THE AUTHOR FILE

# Loren L. Looger

## Engineering protein sensors to light up split-second signals in the brain

Spotting Loren Looger from afar is easy: look for pink, green, purple or cyan—his favorite shirt colors. Bright is how he likes his wardrobe, and bright is how he likes his biosensors. By lighting up spurts of signals passing between neurons as animals move or learn, these engineered protein sensors give scientists visible readouts of brain events that happen in a fraction of a second. One of his previous inventions made the signaling molecule calcium shine brightly. His newest one is a glutamate sensor called iGluSnFR, which is made from bacterial proteins.

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Glutamate is a widespread food additive, but it is also a ubiquitous signaling compound in bacteria, fungi, plants, animals and humans. In the brain, glutamate is a neurotransmitter, part of a family of molecules that relay messages from one neuron to another. Looger, who leads a research group at the Howard Hughes Medical Institute's Janelia Farm Research Campus in Virginia, and his colleagues have tested iGluSnFR in multiple organisms *in vivo* as well as in brain slices *in vitro* using two-photon imaging.

"Sensors for glutamate already exist, but none are currently usable for hard experiments," says Looger. The new sensors offer 10–100 times the signal-to-noise ratio of previous indicators and are the first to show responses *in vivo*, he says. Furthermore, iGluSnFR responds more rapidly and consumes less spectral bandwidth than previous indicators. "Imaging glutamate tells you about the precise inputs into a neuron, whereas calcium can tell you that, but it also tells you a lot more." Attributing the parts of the calcium signal that correspond to synaptic input or an action potential or metabolic processes can thus often be difficult, he says.

Looger has already given the glutamate sensor to scientists in over 100 labs because it is important to "get these tools in people's hands way early on." Besides helping to iron out any kinks, the early distribution approach also helps others in their research, he says.

"When you talk to Loren, you realize—to most people's initial amazement—that he is indeed sincerely asking: 'What can I do to help you with your work?'" says biologist Gerald Rubin, executive director of the Janelia Farm Research Campus. "'What tools do you need that you don't have that I might develop for you?' rather than 'What do you know that would help me?'"

"Proteins are pretty [expletive] awesome," says Looger. "They are everywhere, doing everything," handling many biological jobs from lending Spinosaurus its size and a cheetah its speed to helping organisms survive and adapt. To harness that versatility, he engineers proteins with methods that are "equal parts conceptual, modeling based and recreating Darwinian selection in the lab."

Proteins, in his view, are not only born to do chemistry but also "made to be engineered to do chemistry." The combination of recent technological and research advances that support his engineering process includes less costly sequencing technologies, an increased number of solved protein structures, better protein modeling tools, faster computers and robots that help with high-throughput screening.

He hopes the new sensor can open plenty of research doors, which is an aspect he enjoys about his work. Rattling off an extensive list of neural signaling molecules he would like to render visible in the future using this protein engineering approach, he also has even longer-term projects.

Looger wants to design sensors that go further than tracking excitatory messages relayed by neurotransmitters such as glutamate. Communication in the brain includes excitation but also inhibition, when a neuron tells its neighbor to cease signaling. Making inhibitory transmitters light up is a "wide open but absolutely critical area." An engineering feat that might daunt others, to him this is "just a matter of tweaking the right proteins to bind them."

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Originally from Huntsville, Alabama, Looger studied chemistry and mathematics. He took part in international Olympiad training camps in both subjects before deciding to do his PhD in biochemistry at Duke University.

At the ripe age of 4, he knew he wanted to be a scientist, and now he can't imagine doing anything else. His devotion to science has spread to his toddler. "He now can point at pictures and say 'That's a fly brain! Those are neurons!'" Looger says. "He often says he wants to be a paleontologist; I think it's a great idea."

**Vivien Marx**

Marvin, J.S. *et al.* An optimized fluorescent probe for visualizing glutamate neurotransmission. *Nat. Methods* **10**, 162–170 (2012)