Loren Looger likes to solve other people's problems—at least their technical ones. That's working out well for his Janelia Farm colleagues.

by Jennifer Michalowski
photography by Dustin Aksland
of Loren Looger’s office, a jumble of colored leather and shoelaces lies in a heap: black and red soccer cleats for games on the nearby field; a pair of sleek, red soccer shoes for when the weather forces games indoors; high-top basketball shoes; bright-green running shoes; and some weathered Tevas for mucking around in the creek. Glancing at the pile, Looger says he’s had to trim back his activities since coming to the Janelia Farm Research Campus six years ago.

Cutting back has been tough for a man who admits to being “interested in everything,” but he’s given up most of his hobbies to focus on his research program and, in off hours, indulge in silliness with his four-year-old son, Hampton. The kayak commute he envisioned when he moved to the riverside campus never had a chance.

The long workdays have done nothing to squelch his far-flung curiosity, however. Fortunately, he has found a way to let his scientific pursuits embrace diversity as much as his athletic ones. As his pile of footwear attests, Looger—sporting moss-colored velvet slip-ons—believes in having the right tool for the job, and his lab is dedicated to making that possible. His mission at Janelia Farm, he says, is simple: “do whatever needs to be done.”

Unlike many scientists, Looger doesn’t frame his work around a central question. Instead, by building molecular tools that let his collaborators explore their own questions in new ways, he has constructed a research program that branches into a broad range of biological investigations. At Janelia, where a central goal is learning how circuits in the brain process information, doing what needs to be done means improving researchers’ abilities to visualize neurons, monitor their activity, and manipulate their behavior.

With his knowledge of protein structure and function, Looger can build tools that allow researchers to explore all kinds of biology. He says such tools can be truly transformative for the field of neuroscience, where so much remains unknown. “A little insight can go a long way when applied to questions that are wide open,” he says.

With the success he’s had so far, Looger is coming up with strategies—some rather unconventional—to maximize the impact of his work. He’s not often in the lab, but that doesn’t mean he’s not doing science. He spends most of his day in front of a computer—scouring DNA sequences in search of molecular tricks he can borrow from evolution, using them to alter proteins’ properties in predictable ways, and planning assays to screen for useful tools. He is also likely to be found sifting through articles about research for which his tools might be useful or proposing a new collaboration while he fetches a cup of tea from the campus pub.

He calls himself a protein engineer. His Janelia Farm colleague Karel Svoboda calls him a samurai.

WHAT’S CALCIUM GOT TO DO WITH IT?

“Loren is the consummate collaborator. He has a very unique skill set, and he is looking for damsels in distress,” Svoboda says. “He’s the kind of person who loves getting involved in other people’s problems, in the very best sense.”

For Svoboda, who investigates the neural circuits that link sensory information to behavior, the most urgent problem is a lack of adequate tools to watch nerve cells signal one another in the brains of active animals. He approached Looger during Janelia Farm’s earliest days, asking the biochemist when they met in 2005 if he could build a protein that signaled the presence of calcium inside cells.

Looger—fresh from a postdoctoral stint in a plant biology lab—couldn’t imagine what calcium had to do with the brain. Svoboda explained that soon after a nerve cell fires, calcium surges inside the cell. By watching the ion’s concentration grow, neuroscientists can monitor neural activity. Protein sensors that emit a fluorescent light to signal the presence of calcium had been used in animals since the late 1990s, but the signals were too weak to reveal much meaningful activity.

By solving the structure of a recent calcium indicator and tweaking its sequence to swap four of the protein’s amino acids for different ones, Looger’s team created an indicator that bound calcium more tightly and fluoresced at least three times as brightly. The most in demand of any of the tools he has developed, that indicator, GCaMP3, has been distributed to hundreds of labs.
where it illuminates neural activity that went unnoticed with earlier sensors. Still, neuroscientists are demanding a suite of similar tools that excel at different aspects of calcium sensing, so the overall effort to build better genetically encoded calcium indicators has, like GCaMP3, spread beyond Looger’s lab. Thanks to a large-scale push to generate and evaluate new versions of the protein, GCaMP3 has been mostly superseded by GCaMP5, which produces even less background fluorescence, gives a greater signal in the presence of calcium, and picks up more activity in the brains of living animals. Looger remains integral to that effort, but with a team of Janelia colleagues now sustaining its momentum, he has diverted most of his attention to new projects—lots of them (see Web Extra, “A Kaleidoscope of Projects”).

Each project has its own quirks, but the modular nature of proteins makes the job easier, Looger says. If nature has evolved a protein that lets an ocean coral glow red far beneath the sea, the relevant parts of that protein can be borrowed and adapted to bring the same fluorescent hue inside the lab. Likewise, a brittle star whose predator-dazzling luminescence triggers fluorescence that lingers for days offers clues to a longer-lasting “integrator” that could record a history of neural activity.

By changing the genetic sequence that encodes any protein, Looger, using “intuition and a relatively easy bag of tricks,” can alter the molecule in predictable ways, shifting its shape so it becomes more stable or binds more tightly to its target, for example.

Marveling at the opportunities he has to affect science by solving biochemical puzzles, Looger says he can imagine few careers that could be as invigorating, satisfying, and just plain fun. “Science,” he says, “is an absolute scream.” Yet he insists that his path to Janelia Farm has been almost entirely haphazard. “If any one of 10 different things hadn’t happened, I wouldn’t be here.”

**WANTED: TOOL BUILDERS**

For much of his life, Looger assumed his future was in mathematics. But when he realized as a graduate student that a career in the field would be less about the puzzle-solving camaraderie of youth math camps and more about a solitary pursuit of knowledge, he altered his course. He fled to biology, he says, selecting a biochemistry program at Duke University largely because his girlfriend, Covington Brown (now his wife), was working nearby. Four years later, he left Duke with a Ph.D. in biochemistry and no plan for the future. An unexpected phone call determined his next step: Wolf Frommer, a plant scientist at Stanford University, about 45 minutes south of San Francisco, had read about the protein biosensors Looger designed as a graduate student. He wanted a reagent to detect glucose inside living plants. Looger, who happened to be traveling on a train outside San Francisco, told Frommer he would come to his lab to discuss the matter straight away. By the end of the day, he had accepted a postdoctoral position.

In Frommer’s lab, Looger grappled for the first time with the challenges of creating sensors that function inside living cells, helping to engineer not just sugar sensors (the main task) but also a protein that would detect a different plant metabolite.
glutamate. As a side project, Looger helped test the glutamate sensor in neurons, which use the molecule as a key signal transmitter. Soon after that first dabbling in neuroscience, he set out to land a job at HHMI’s nascent Janelia Farm Research Campus.

As Janelia Farm began recruiting its very first lab heads, HHMI leaders had made clear that they wanted tool builders to be an integral part of the scientific community, where they would contribute to an anticipated synergy between technology development and biological research. When Looger stood before the selection committee in red bell bottoms and a flowered shirt to convince its members he had the skills and creativity they needed, he unabashedly announced that he knew nothing about neuroscience that he hadn’t read in the past two weeks. The roomful of accomplished neuroscientists listened with undisguised skepticism to his proposed plan to “reengineer the brain,” and Looger began to regret not applying for other jobs.

That’s when Svoboda approached him to consider developing new calcium sensors. And Janelia group leader Scott Sternson, who was also applying for a job at Janelia, asked Looger if he could help design ion channels that would respond to novel drugs so biologists could manipulate brain activity (see February 2012 HHMI Bulletin Web Extra, “Cowboy Chemistry”). Looger was game. So when Janelia Farm director Gerry Rubin, impressed by Looger’s bravado and open mind, surprised him with a job offer—as long as he promised not to work on the project he had proposed in his seminar—Looger didn’t hesitate.

"LOREN IS NOT OUT TO PROVE ANYTHING, HE JUST WANTS TO GET THE RIGHT TOOL TO THE RIGHT PERSON SO THEY CAN LEARN SOMETHING NEW ABOUT BIOLOGY." LUKE LAVIS

Six years of immersion in the Janelia Farm community have given Looger a new perspective on the complexity of the brain. “My naïve idea, until I actually got here, was that a bunch of neurons hook together to make a brain, and they all basically do nothing until they decide to signal something. That turns out to be absolutely not the case.” Working alongside neuroscientists—huddling in a tiny room searching for glimmers of activity in a zebrafish brain, or witnessing unexpected behavior in a worm expressing a slightly toxic protein sensor—has given him an understanding that textbooks and journal articles could not. “In the beginning, I was clueless about what people wanted tools to really do, but now I get it.”

To generate and evaluate their tools, biologists and chemists work side by side in Looger’s lab. Graduate students, technicians, and senior scientists pursue their own projects with considerable autonomy and independence—an advantage, they say, of the lab’s diverse portfolio. Their airy, glass-walled workspace, where bacterial DNA is manipulated and three-dimensional protein structures are examined, feels industrious but calm. Step into a smaller windowless back room, however, and it becomes immediately apparent that Looger’s team is churning out high-volume science. Plastic plates, each sectioned to contain 96 populations of bacteria, are stacked high on counters and incubators. Looger says the system is set up to isolate as many as 10,000 different proteins from bacterial colonies and crudely characterize their biophysical properties—fluorescence, stability, and light absorption, for example—in a day. Yet there is no bustle inside this room. Robotic instruments handle the more tedious tasks of protein design with quiet precision.

All that effort, Looger emphasizes, is ultimately about getting working tools into people’s hands. New tools are thoroughly tested, not just in living cells but in living organisms, and adjusted as necessary to make them more practical. “Loren is not out to prove anything, he just wants to get the right tool to the right person so they can learn something new about biology,” says Luke Lavis, a chemist with whom Looger recently designed a system to target chemicals to specific cells by masking them with chemical shields that can be removed only by a corresponding enzyme. The two tool builders share a friendly rivalry as to whose technique will yield the best results, but ultimately they are working toward common goals. That’s what being a tool builder is all about, Looger says. “If I find a tool in the gutter and it works … we’re done here.”

HYPER TO COLLABORATE
Despite his accumulating successes, Looger acknowledges there’s little glory in designing and optimizing reagents for other people’s experiments. “Being a toolmaker can be a bit thankless,” he says. No matter how much it advances science, “the BBC is never going to call you up to talk about the calcium sensor that you made a few percent better.”

He didn’t come to Janelia Farm seeking fame, but it’s an issue he thinks about a lot. To maximize the impact of his work, Looger knows he has to overcome a problem that stymies many toolmakers. Sensors that bind more tightly or shine more brightly than their predecessors tend to be reported in chemistry and engineering journals, which are not widely read by biologists. Subsequent publications, in which the sensors reveal something new about biology, might catch potential collaborators’ attention—but at that point, the toolmaker’s contributions have often been relegated to the fine print.
He has a solution—or at least a strategy. “We are going to hyper-collaborate,” he declares. “We’ll send tools to 1,000 people, and even if just 200 of those acknowledge us, we’ll be hooked into new fields. I have faith that it’s going to work out.”

Discovering ways he can contribute to projects he doesn’t yet know he should care about—that’s what energizes Looger most. Though his tools are born out of needs within the neuroscience community, those needs are often mirrored in other fields; in the brain, calcium is a sign of neural activity, but in red blood cells it can signal the presence of a malaria parasite, for example. And Looger’s intuition and “bag of tricks” can be even more broadly applied. A conversation with him can careen from fluorescing starfish arms to the genetics of sex determination in no time, and when he talks about how fortunate he feels to be a protein engineer at Janelia Farm, he ticks off the fields he’s involved with as evidence of his unbelievable luck: “We’re not just working on neural imaging,” he says. “Our tools are being used to study tuberculosis, malaria, diabetes, and cancer, to name a few. I’ve also been dabbling in lupus on the side.”

Committed to his model of hyper-collaboration, Looger says he has 120 projects catalogued on his computer. A few are “some-day” ambitions, but most merit Looger’s active attention at least some of the time. A handwritten list of in-progress manuscripts runs two columns in Looger’s notebook and helps keep things on track: circles and stars and sweeps of color compete for urgency, while a handful of completed items are emphatically stricken from the list.

Colleagues at Janelia Farm and elsewhere seek Looger out for his protein-modeling expertise, but he doesn’t wait for people to come to him. “I definitely spam a lot of people,” he laughs, meaning he never hesitates to stop by a colleague’s lab or dash off an email to a stranger saying, in essence, “What if you had a reagent that did this? Would that be useful?” Usually the answer is yes. Sometimes, the answer is “yes, but that’s not possible,” but Looger doesn’t seem to hear the last part.

That willingness to dive in and find out what works strikes colleagues as part of Looger’s inherent optimism, but he says it comes largely from his outsider perspective. Because he’s not entrenched in the dogma of his collaborators’ disciplines, he says, the assumed limits of those fields rarely restrict his imagination. “I don’t know what’s impossible,” he declares. “So we try a lot of things that people say will never work … and a lot of it has been successful.”

WEB EXTRA: Learn about some of Looger’s research projects at www.hhmi.org/bulletin/may2012.

Looger doesn’t wait for collaborators to come to him. He takes every opportunity—hallway run-ins at Janelia Farm or emails to unfamiliar researchers—if he thinks he can help.