Team seeks to create genetic map of worm's nervous system

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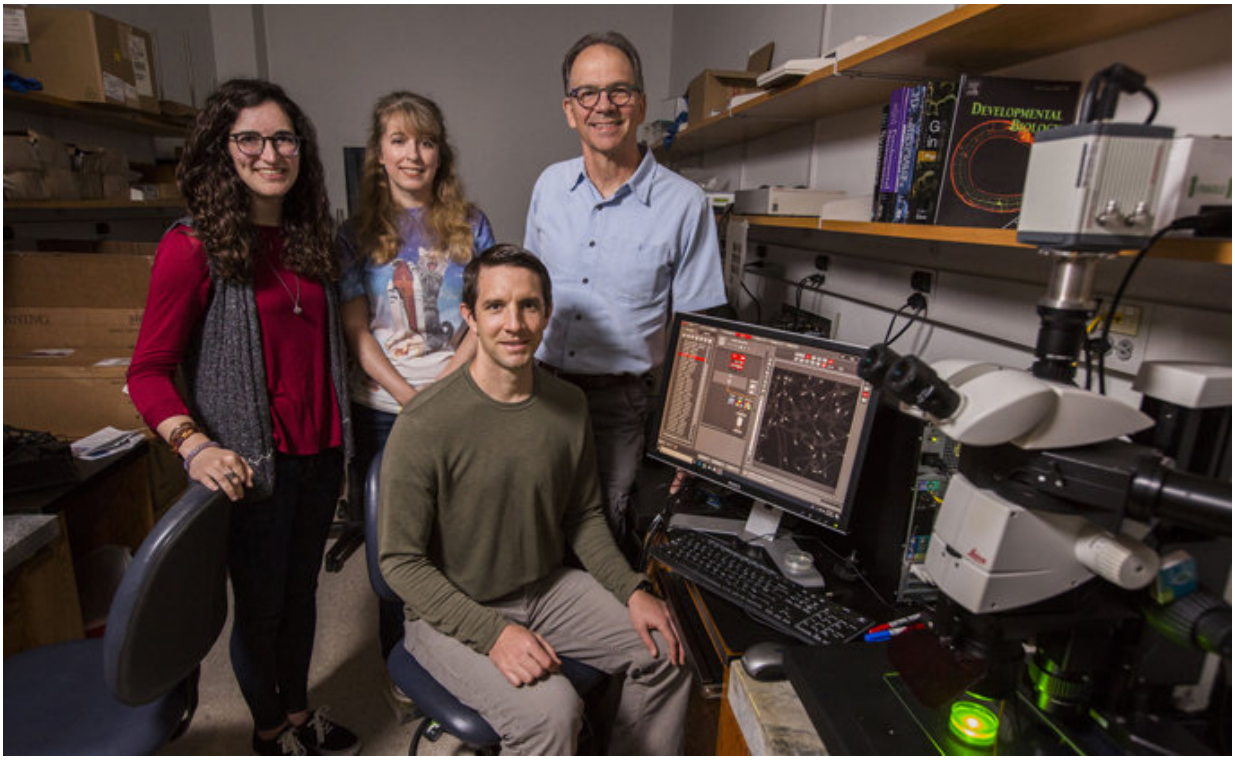

Abby Poff, left, Rebecca McWhirter, Seth Taylor, David Miller, PhD, and colleagues are working to define the genetic program for the entire nervous system of the worm C. elegans. Credit: Anne Rayner

How do you build a brain? What "rules" govern where neurons end up, how they connect to each other, and which functions they perform?

"Most of the information that you need to create this extraordinarily complex network of connected cells—the brain—is genetically encoded. The overall architecture is a readout of a genetic program," said David Miller, Ph.D., professor of Cell and Developmental Biology. "If you really want to understand how to make a brain, you need to know the genetic program."

Miller and his team at Vanderbilt are working with investigators at Yale University and Columbia University to define the genetic program—the gene expression—for the entire nervous system of the nematode worm C. elegans.

They believe that a complete map of gene expression for the worm will help address broad questions in neuroscience about how gene expression programs establish diverse sets of neurons—and how genetic differences contribute to neuronal function in healthy and disease conditions.

"Of course, worms are not people," Miller said. But more than half of the genes in worms are conserved in people, he noted, and the cellular machinery of neurons is very highly conserved.

"We have to start with an experimentally tractable system. The worm is. We're not."

The project, CeNGEN (C. elegans Neuronal Gene Expression Map & Network), is being supported by a five-year, $6 million grant from the National Institute of Neurological Disorders and Stroke. Miller's co-investigators are Marc Hammarlund, Ph.D., Oliver Hobert, Ph.D., and Nenad Sestan, MD, Ph.D.

C. elegans worms have long been darlings of biomedical research. Developmental biologists have characterized each cell division from the egg to the adult organism. They know how many neurons there are

(302), where they are, and how each one is connected—the nervous system's "wiring diagram." And they can genetically manipulate the worm to study gene function.

"We have all this descriptive information about structure and wiring, and we have a lot of functional information," Miller said. "What we don't have, yet, is a gene expression map—which genes are turned on in each neuron to make it unique and different from another."

To build an atlas of worm neuron gene expression, the CeNGEN project is using methods developed by Miller's group to isolate thousands of neurons of each type with fluorescence-activated cell sorting in the Flow Cytometry Shared Resource.

The Miller group, which includes Rebecca McWhirter, Abby Poff and Seth Taylor, Ph.D., is taking advantage of many available worm strains genetically engineered by other investigators to express certain fluorescent markers. By cross-breeding various strains, researchers at Columbia will be able to uniquely label each of the 118 different classes of worm neurons for isolation in the Miller lab. Colleagues at Yale are then sequencing the RNA for each class of neuron. The gene expression data will be released to the scientific community as they are produced.

The investigators are also using new powerful "single cell" sequencing methods to obtain the RNA profile of individual neurons. This single-cell approach could reveal that the worm contains even more than the current tally of 118 different neuron types.

"This is going to be a rich resource of high-resolution information about the worm nervous system that can be used to develop testable hypotheses," Miller said.

"We still have so many basic questions about our brains, and one of the

biggest and most complicated questions is: How does a genetic program instruct neurons to make connections with some partners and not others? I think a simple model is the best place to start asking this question."

An overview of the CeNGEN project was reported in the journal *Neuron*.

More information: Marc Hammarlund et al. The CeNGEN Project: The Complete Gene Expression Map of an Entire Nervous System, *Neuron* (2018). DOI: 10.1016/j.neuron.2018.07.042

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