Scientists

Letting the Animals Teach

Jeff Lichtman

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Jeff Lichtman's research on neuronal development and his role in creating the Brainbow mouse caught our attention.

What has been your most significant scientific insight?

The most surprising insight I've had is that the mammalian brain reduces its wiring complexity as animals accumulate information about the world and hone their behaviors to fit in. As a brain becomes more adapted and able to do remarkable things, the branching complexity of the wiring is actually simplified.

How did you discover this?

As a graduate student, I studied the connections between neurons in the brain stem and a rather insignificant part of the peripheral nervous system that drives salivary secretion. In newborn rats, I noticed that each nerve cell from the brain stem initially contacted many neurons in the periphery and each of these neurons received innervation from many brain stem cells. But a month later, each of these peripheral neurons was contacted by only one brain-stem nerve cell. At that time, others were observing similar changes in spinal cord connections to muscle fibers. These observations suggested that the entire brain might be undergoing a selection process during development regarding which connections to maintain and which to eliminate.

What is currently the most important research question in your discipline?

There are many deep mysteries in neuroscience, but for me, the driving question is

how information is recorded in the brain. When you learn something such as how your grandmother looks, or the capital of Chile, how is that information physically encoded in your brain? Where is it? What is it? One reasonable idea is that the wiring diagram of the adult brain is permanently changed by experience, just as it is during early development. And if we really want to study this, we have to study the wiring diagrams.

Did you develop the Brainbow mouse for this purpose?

Absolutely. The aim of the Brainbow mouse was to allow us to differentiate the wiring of each neuron through transgenic expression of fluorescent proteins. My early career focused on the mechanisms by which two or more nerve cells that converge on the same target cell compete for the territory. We noticed that the winning neuron usually enlarges its territory on the target cell to take over the sites that were previously occupied by other neurons, suggesting that a very nasty competition for synaptic space occurs during development.

Which connection stays and which leaves is not easily predictable. When watching these competitions, we often saw a weakening connection strengthen and overcome a stronger one. We realized that one reason for the changes in the competitive vigor of these inputs was that each nerve cell participates in many competitions simultaneously. Loss of one connection frees up more resources for the remaining connections. The insight that the outcome of one synaptic competition affected other competitions was very important for us because we learned that by focusing on a single target cell, we might never fully understand this process. We need to see the full circuit.

So Jean Livet, a former postdoctoral fellow in my lab, devised a clever technique to randomize the expression of red, green, and blue fluorescent protein transgenes in individual neurons so that each neuron would have its own distinct hue. The

result was the Brainbow mouse, our first connectomics animal. Brainbow allows us to see the connectome—or map of the neural connections in the brain—and to watch competitions on all the developing branches simultaneously.

How is your approach to science unique?

In my work, I take advantage of descriptive approaches. I have the conviction that if we just look, we will see the unexpected and learn what these neural competitions accomplish. That's an article of faith with me.

In much of modern cell and molecular biology, there is a strong emphasis on deductive research where you begin with a hypothesis and do experiments to formally disprove it. Most people doing that kind of work are hoping to fail because they like their hypothesis; being unable to disprove it gives them confidence that they're on the right track.

My approach to science is more inductive, where I accumulate a lot of information and then generate a hypothesis based on the data. A downside of this approach is that we are at the mercy of the data. Sometimes we don't understand what we see because it doesn't fit with our preconceived notions. But our work never becomes boring because we are often surprised by seeing things we didn't expect. The animals are in charge. We let the animals talk to us and they teach us things we wouldn't otherwise learn. Viktor Hamburger, the late experimental embryologist formerly at Washington University in St. Louis, MO whom I respected a great deal, said that of all his teachers, the only one who was always right was the chick embryo. I think there is a lot of wisdom in that idea; that principle has guided my work.

Interviewed by Kristie Nybo, Ph.D. Image courtesy of Harvard University.

BioTechniques 49:489 (July 2010)
doi 10.2144/000113433