Scientists regenerate optic nerve for the first time

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New hope for sufferers of glaucoma and spinal cord injuries

For the first time, scientists have regenerated a damaged optic nerve -- from the eye to the brain. This achievement, which occurred in laboratory mice and is described in the March 1, 2005 issue of the Journal of Cell Science, holds great promise for victims of diseases that destroy the optic nerve, and for sufferers of central nervous system injuries. "For us, this is a dream becoming reality," says Dr. Dong Feng Chen, lead author of the study, assistant scientist at Schepens Eye Research Institute and an assistant professor of ophthalmology at Harvard Medical School. "This is the closest science has come to regenerating so many nerve fibers over a long distance to reach their targets and to repair a nerve previously considered irreparably damaged."

This research, which has been supported in part by grants from the National Institutes of Health, the Department of Defense and the Massachusetts Lions Club, has always been a priority of the institute, but in recent times, urgency around it has increased, according to Dr. Michael Gilmore, director of research at Schepens Eye Research Institute and professor of ophthalmology at Harvard Medical School. In addition to the thousands of Americans blinded by glaucoma and injuries that destroy the optic nerve, and hundreds of thousands disabled by spinal cord injuries, "we were hearing stories of soldiers in the Middle East whose lives were saved by body armor, but who were returning with severe damage to limbs and eyes," he says. "At the same time, we learned of the untimely death of Christopher Reeves. It was, therefore, a

priority for us to redouble our efforts to find ways to restore damaged nerves."

According to Senator John Kerry, who supported funding of this important work, "Schepens is doing cutting-edge research that can make a real difference for a new generation of troops returning home with nerve damage. We need to support our troops in actions, not just words, and I am glad that we have been able to get funding for this important work." Adds Congressman Lynch, "Last month, I visited the Walter Reed Army Medical Center in Washington and met with dozens of service men and women who could benefit directly from the good work of the people at Schepens. Their vital research will not only enhance the lives of our soldiers but also gives hope to every American who suffers from diseases of the central nervous system."

Many tissues in the body continually renew themselves if injured. However, this is not true for nerve cells or their fibers (axons) in the Central Nervous System (CNS). The CNS consists of the brain (of which the eye and optic nerve are part) and the spinal cord. For all mammals, including human beings, CNS nerves lose their ability to regenerate after injury at the point in their development when they are fully formed. For example, the optic nerve loses this ability shortly before birth. So for those afflicted by glaucoma, which destroys the optic nerve through excessive internal pressure, or with injuries that sever the optic nerve after that developmental milestone, destruction can be permanent and blinding.

Chen and her research team have dedicated themselves to learning the reasons why CNS tissue stops regenerating and to finding ways to reverse that process, using the optic nerve as their research model. The optic nerve, which connects the eye to the brain, consists of millions of nerve cells, which, when uninjured, transmit visual information from the retina to the brain for interpretation

In earlier research, Chen's team discovered several processes that they believed "locked up" the optic nerve's ability to regenerate. The first lock, they found, was the turning off of a specific gene – BCL-2 – which, when turned on, activates growth and regeneration. The second lock, they theorized, was a scar on the brain created shortly after birth by "glial" cells. (glial cells have many functions in the brain, one of which is to create this kind of scar tissue). The researchers believed that the scar puts up a physical as well as molecular barrier to regeneration. Although there may be other "locks" to the regeneration door, Chen and her colleagues believed these two were the most important.

In the current research, Dr. Kin-Sang Cho, research associate in Chen's laboratory and the first author of the paper, tested two keys to unlock regeneration. The first key involved the development of a mouse model in which the BCL-2 gene is always turned on (or is overexpressing). The second key was the use of a mouse line carrying mutations of "glial specific genes" that lead to the reduced "glial scar" formation.

By unlocking the regeneration with the first key, for the first time, they observed robust optic nerve regeneration in postnatal mice, which nerves grew rapidly and reached from the eye to the brain in four days. But the regeneration happens only in the younger mice whose brains had not yet formed a "glial scar." In the mice that were slightly older and had developed the "glial scar," regeneration failed again.

Dr. Cho then added the second key by combining BCL-2 overexpresser with the "glial gene" mutation to prevent the development of the "glial scar" in the older transgenic mice. He found that the combination of the turned-on BCL-2 and the mutation of "glial specific genes" caused the optic nerves to return to an embryonic state and stimulated rapid, robust regeneration of the optic nerve--again, as with the younger mice – within only a few days.

"We could see that at least 40 percent of the optic nerve had been restored," says Chen, "but we believe that an even higher percentage actually regenerated."

The next step for Chen and her colleagues is to determine if the regenerated optic nerves were functional. In other words, did they cause the mice to see again?

Chen also believes that this combination BCL-2 and scar prevention technique could work to regenerate other Central Nervous System tissue, increasing the possibility that spinal cord patients could walk or move again.

This work has important implications. "The possibility of restoring sight following optic nerve injuries is tremendous. Fifteen percent of all wartime injuries include the eye and those with optic nerve trauma are the most grave. Today's medicine has little effective treatment to offer and blindness is often the end result," says Retired Lieutenant Colonel Robert C. Read of the Clinical Applications Division at the Department of Defense's Telemedicine and Advanced Technology Research Center.

"This outstanding breakthrough by Schepens scientists offers new hope to those who suffer from blinding diseases and injuries, including our returning soldiers. The potential application of this discovery to treatments for other central nervous system injuries is yet another reason why I have been proud to support the Department of Defense's funding of the Center for Excellence in Military Low Vision Research," stated Congressman Mike Capuano.

Adds Congressman Stephen F. Lynch, "This extraordinary breakthrough demonstrates what we can achieve when we support public and private partnerships between the Defense Department and the best researchers and scientists in the field. Because of the decades of work and progress

by Dr. Gilmore and Dr. Chen and the entire team at the Schepens Eye Research Institute, the search for a way to repair nerve damage in the human body has taken a giant leap forward."

"I'm so pleased with the work going on at Schepens," Rep. Jim McGovern says. "They are on the frontiers of research that will dramatically improve people's lives. And the Federal Government must continue to be a partner in this vital effort."

Source: Schepens Eye Research Institute