FKBP—a family of chaperone proteins found naturally at high concentrations in the cell. The other end of the linker attached to a dye molecule called Congo red, which selectively stains amyloid in muscle and nerves.

In test-tube studies, the researchers found that their Trojan-horse molecules did block the growth of amyloid aggregates from their Aß peptide components. In particular, they found that the molecules inhibited growth of the shorter amyloid chains, which are believed to be more toxic to neurons. They also found that, by varying the linker molecules, they could optimize certain pharmaceutical properties of the Trojan-horse assemblage—regarding, for example, its ability to penetrate the cell membrane to enter the cell.

A second round of optimization with their linkers enabled the scientists to achieve even better results. "In fact," says Crabtree, "we achieved much better protective effects at low concentrations than have been achieved by pharmaceutical companies and by other academic groups using other approaches to inhibiting Aß aggregation."

The next step will be to test the Trojan-horse molecules on mouse models of Alzheimer's disease and determine whether they impede disease progression.

Crabtree says that if it is successful in these tests, the Trojan-horse approach ultimately might complement other therapies now being tested for Alzheimer's disease, including anti-inflammatory treatments to prevent neuronal cell death from toxic aggregates and inhibitors of aberrant molecular signaling pathways in Alzheimer's disease.

Crabtree also speculates that his group's approach could be applied widely. For example, it might be used to interfere with other clinically important protein-protein interactions, such as those involving enzymes critical to the replication of HIV.

"HIV proteins are difficult drug targets because they can mutate rapidly to render small-molecule inhibitors inefficient," he says. "Such drugs typically bind only to a few amino acids in the protein, which the virus can easily alter by mutation. But in our approach, we could distribute the binding over a large protein-protein interaction surface, which would be far more difficult for the virus to block. A similar approach could also be taken with rapidly mutating targets of cancer chemotherapeutics."

—DENNIS MEREDITH

The germination of Yishi Jin's recent research on nerve regeneration came in a serendipitous social hour.

TIM ARCHIBALD

Nerve Verve

Bridging physics and biology, researchers use laser-assisted nanosurgery to explore nerve regeneration in the roundworm Caenorhabditis elegans.

When several scientists from Turkey got together in northern California for Thanksgiving 2003, they shared more than just an American tradition and a tasty dinner. Hulusi Cinar, his wife Nese, and Mehmet Fatih Yanik talked about how they might collaborate on an interesting experiment. Yanik, based at Stanford University's department of applied physics, was building a femtosecond laser nanosurgery system—which shoots pulses of intense laser light that can cut or vaporize a structure precisely within a few hundred nanometers—and he wanted to test it on organisms. The Cinars, both biologists at the University of California, Santa Cruz (UCSC), had been studying the roundworm *Caenorhabditis elegans,* and they were intrigued by the prospect of observing behavioral effects in the animal that resulted from precisely cut nerves.

Eager to proceed with the experiment—and help bridge the fields of physics and biology along the way—the three enlisted the aid of UCSC biologists Yishi Jin and Andrew D. Chisholm as well as engineering physicist Adela Ben-Yakar (then at Stanford, now at the University of Texas at Austin). By the following Thanksgiving, the group had obtained its experimental results, since published in the December 16, 2004, issue of *Nature.* "This is why it's good to have social hours," says Jin, an HHMI investigator. "Although many times ideas are not followed up, this time they were."

Best of all, the team developed a new model for studying nerve regeneration that might shed light on how to treat neurodegenerative diseases, nerve damage, and spinal-cord injury.

The two groups, it turned out, made for an excellent collaboration. The Santa Cruz researchers knew *C. elegans* intimately as a model for studying nervous-system development. Using green-fluorescence markers, they could observe under a microscope the worm's physical structures—such as its nerves. And they knew exactly which nerves controlled an easy-to-observe behavior: the ability to move backward. If, for instance, the genes for those particular motor neurons were mutated or knocked out, the worm could not contract the muscles that shift it into reverse gear.

For its part, the Stanford group had developed the femtosecond laser into a tool that in principle could cut such nerves without damaging surrounding tissues, although Ben-Yakar and Yanik had to spend several months adapting the behemoth machine to focus its power on a tiny worm. By summer, they were ready to operate. "Fatih [Yanik] was calling us on the phone," Jin recalls, "saying 'I have the worm right here now—where do you want me to cut?'" After getting directions, he would sever the axons—the long part of the neuron—and send photos for confirmation.

Mastering the surgery and making it repeatable was a technical coup, but the real surprise came when the team observed the worms, over 3-day periods, as they recovered. After surgery, Yanik would wake up a worm and touch it on the head every few hours. As expected, the creature did not behave normally—it could not back up. But then Yanik and Hulusi Cinar saw one that, after 12 hours, regained the ability to move in reverse, and they jumped for joy. "It was a very exciting moment—like a miracle," Yanik recalls. More operations on more worms revealed that, in about half the cases, the severed axons reconnected and once more became functional.

"This experiment is a beautiful entry point into further studies on nerve regeneration." —Oliver Hobert

"It's pretty amazing that the two ends can fuse and work again as a nerve fiber," says Oliver Hobert, a neuroscientist at Columbia University Medical Center in New York City. Consequently, "this experiment is a beautiful entry point into further studies on nerve regeneration." For starters, researchers could test whether certain factors involved in the normal development of the nervous system might also spur repair. They need only repeat the experiment on mutant worms missing a particular factor and see if their nerve-regeneration process is diminished or enhanced.

Indeed, Hulusi Cinar has already embarked on such an investigation, driven by the possibility of discovering new drugs. For example, he says, studies might quickly point the way to new treatments for diabetic patients with damage to peripheral nerves, which—like those in *C. elegans*—lack a protective sheath of myelin tissue. "What's going wrong with those nerves? Can we slow the process? Can we regenerate them? Our model could be used to study those questions," says Cinar.

Meanwhile, Jin hopes to explore other questions, such as why half the worms do not regain function, whether different types of nerves have different regenerative properties, and whether young worms have a higher rate of recovery than do elderly worms. If the femtosecond laser becomes part of biologists' toolkits in other labs, new investigations using nanosurgery should flourish. "It's just the beginning and we have no predictions about what to expect," she says. For now, "every single observation is going to be exciting." —KAREN F. SCHMIDT

Hughes on the Big Screen

Leonardo DiCaprio plays the young Howard Hughes in the hit movie *The Aviator,* released in December by Miramax. Through the vision of director Martin Scorsese, *The Aviator* explores Hughes' life, work, and loves from the 1920s through the 1940s, when the industrialist was at the height of his powers as an inventor, businessman, and movie producer. HHMI President Thomas R. Cech says that Hughes' drive to "push back frontiers, take risks, and succeed at the very highest level" parallels the determination of HHMI investigators and grantees. The movie's time period does not include the formation of HHMI, leading Cech to suggest a sequel that connects Hughes with what Cech calls his most enduring legacy—the medical institute that bears his name.

ANDREW COOPER/MIRAMAX FILMS