What cell biologists should know about the National Institutes of Health BRAIN Initiative

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ABSTRACT **The BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative is an ambitious project to develop innovative tools for a deeper understanding of how the brain functions in health and disease. Early programs in the National Institutes of Health BRAIN Initiative focus on tools for next-generation imaging and recording, studies of cell diversity and cell census, and integrative approaches to circuit function. In all of these efforts, cell biologists can play a leading role.**

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After President Obama announced the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative in 2013, we heard three decidedly mixed reactions from the scientific community (Underwood, 2013). While some neuroscientists were understandably enthusiastic, many other scientists responded with concern. With so many areas of science underfunded, why choose one for a large new initiative? Others criticized a top-down, big science initiative especially at a time when investigator-initiated research was not getting funded. And even among neuroscientists there was disagreement, with both clinical researchers and basic scientists worried the project would neglect their specific area of interest.

National Institutes of Health (NIH) director Francis Collins, no stranger to big science projects or to the controversy that surrounds them, asked an advisory group for a 10-year plan for the NIH BRAIN Initiative, including what new funds should be allocated to fulfill this plan. The group, led by Cori Bargmann and Bill Newsome, met four times in different parts of the country to hear from many stakeholders and to discuss among themselves the highest priorities. While the group acknowledged the concept that led to the president's announcement, the Brain Activity Map (Alivisatos, 2012), a comprehensive effort to record from all cells and all connections in real time, they recommended a different approach. The group's final report, BRAIN 2025, called for new tools to guide a deeper understanding of the brain at the "mesoscale," the level of cells and circuits (NIH, 2014) According to the work group, the microconnectome, mapping every cell and connection, was critically important but not sufficient for understanding how the brain supports behavior. Conversely, the macroconnectome, exemplified by current human neuroimaging, could not decode brain activity at the level of cells or at the speed of thought.

Addressing the concerns of the critics, BRAIN 2025 called for new funding, not offsets to current funding. The report also noted the importance of including bottom-up more than top-down science. That said, they suggested the success of this venture would depend on teams of engineers, materials scientists, nanotechnologists, computational scientists, and many others working with neurobiologists to create the tools for a deeper understanding of how the brain works.

What does this mean for cell and molecular biologists? Are they neglected by yet another big science initiative? Not at all. The first priority area of BRAIN 2025 is "mapping the structure and components of circuits" to create a "parts list" of the brain—a taxonomy of the different kinds of cells and census of each in brains across phylogeny. In contrast to most organ systems, a fundamental map of the diversity of cell types in the brain is lacking. And we do not truly understand the very concept of a circuit. Unlike electrical circuits, brain pathways are fully recursive without the simple directionality implied in most textbooks.

What keeps us from getting a parts list? Our tools are no match for the fundamental complexity of the brain. Of course, we have highly precise tools for measuring membrane conductance and mapping the projections of single cells. And yes, with RNA-Seq we can define the transcriptome of single cells. But some of the most basic questions about cell types in the brain remain unanswered. How many types of inhibitory neurons are found in the human cortex? How many of each of these cell types are found in the healthy

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Abbreviations used: BRAIN, Brain Research through Advancing Innovative Neurotechnologies; NIH, National Institutes of Health.

brain? Are there cell types specific to humans? What is the best way to define a cell type: Morphology? Transcriptome? Physiology? Connections? These are the kinds of questions being addressed by the NIH BRAIN Initiative's projects on cell diversity.

Although we are still at the beginning of what should be a 10-year initiative, early results already indicate what we can all expect from this initiative. A team from the Broad Institute recently described a high-throughput approach to cell typing with RNA-Seq (Macosko, 2015). Using bar coding with individual cells isolated in nanodroplets, this new method can prepare 10,000 single-cell libraries for sequencing in 12 h, for ~6.5 cents per cell. The team, led by Evan Macosko and Steven McCarroll (both of whom had trained with Cori Bargmann), used this technique to identify 39 cell types among nearly 45,000 cells in the mouse retina. Other groups are developing new approaches for labeling cells, creating new versions of chemogenetics (DREADDs) and optogenetics, and combining current technologies to get insights into cell and circuit function.

Not all of the NIH BRAIN Initiative will be geared to cell and molecular biology. There are currently programs for next-generation imaging, large-scale recording and modulation, and integrative approaches to understanding circuit function. Future projects will look at invasive and noninvasive technologies for understanding human brain activity. The ultimate goal, as noted in BRAIN 2025, is to map the circuits of the brain, measure the fluctuating patterns of electrical and chemical activity flowing within those circuits, and understand how their interplay creates our unique cognitive and behavioral capabilities. But the early phases of this bold project need to provide the fundamentals, and those fundamentals rest on a deeper understanding of cell diversity and cell function.

How will we measure the success of the NIH BRAIN Initiative? For us, an early indicator of success will be seeing unfamiliar names in the funding list. We believe that the tools we need will require scientists from diverse fields, not as consultants but as full partners with neurobiologists. Going beyond the "usual suspects" to include engineers and computational scientists as well as the next generation of neuroscientists will be an important milestone. A slightly later measure of success will be the scaling up of our current tools. Advances in the past decade have given us extraordinary progress in the monitoring and manipulation of cell and circuit activity in model organisms, from flies to mice. Techniques like optogenetics and chemogenetics have facilitated studies of causality in neuroscience, bringing the field to a new level of maturity. Bringing this same kind of precision to the primate brain, including the human brain, will likely take another decade.

BRAIN 2025 notes that "our focus is not on technology per se, but on the development and use of tools for acquiring fundamental insight about how the nervous system functions in health and disease. We have considered how mature technologies can be applied to neuroscience in novel ways, how new technologies of obvious relevance can be rapidly developed and integrated into regular neuroscience practice, and what longer-term investments should be made in "blue sky" technologies with higher risk but potentially high payoff. As the BRAIN Initiative advances, these technologies should increasingly be used to shed light on the healthy brain and on tragic human brain disorders" (NIH, 2014, p. 12) Ultimately, the success of the NIH BRAIN Initiative will be measured in its impact on our understanding of the human brain in health and disease. But the foundation for this lofty goal depends on the fundamental study of cells and circuits.

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