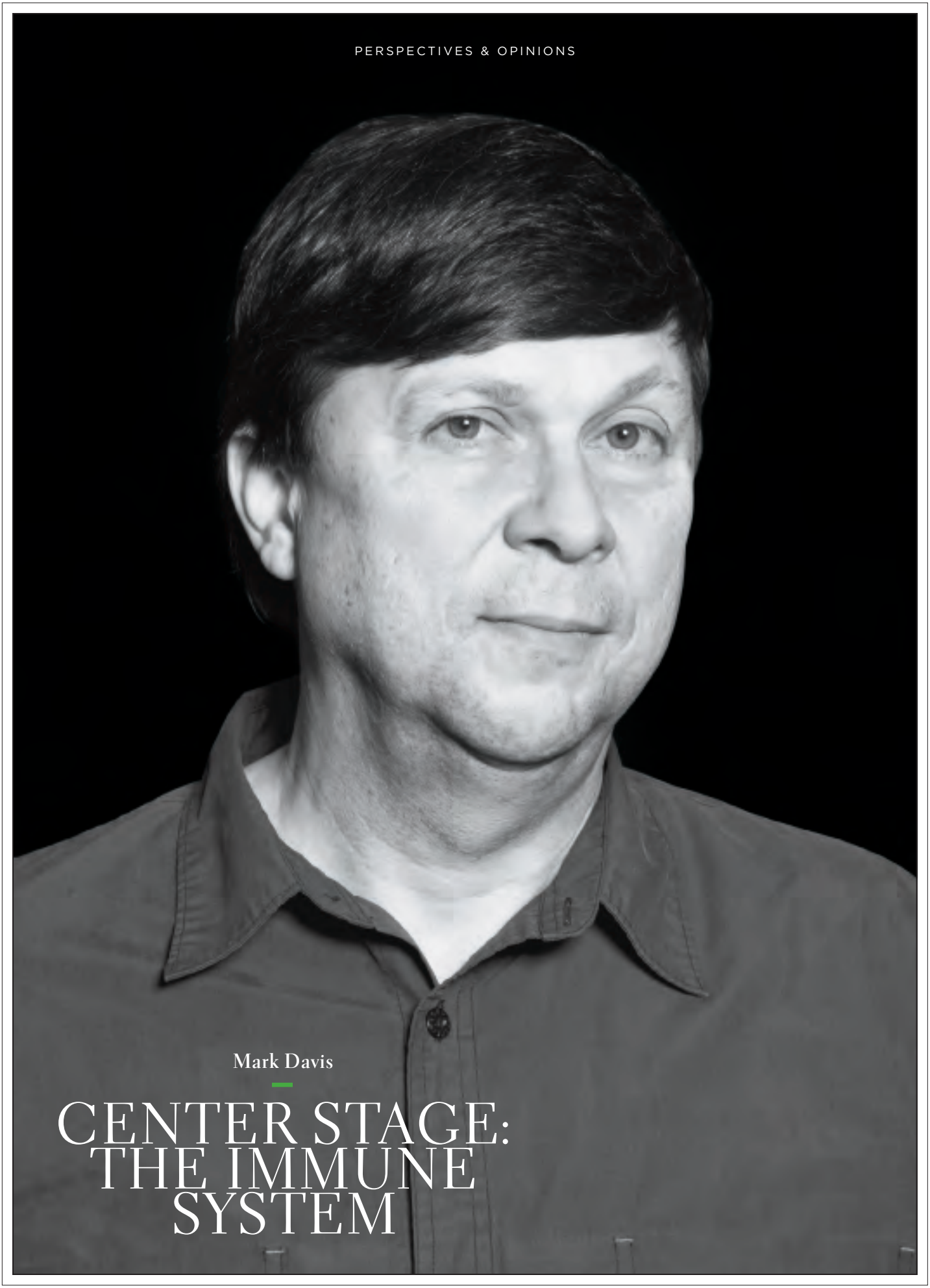

Mark Davis

CENTER STAGE: THE IMMUNE SYSTEM

Mark Likosky

The field of immunology is stuck in the lab and needs a major overhaul to become more relevant to human health, says Mark Davis, an HHMI investigator and immunologist at Stanford University. He argues that now is the time for large-scale human studies of the immune system—a human immunology project.

The immune system is one of our major health systems and is just as important as our cardiovascular system or nervous system. If your immune system goes haywire, you're in deep trouble. But for many years, the immune system has been a black box. That situation has now changed dramatically over the past few decades in that enormous progress has been made in basic immunology. But unfortunately, very little of this knowledge is being applied medically. After decades of study, immunologists still can't define what constitutes a healthy human immune system.

We know a lot about what the immune system can do and should do, but no one has put together a test that can identify whether a patient's immune system is working correctly. Such a test would be more complicated than, say, a cholesterol test, but it would serve a similar vital function: providing clinicians with an easy-to-understand readout of the health of the patient. That way, trouble could be spotted early and interventions taken when necessary. Cholesterol tests are a good model because they're proactive. We need a similar, proactive test for immune function that lets physicians and patients know when a big problem lies ahead.

If such a test were developed, it might help reduce the burden of the almost 90 known autoimmune diseases and the 120 known immune deficiency diseases. More recently, immune dysfunction has been found to play a role in big killers such as Alzheimer's disease and atherosclerosis, the inflammation and hardening of the arteries that causes heart disease. These diseases could be handled better if we had a deeper understanding of how the human immune system works and what goes wrong with it.

Much of the lack of progress in human immunology is due to the tremendous success of inbred mice as a scientific model. As a result, the whole field is severely tilted toward studying mice, with some 80 percent of articles published in immunology journals involving rodents, not people. Yet the mouse is a poor clinical model.

Sure, the thousands of immunology studies conducted on mice have provided, and continue to provide, major insights into how the mammalian immune system functions. Yet mice aren't people, and the mouse immune system does not accurately mimic the human immune system. Sixty-five million years of evolution separate mice and men, a vast divide. Researchers can regularly cure cancer and autoimmunity in mice, but almost none of those cures work in people.

Here's one example: Recently, an antibody developed as an antitumor therapy showed outstanding results in laboratory mice, leading to human trials. But after hundreds of millions of dollars and two large human studies, only 14 percent of patients showed any benefit. Everyone involved with this therapy had great hopes for it. But it's been very disappointing, and it's unclear if the Food and Drug Administration will ever approve the drug. Dozens of similar examples litter the drug development landscape.

Part of the solution is that some of the money spent on mouse research should be funneled into explicating the differences between human and mouse immunity. Defining this gap would be incredibly valuable. Another part is to begin a human immunology project focused on defining immunological health, taking some important cues from the human genome project. In the 1970s, human genetics was a very limited field with almost no ability to inform medical care. But after a huge investment in sequencing and cataloguing the human genome, genetics is now at the center of the search for cures.

A large-scale human immunology project could work similar wonders. Such a project would focus the field on human, instead of mouse, immunology. The project would create or ease access to large banks of blood samples from clinical trials. And it would encourage researchers to mine these large samples for critical information on immune function in healthy and ill people.

As a step toward that goal, I've helped organize the Human Immune Monitoring Core at Stanford. Clinicians running human trials are encouraged to send patient samples to the facility, where we can collect data across patient populations. We also aim to combine data from dozens of such studies to learn a lot in a hurry and to uncover previously unrecognized similarities between diseases.

More projects like this are needed. Immunology has always held the potential to be clinically useful across a broad spectrum of devastating diseases. But it's going to take a serious rethinking of the whole field to achieve that potential.

INTERVIEW BY BRIAN VASTAG. *Mark Davis is director of the Stanford Institute for Immunity, Transplantation and Infection.*