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Virus, zebrafish enable scientists to map the living brain

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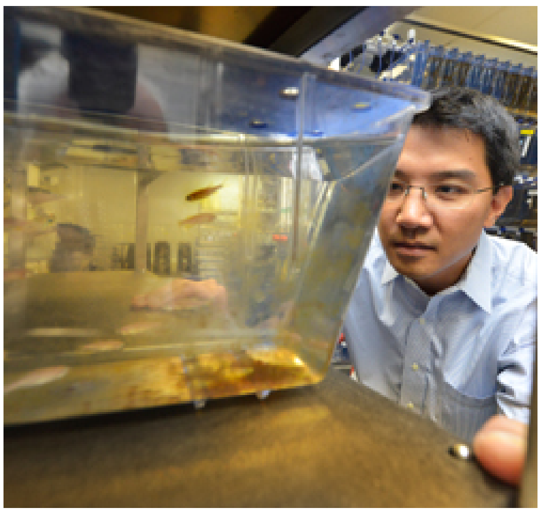

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A virus and a zebrafish are helping scientists map the living brain. "You can kinda draw a diagram and see how cells within it are connected in a functioning brain," said Dr. Albert Pan, neuroscientist at the Medical College of Georgia at Georgia Regents University. "This will help us see how wiring is laid and how it functions."

Miswiring is believed to cause conditions such as mental retardation, autism, and schizophrenia. In autism, as an example, there may be too many connections in some brain areas and too few in others.

"We want everything to happen well in the embryo where a lot of this dividing and migrating and connecting is taking place," Pan said. He recently received a $1.9 million grant from the National Eye Institute to develop a virus-based toolkit that will help scientists understand normal connectivity and, ultimately, what goes wrong in disease.

His model organism is the zebrafish and his model system visual function. While the tiny zebrafish may seem an odd choice, the transparent vertebrate is actually a great model, Pan said. The human brain has 70 billion cells compared to 100,000 in the zebrafish, but the brains have the same basic structure. The fact that the fish develops rapidly and transparently are two other huge pluses, he said.

Zebrafish start out as an external egg in a transparent shell, complete embryonic development in two days, and are full-grown fish by three months. By day 10, Pan equates them to young children who can readily manage most common, important behaviors, such as learning, despite the fact that their brains are still developing.

"It fits the timeframe of a scientist. In very small fish, you can look at very interesting behaviors in a vertebrate brain," said Pan, who is the first to try virus-based brain mapping in zebrafish. Previous efforts to map neural circuits mostly have been done in mice.

"The unique thing about using this fish is that we can actually look at the neuronal activity while we are tracing, we can try different behavior tasks and see which cells are active, which cells are connected, and we can use different techniques to destroy different neurons and see how it affects behavior."

Pan's use of a mutant, super albino that lacks pigment further enhances his ability to keep his eye on functioning cells.

The fish are also transgenic so firing cells naturally light up, but visualizing the nanometer-scale synapses with a light microscope as they form is another matter. "If a cell fires, we can see kind of a spike of light coming out of those cells. So you can see the firing pattern of these cells. But you don't know which cells are connected to each other, so it's difficult to make sense of how the brain is transferring information from one part to another and how this information is processed," he said.

That's where a virus can help "do the heavy lifting." The vesicular stomatitis virus, which is in the same family as rabies but doesn't infect humans, has the uncanny propensity to travel across synapses. So he is using VSV, armed with a fluorescent agent, to fill in the important blanks of when and how cells connect. "What this grant is about is developing a new tool where you can see these connections and how one cell is connected to another cell," Pan said.

The brain's basic organizational structure is neural circuits, groupings of brain cells for a common purpose like sight or smell or movement. "If you think of it like a computer, it's different software that does different things," Pan said. Different circuits also integrate so the brain works as a cohesive unit.

The transparency of the zebrafish is enabling him to watch the visual circuit from essentially the beginning, when neural progenitor cells, destined to be neurons, first appear around the donut hole of the neural tube, a hollow tube that forms the brain and spinal cord.

Neural progenitor cells split, then migrate out, with gradients and the distinctive smell of different proteins guiding them – if all goes well – to their rightful place in the developing brain. Pan uses the analogy of pouring cream in coffee and its natural motion away from that point.

"Cells can sense the proteins and know where they are within the body plan. They know what type cell they should be and where they should migrate," Pan said.

Once in place, neurons wire together and connect by forming synapses that enable communication. Synapses can be short lived, to help you remember how much apples cost until you get out of the grocery store, or long-term, so you always remember your mother's voice and face.

He notes that the additional information he learns about the visual neural circuit will lead to better understanding of this important neural circuit as well as related behaviors – like how the eyes naturally follow a moving car – in addition to providing a model for studying other circuits.

"A lot of what we already understand about the brain comes from vision research," said Pan. His studies will include eliminating some cells, seeing if the zebrafish, also known for its regenerative ability, will regrow the cells, and if those new cells will integrate into the existing circuitry.

Provided by Medical College of Georgia