This result is a big advance in the field, says Robert Steiner of the Oregon Health and Science University who was a principal investigator on the trial. "This is a much more sophisticated approach to doing neural cell transplants by actually purifying and only using fetal neural cells rather than the mix of cells used in the earlier trials," he notes.

Achieving high degrees of purity—that is, assuring that the vast majority of cells being transplanted are only neural stem cells—requires careful separation of cells. StemCells in Palo Alto, Calif., which produced the cells for the trial, employed a technique that labels fetal neural stem cells with a fluorescent tag. That makes them easy to see and sort from other cells. With the technique, the firm says that at least 90 percent of their proprietary cells are neural stem cells—a critical benchmark for FDA approval in clinical trials.

The success of the safety trial has given the FDA confidence to green-light a second trial, this time for children with Pelizaeus-Merzbacher disease (PMD), a genetic disorder that compromises the creation of myelin, a fatty substance that sheaths the axons of nerves. The trial will inject neural stem cells into the brains of four children with PMD and use magnetic resonance imaging to track new myelin formation. Preclinical trials in animal models of PMD have demonstrated that the cells can differentiate into myelin-forming cells called oligodendrocytes and successfully create myelin sheaths, but they have yet to prove they can restore function.

Cells that are more developed might lead to functional results. Steven Goldman of the University of Rochester isolated neural stem cells of fetal origin that had differentiated into the progenitor cells of oligodendrocytes. When injected into mouse models of PMD, the precursor cells improved the health of afflicted rodents, which also lived a normal life span.

Scientists debate the best method of obtaining the cells. Rather than sorting primary cells in various stages of differentiation, for instance, Geron in Menlo Park, Calif., can induce the appropriate precursor cells from human embryonic stem cells. (Geron received FDA approval to use the cells for trials last year.) But in the end, only clinical trials can determine the best strategies. "Because now we have better ways of identifying the potentially regenerative cells in the fetal populations, we can probably perform more powerful and better targeted studies than before," remarks Charles ffrench-Constant, an expert in regenerative neuroscience at the University of Edinburgh. Certainly for advocates, fetal cell transplantations are emerging from their dark days and moving into a reenergized spotlight.

M. A. Woodbury is a science and medical writer based in New York City.

Technology

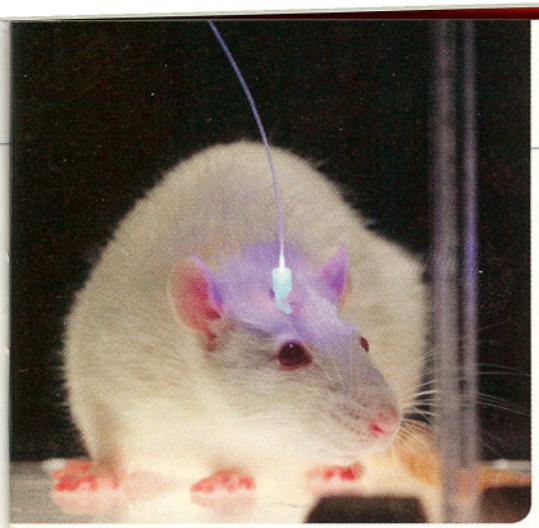
A Light in the Brain

Optogenetics emerges as a potent tool to study the brain's inner workings

BY GARY STIX

In 1979 Francis Crick, famed co-discoverer of DNA's structure, published an article in *Scientific American* that set out a wish list of techniques needed to fundamentally improve understanding of the way the brain processes information. High on his wish list was a method of gaining control over specific classes of neurons while, he wrote, "leaving the others more or less unaltered."

Over the past few years Crick's vision for targeting neurons has begun to materialize thanks to a sophisticated combination of fiber optics and genetic engineering. The advent of what is known as optogenetics has even captured popular attention be-



COURTESY OF JOHN CARNETT, VIVIANA GRADINARU, MURTAZA MOGRU AND KARL DEISSEROTH *Stanford University*

MIND CONTROL: Blue light piped into the brain of a genetically engineered rat turns on a set of neurons.

cause of its ability to alter animal behavior—one research group demonstrated how light piped into a mouse's brain can drive it to turn endlessly in circles. Such feats have inspired much public comment, including a joke made by comedian Jay Leno in 2006 about the prospect for an optogenetically controlled fly pestering George W. Bush.

Controlling a subordinate or a spouse with a souped-up laser pointer may be essential for science-fiction dystopia and late-night humor, but in reality optogenetics has emerged as the most important new technology for providing insight into the numbingly complex circuitry of the mammalian brain. It has already furnished clues as to how neural miswiring underlies neurological and mental disorders, including Parkinson's disease and schizophrenia.

A seminal event that sparked widespread neuroscience interest came in 2005, when Karl Deisseroth and his colleagues at Stanford University and at the Max Planck Institute for Biophysics in Frankfurt demonstrated how a virus could be used to deliver a light-sensitive gene called *channelrhodopsin-2* into specific sets of mammalian neurons. Once equipped with the gene (taken from pond algae), the neurons fired when exposed to light pulses. A box on Crick's list could be checked off: this experiment and ones that were soon to follow showed how it would be possible to trigger or extinguish selected neurons, and not their neighbors, in just a few milliseconds, the speed at which they normally fire. Hundreds of laboratories worldwide have since adopted Deisseroth's technique.

A 38-year-old psychiatrist by training who still sees patients once a week, Deisseroth entered the field of bioengineering because of his frustration over the inadequate tools available to research and treat mental illness and neurodegenerative disorders. "I have conducted many brain-stimulation treatments in psychiatry that suffered greatly from a lack of precision. You can stimulate certain cells that you want to target, but you also stimulate all of the wrong cells as well," he says. Instead of just observing the effects from a drug or an implanted electrode, optogenetics brings researchers closer to the fundamental causes of a behavior.

Since 2005 Deisseroth's laboratory—at times in collaboration with leading neuroscience groups—has assembled a powerful tool kit based on *channelrhodopsin-2* and other so-called opsins. By adjusting the opening or closing of channels in cell membranes, opsins can switch neurons on or turn them off. Molecular legerdemain can also manipulate just a subset of one type of neuron or control a circuit between groups of selected neurons in, say, the limbic system and others in the cortex. Deisseroth has also refined methods for delivering the opsin genes, typically by inserting into a virus both opsin genes and DNA to turn on those genes.

To activate the opsins, Deisseroth's lab has attached laser diodes to tiny fiber-optic cables that reach the brain's innermost structures. Along with the optical fibers, electrodes are implanted that record when neurons fire. "In the past year what's happened is that these techniques have gone from being something interesting and useful in limited applications to something generalizable to any cell or question in biology," Deisseroth says.

Most compelling, however, are experiments that have demonstrated the relevance of optogenetics to both basic science and medicine. At the Society for Neuroscience meeting in Chicago last October, Michael Häusser of University College London reported on an optogenetics experiment that showed how 100 neurons could trigger a memory stored in a much larger ensemble of about 100,000 neurons, suggesting how the technique may be used to understand memory formation.

Last spring Deisseroth's group published an optogenetics study that helped to elucidate the workings of deep-brain stimulation, which uses electrodes implanted deep in the brain to alleviate the abnormal movements of Parkinson's disease. The experiment called into question the leading theory of how the technology works—activation of an area called the subthalamic nucleus. Instead the electrodes appear to exert their effects on nerve fibers that reach the subthalamic nucleus from the motor cortex and perhaps other areas. The finding has already led to a better understanding of how to deploy deep-brain electrodes. Given its fine-tuned specificity, optoelectronics might eventually replace deep-brain stimulation.

Although optogenetic control of human behavior may be years away, Deisseroth comments that the longer-range implications of the technology must be considered: "I'm not writing ethics papers, but I think about these issues every day, what it might mean to gain understanding and control over what is a desire, what is a need, what is hope."

Sound Approach

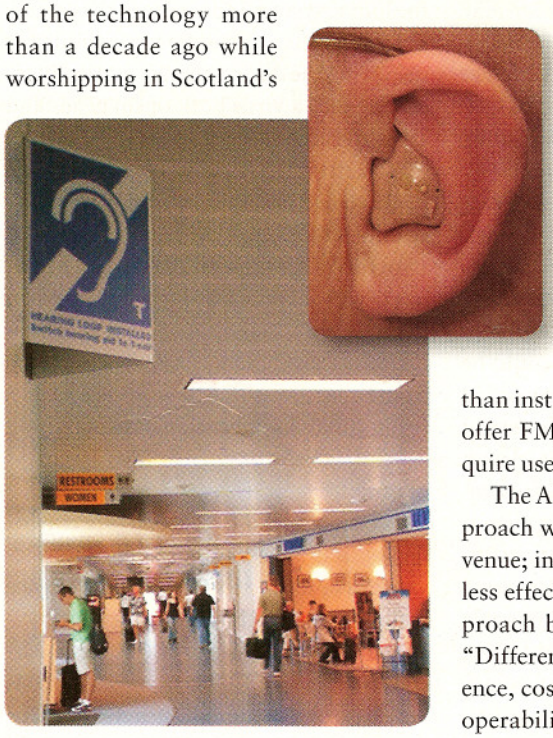
Loopy idea brings in speech loud and clear BY LARRY GREENEMEIER

STANDARD HEARING AIDS CAPTURE sound via a microphone and then send an amplified version to an earpiece. They work well in relatively quiet, intimate settings, but in public spaces filled with background noise, most users find them of little use. A simple technology that sidesteps the problem, long available in Europe, has finally begun entering the U.S. market. Advocates hope that with the success of pilot projects, the hearing impaired will be able to find public address announcements and other kinds of speech more intelligible.

The technology is an induction-loop system (known as a hearing loop), whereby electromagnetic waves produced by a microphone, public address system or telephone receiver induce an analogous current in the loop. The loop can broadcast the signals directly to a hearing aid equipped with an appropriate detector—specifically, a tiny copper telecoil wire, which picks up the signal (also via induction) and then sends it for amplification and transmission out of the earpiece. (Hearing loops can also broadcast signals to cochlear implants, which are surgically implanted devices that directly stimulate the auditory nerve.)

Telecoils work somewhat like Wi-Fi for hearing aids, enabling them to serve as customized, wireless loudspeakers, says David Myers, a psychology professor at Hope College and a strong advocate for the devices. Makers of hearing aids are increasingly equipping their devices with telecoils, whose original use was to boost telephone sounds. More than 60 percent of hearing aids come with telecoils, up from 37 percent in 2001, according to a survey report in the April 2008 *Journal of Hearing*.

Still, Myers notes, although about 36 million Americans suffer from hearing loss, the loop technology has not been as widely embraced in the U.S. as it has been in other regions of the world, particularly in northern Europe. Myers, who himself has impaired hearing, first became aware of the technology more than a decade ago while worshipping in Scotland's Iona Abbey, where the building's poor acoustics prevented him from clearly hearing the service. At his wife's prompting, Myers switched on his hearing aid's "T" (for telecoil) setting to see what would happen. "The sudden clarity was overwhelming," he adds, "an experience that I have since had in countless other British venues, from auditoriums to cathedrals to the backseats of London and Edinburgh taxis."



HEARING AIDS with an embedded "T" switch (for telecoil) can pick up clearer sound in the Gerald R. Ford International Airport in Grand Rapids, Mich., which has an induction-loop system (identified by blue signs).

COURTESY OF LOU SCHAKEL *Hope College Public Relations (ear)*; COURTESY OF HOPE COLLEGE PUBLIC RELATIONS *(airport)*

Since then, Myers and others have worked to introduce the technology to the U.S., which has lagged in adopting the hearing loops because the technology is not a requirement for public venues, Myers says. Since its 2004 revision, the Americans with Disabilities Act (ADA) has required public venues to offer assistive-listening systems. But rather than installing hearing loops, a venue can offer FM or infrared systems, which require users to borrow equipment.

The ADA's position is that no single approach works for every person and every venue; infrared systems, for instance, are less effective in sunlight than the FM approach but are generally more private. "Differences in [confidentiality], interference, cost, installation requirements and operability make it impossible to simply use one type of [assistive-listening system] in every place," ADA guidelines state.

Myers disagrees, pointing out that many individuals with hearing loss are self-conscious about asking for an ear-