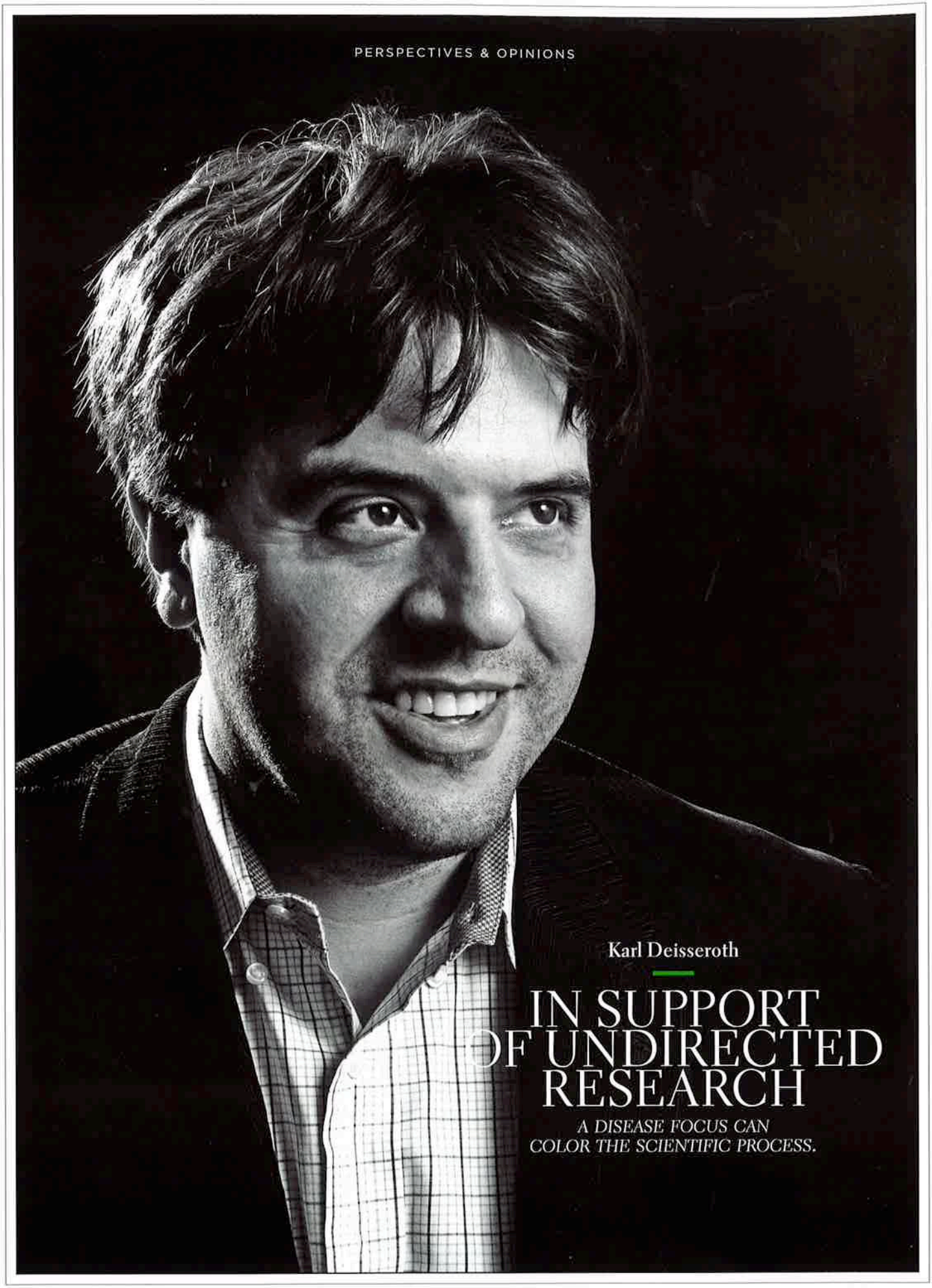

Karl Deisseroth

IN SUPPORT OF UNDIRECTED RESEARCH

A DISEASE FOCUS CAN COLOR THE SCIENTIFIC PROCESS.

Ramin Rahimian

Karl Deisseroth surprised his neuroscience colleagues at a February 2011 panel discussion by defending the legitimacy of doing science for its own sake rather than being motivated solely by the need for cures. In recalling that moment, the HHMI early career scientist at Stanford University—a practicing psychiatrist, neuroscientist, and bioengineer—urges public and private funders to diversify their portfolios when they invest in science and biomedicine.

At that AAAS symposium in Washington, D.C., panelists were invited to discuss neuroscience research. After we presented our work, the moderator, Story Landis, head of the National Institute of Neurological Disorders and Stroke, observed that every speaker had tried to link their work to a brain disease. She asked, was this necessary?

That was a provocative question. Do we neuroscientists always have to justify what we do in a disease context, or can we make a sufficiently compelling argument for the intrinsic excitement of doing biology?

As the only practicing physician on the panel, I was expected to advocate for tying research to disease, but I took the opposite viewpoint. I argued that we must support work that is not related to disease models and value completely undirected research with no implications for health.

That answer may seem surprising, because I still practice psychiatry and have always had a translational motivation. In the 1990s, I went through an M.D./Ph.D. program at Stanford and became fascinated by psychiatry. The patients were suffering severely, and I felt a need to develop methods to understand their diseases. My psychiatry colleagues were brilliant, thoughtful, and caring but lacked tools to probe the brain with precision, and our interventions often lacked specificity. So when I set up my lab in July 2004, I wanted to create targeted approaches for understanding brain disease, which led to my development of optogenetics.

In optogenetics, we take genes encoding light-responsive proteins from microbes and introduce them into neurons, even within freely moving mammals. Using a variety of proteins, we have shown that we can stimulate or inhibit neurons with millisecond-precision flashes of light. By switching specific populations of neurons in the brain on or off to define what they do, we've obtained insights into neural circuit function relevant to Parkinson's disease, anxiety, substance abuse, depression, narcolepsy, and autism.

But the roots of the field extend to 1971 when the first light-responsive microbial opsin protein, bacteriorhodopsin, was identified. Scientists studying microbes for their own sake characterized more opsins in 1977 and 2002. They did not give a thought to neuropsychiatric disease; attempts to link their work with psychiatry would have been laughed at. These researchers were simply studying an elegant biological system. No disease-driven donor or agency would have funded them.

Yet we now stand on their shoulders. Based on that history, I offer a challenge. Let's make the explicit absence of a potential disease justification—a health relevance of zero—a priority when evaluating scientific programs supported by funding agencies, even those with a disease mission.

Disruptive, landscape-shifting ideas that enhance our understanding of disease processes will likely come from research with little apparent disease connection. Talented young scientists will always choose problems that illuminate the complexity of the biological world. How an organism turns light into ion flow—now *that* is an interesting question! But if in 1971 a funding agency had called for new ideas to study Parkinson's disease or anxiety, the likelihood of supporting bacteriorhodopsin work would have been zero. It took decades of poking around algae and bacteria for us to understand how light-sensitive channels work, followed by the unlikely step of putting them into neurons.

Donors interested in funding high-impact science should know the optogenetics story. Its lesson is that we don't know enough to guide research fully and should instead seek to understand the complexity of the natural world.

Scientists constantly think about how to fund their research, and many funding agencies favor a clinical justification. Nobody wants to criticize those agencies, because funders have their own reasonable constraints. Making a disease-related justification has become almost an instinctive part of science culture, particularly in the United States.

As it becomes universal, students come to see this disease-relevance aspect as essential to the scientific process, and the resulting value judgments color the scientific process and guide national and global priorities. But I have long made it a point to underscore to my students and postdocs the importance of undirected research.

For me the question of basic versus applied research is not a choice. Translational work is essential. But every funding agency—even those with a disease focus—should examine its portfolio, and if all is translational or even disease inspired, this should be viewed as a serious weakness. Despite shrinking budgets, undirected basic science funding must be preserved and even encouraged if we are to reach our disease-curing goals.

INTERVIEW BY ELISE LAMAR. *Karl Deisseroth is a member of the Institute of Medicine.*