THE AUTHOR FILE

Joshua Sanes

New features are added to a neuron-painting toolbox that could contribute to the recently announced US brain-mapping initiative.

Rainbows present the eye with a color splash. Brainbow, a molecular technique developed by a Harvard University team including neurobiologist Joshua Sanes, visually labels neurons in pointillistic splendor. Leveraging the Cre-loxP genetic recombination system, the approach labels mouse neurons in nearly 170 different hues.

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The work advances Cajal's classic use of Golgi silver staining and reflects Sanes's active development of imaging tools for neuroscience. With improved reagents and transgenic mice, the team has now enhanced the way color splashes across neurons in the mouse brain.

Developed 6 years ago, Brainbow was intended to help scientists create connectomic maps, which are detailed views of cellular interactions in the brain. "It was apparent from the first that the initial set of Brainbow mice generated gorgeous images but had a number of limitations," says Sanes. Some fluorophores bleached too fast, some fine neuronal processes did not label well and some colors were expressed in too many cells, which hindered their identification. New transgenes and viral vectors address these shortcomings. "Hopefully, these new tools will help bring us back to where we wanted to be."

Sanes was drawn to neuroscience by a curiosity about the biological underpinnings of mental illness. Knowledge remains scant about the disarray in the brain these disorders cause. This challenge is at the nub of the new US government–funded Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. Scientists first need to understand the healthy brain's workings to approach disorders such as Alzheimer's disease or autism, says Sanes.

Researchers in the BRAIN Initiative seek to map the brain's activity patterns in thousands of neurons connected in circuits that underlie behavior. "The BRAIN Initiative is exciting," Sanes says. "For one thing, it is rare and wonderful to have the President voice enthusiasm for basic research—let alone research aimed at understanding how the brain works."

Sanes has been asked to join the BRAIN Initiative's committee that advises the director of the US National Institutes of Health, Francis Collins. Brainbow is among the contenders of tools that can help BRAIN teams collect structural information. As the committee explores strategies, "there is likely to be some debate about how much structure we need before moving on to function," says Sanes.

By summer's end, he and his colleagues will hammer out a tentative research agenda to include plenty of technology development. Tools are lacking to measure activity on a cellular level across the entire brain. "My guess is that the first stages of the BRAIN Initiative will be devoted to developing those tools and applying them to relatively simple model systems—for example, *C. elegans* or mammalian retina—so that we can figure out what we need to tackle the mammalian and, eventually, the human brain."

That project will involve much collaboration and mentoring, which is familiar territory to Sanes. Paul Greengard, a neuroscientist at Rockefeller University, says he has grown from being Sanes's mentor to his colleague and admirer. "I was Josh's undergraduate thesis advisor, and I remain a friend," he says. "He was brilliant when he was 18, and he remains brilliant."

With neuroscience on the political agenda, Sanes returns to Washington. "It was fascination with Watergate that made me want to be a voyeur at the fringes of Washington," he says. After completing his PhD at Harvard, he took his political interest to the US Congress to work for a year at the Office of Technology Assessment. Although he considered staying on, he returned to science for a postdoctoral fellowship at Harvard and then another at the University of California in San Francisco.

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For over two decades, Sanes was a faculty member at Washington University, where he began working with neurobiologist Jeff Lichtman. Both men were recruited to join the Harvard faculty in 2004, where they have since continued to work together. "I enjoy what I do," is how Sanes describes the way he splits his time between research, teaching and directing Harvard's Center for Brain Science.

Neurobiologists have learned much about individual neurons and synapses, but understanding how hundreds, thousands or millions of neurons cooperate to generate thoughts, emotions, decisions, movements and perception is only starting, Sanes says. "I view this as the biggest scientific challenge of the next half century."

Vivien Marx

Dawen, C., Cohen, K.B., Luo, T., Lichtman, J.W. & Sanes, J.R. Improved tools for the Brainbow toolbox. *Nat. Methods* **10**, 540–547 (2013).