THE AUTHOR FILE

Don Arnold

To the tune of a classical guitar, finding a way to watch learning as it happens.

"I didn't really get it," says neuroscientist Don Arnold at the University of Southern California, referring to the moment when he first learned about the optogenetic techniques that his friend and colleague Richard Kramer at the University of California, Berkeley, worked with. Over time, though, Arnold became enamored with optogenetics in that "you can really see what the cells do," he says.

Tina Ogata

Don Arnold

Beyond having the ability to excite individual neurons with optogenetics, Arnold has long wanted to visualize precise changes in synapses, which are junctions between neurons. When animals or people learn and form memories, some synaptic connections are thought to get stronger, others weaker. He sought probes in order to label synaptic proteins and start parsing how the patterns of labeled proteins change when, for example, a zebrafish learns a task. It's challenging, he says, to patiently distinguish signal from noise and to not skew physiology in the process.

In his latest work, Arnold uses his previously developed FingR, which, he explains, is a recombinant antibody that "takes along whatever you stick to it" and binds tightly to a synaptic protein. He and his team linked a FingR to an E3 ligase, creating a probe called GFE3. First the targeted protein is ubiquitinated, then the protein is taken to the proteasome for destruction. In the cell, this ubiquitin–proteasome system is constantly at work degrading proteins that are then recycled. "What we're doing is essentially hijacking the system," says Arnold.

The scientists targeted the probe to gephyrin, an important protein in inhibitory synapses. Eliminating gephyrin is quick—it possibly occurs within minutes, says Arnold—and that does away with inhibitory neurotransmission.

Arnold hopes the GFE3 system can help many labs explore how disrupting the inhibitory input in certain cells affects cell behavior. "It's a way of very precisely manipulating the connectivity between neurons, rather than the excitatory state," he says. And just as optogenetic approaches affect networks by changing neuronal activity in specific cells, these probes can reveal network changes by tuning connectivity between specific cells. GFE3 addresses the experimental difficulty of discerning neuronal output from a group of neurons. When modeling connectivity, experimenters can use it to eliminate specific connections, he says.

Arnold is intrigued by the fact that the inhibitory synapses appear to grow back after GFE3 expression ceases. "How does the cell know it doesn't have any inhibitory synapses?" he asks. He and a few colleagues have set out to explore the mechanism by which this happens, how the cell registers that it needs these synapses and 'knows' to replace them.

Arnold brings an engineering mindset to biology. "As an experimentalist, you're basically fighting the noise," he says. As an undergraduate he studied engineering physics, but neuroscience caught his attention. "That's what I wanted to do," he says, explaining his motivation as an undergraduate.

Arnold did two years of medical school but switched to a PhD program in biomedical engineering and systems neuroscience at Johns Hopkins University. During his postdoctoral fellowship at Rockefeller University he felt systems neuroscience was hampered by a lack of tools and chose to work on protein trafficking. He continued this cell biology work as a postdoctoral fellow at Harvard University, where he transfected neurons with a gene gun, a technique he previously developed. It was enabling technology, he says, almost like a Golgi stain for neurons. "I got hooked; I would just sit there and look at them by the hour, it was incredible," he says. Among Arnold's awards is one for technology innovation in neuroscience. "I just kind of like tinkering with things," he says.

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When he is not in the lab, Arnold plays classical guitar, which he started learning when he was seven. He enjoys playing Bach or one of the many classical Spanish pieces written for the guitar, and, he says, "I've done a little bit of composing of my own stuff."

Arnold is an electric guitar hero who trades riffs with his teenage son, says Richard Kramer, Arnold's longtime friend. "Don is a creative and fearless molecular innovator," and is always willing to talk and think about fresh scientific ideas, says Kramer. The men have struck up a collaboration to study the function and plasticity of $GABA_A$ receptors.

Arnold got married during his second postdoctoral fellowship. At the time his wife, who is also a neuroscientist, was in Boston, too. They then both got job offers from the University of Southern California. "Luckily my wife is a very good scientist so I was able to just ride her coattails," says Arnold.

Gross, G.G. *et al.* An E3-ligase-based method for ablating inhibitory synapses. *Nat. Methods* **13**, 673–678 (2016).