

Restoration Hardware

A signaling molecule important during neuron development is critical to adult neuron repair as well.



*To rescue injured nerves, Yishi Jin is studying fast-growing *C. elegans*.*

Lou Mora

SITTING IN HER SUNLIT OFFICE AT THE UNIVERSITY OF CALIFORNIA, San Diego, Yishi Jin laughs as she describes herself as an impatient person, ill-suited to waiting for an animal to progress through its life span. Her model organism of choice, one that can reproduce just three days after birth, reflects her need for fast answers. ¶ And yet, as the HHMI investigator describes the 15 years of research leading to her

most recent discovery—a potential way to force injured adult neurons to regrow—impatience isn't exactly the word that comes to mind. Tenacity seems more suitable.

Jin grew up in a small village outside Beijing during China's Cultural Revolution. She came to the United States in 1985 to earn her Ph.D. and was lured by the pure logic of genetics. In her postdoc, she chose to study neural development. She became enamored with the tiny, short-lived round-worm *Caenorhabditis elegans*. With only 302 neurons, all meticulously mapped, the worm was an attractive subject. Its rapid development was a big plus: Jin could create mutants and knock-out animals almost faster than it took most postdocs to get their mice to breed.

Synapses are the site of communication between the axon, or sending end, of one neuron and the receiving end of another. Using green fluorescent protein, Jin could visualize details of the synapses. She could also perturb them—creating mutants with visible changes to their synapse structure—and then track those changes into the worms' genomes, determining which genetic mutations caused the altered synapses.

Jin began by trying to understand the molecular signals underlying synapse development in *C. elegans*. One of the very first mutants her lab produced had fewer total synapses, which looked abnormal in shape and size. To figure out why, Jin and her colleagues cloned the responsible genes and discovered that the mutant worms lacked a never-before-described enzyme that seemed to be involved in protein degradation. The

enzyme appeared to be controlling the activity of a signaling molecule called MAP kinase—which she later showed was important in synapse development. But Jin had yet to figure out why it was involved in degradation, too.

In a second line of research Jin began to explore adult nerves and their regenerative ability. Using a blazingly fast, precise laser, called a femtosecond laser, Jin and her colleagues found that when they sliced through axons in live *C. elegans*, the neurons could regenerate, navigating around the injury site

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and sometimes even restoring the nerve's original function (see “Nerve Verve,” *HHMI Bulletin*, Winter 2005).

Jin's two lines of research came together late last year, in work published in the September 4, 2009, issue of *Cell*. She knew that MAP kinase had to be controlling something else at the synapse, and she and her colleagues found a likely target: it was regulating the speed of messenger RNA (mRNA) decay, which occurs to signal the synapse to reset itself to prepare for the next stimulus. But as far as anyone knew, mRNA was produced in the neuron's main cell body, far from MAP kinase at the synapse.

They predicted that the mRNA existed and was being regulated at the synapse.

Long-distance control didn't make sense. Using a second fluorescent marker, they found mRNA molecules were present both in the cell body and at the synapse.

To confirm that mRNA regulation was happening at the synapse, they turned to the femtosecond laser. But when Jin and her colleagues severed an axon in a MAP-kinase-deficient worm, they were startled to see that the neuron couldn't regenerate. The MAP kinase molecule that is so important in creating synapses also appears to play a vital role in rescuing injured neurons.

“The entire MAP kinase pathway is reused in adult neurons,” Jin says. When neurons are injured, it's devastating. “They need to trans-

mit an injury response: regrow your axon, and grow it quickly.” And it happens locally.

Jin is now anxious to manipulate the kinase activity to promote faster injury response, to push the regrowth of injured nerves and guide them to their original target—something essential to restoring function in humans and other species that have much more complex neural systems than worms.

She calls herself impatient, but Jin's persistence and drive are pushing her to solve the ultimate neural puzzle, even if it helps only the worms at first: “I would be totally thrilled if one day, even in *C. elegans*, an injured axon could completely go back to its normal position.” ■ —LAUREN GRAVITZ