized fashion among very large groups of people — some in excellent health, others suffering from one or another disease — would greatly advance immunological discovery, said Davis.

"What if we could define the normal range for all these parameters, and then see how they're changed by any of the over 100 infectious diseases, or 90-odd autoimmune disorders, or more than 120 inherited immune deficiencies that afflict us — or, for that matter, by aging or even vaccination? Maybe we could see something coming early on and start applying remedies to restore the normal balance and prevent the disease's progression."

Davis envisions routine clinical tests that, analogous to the serum lipid tests we take to learn our predisposition to cardiovascular disease, tell us what shape our immune system is in or what disease we're starting to get.

"The game here is that we don't know quite what we're looking for yet," he said. "But some of this information is going to be useful."

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