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Friday, May 29, 2009

Restoring Sight

Gene therapy to make cells sensitive to light takes a step toward clinical use.

By Emily Singer

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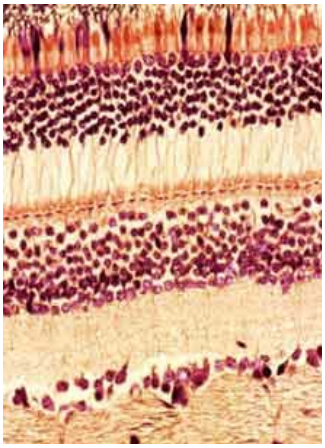

Let there be light: In retinitis pigmentosa, an inherited form of blindness, the light-sensitive photoreceptors (shown in orange and pink at the top of this cross section of the retina) die. Scientists aim to treat this disorder by developing novel gene therapies to make different retinal cells, such as bipolar cells (shown in pink in the middle section), responsive to light.
Credit: Steve Gschmeissner / Photo Researchers

Several years ago, when Ed Boyden developed a novel technology to make nerve cells sensitive to light, he knew that it would rapidly catch on in the research world. But Boyden, now a neuroscientist at MIT, also wanted to employ the technology to help treat patients, using it to activate specific neurons damaged in different diseases, such as some forms of blindness and Parkinson's.

Boyden is moving toward that goal much faster than many scientists expected. He and his collaborators recently published a paper showing that the light-sensitive molecule works well in monkeys and appears to be safe. And he has founded a company to commercialize the technology, focusing first on retinitis pigmentosa, a degenerative eye disease that leads to blindness.

At the heart of the technology is channelrhodopsin-2, a light-sensitive protein derived from algae. The gene for this protein can be modified so that it is only expressed in specific types of neurons. When delivered to the brain or eyes via gene therapy, the protein sits on the cell membrane and opens when exposed to light. Positively charged ions then rush into the cell, triggering an electrical message that is transferred to the next cell in the circuit. Channelrhodopsin and similar tools are now in use all over the world in research using laboratory animals to study psychiatric and neurological disorders, such as depression, addiction, and epilepsy, as well as normal brain functions, including motor control and memory.

In April, Boyden and his collaborators published the first paper testing the channelrhodopsin technology in primates--an important step toward using it in humans. "Because the molecule comes from algae, we needed to test it in an animal more closely related to humans to see if it triggers an immune response, and to determine if illumination of cells is safe over time," says Boyden.

The researchers used gene therapy to express the protein in the frontal cortex of macaque monkeys, and they used an optical fiber in the brain to effectively activate the channel. After nine months, researchers didn't see any signs of damage or dangerous immune reactions. "The fact that it's well tolerated is huge," says Alan Horsager, chief scientific officer at Eos, Boyden's startup. However,

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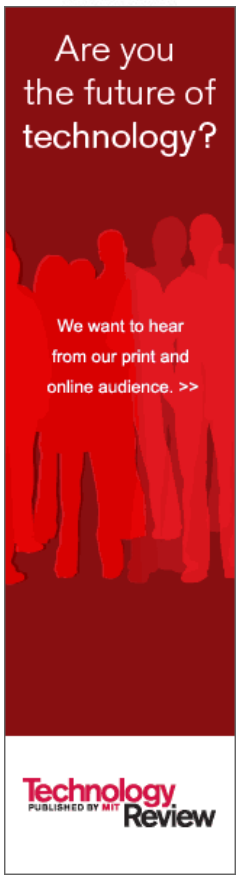

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Boyden cautions that the findings are still preliminary: the researchers tested channelrhodopsin in only two animals. "But it provides hope and reason to scale up to a bigger level," he says.

Horsager is testing the channelrhodopsin technology in the retinas of mice in preparation for developing a gene therapy for blindness. Previous research has shown that making cells in the retinas of congenitally blind rodents light sensitive can restore rudimentary vision. Horsager is working on similar experiments, delivering the channelrhodopsin gene to a specific cell type in the retina of blind mice. According to preliminary results presented at a neurotechnology conference in San Francisco earlier this month, animals given the therapy can swim toward light in a water maze, while untreated animals swim aimlessly. It's unclear exactly what the animals see, but researchers speculate that it is the equivalent of having just one type of photoreceptor: one that is sensitive to blue light.

Ultimately, scientists believe that channelrhodopsin targeted toward different cell types could treat a broader range of diseases, including Parkinson's and epilepsy. Both of these disorders are currently treated with implanted electrodes that deliver electricity to excite specific parts of the brain. Delivering light through fiber-optic cables to cells that have been engineered to be light sensitive via gene therapy could have a similar effect, but with greater specificity. Rather than hitting every cell in the vicinity, as electricity does, only genetically engineered cells would respond to the light.

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What kind of "gene therapy"?
hsfrey on 05/29/2009 at 2:13 AM

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To say "The researchers used gene therapy" is like saying a doctor "used medicine".

Did they insert the gene into an egg, or establish a strain with it in the germ line?

Or did they transfer it into individual animals, with viruses or otherwise? Into an individual tissue or systemically?

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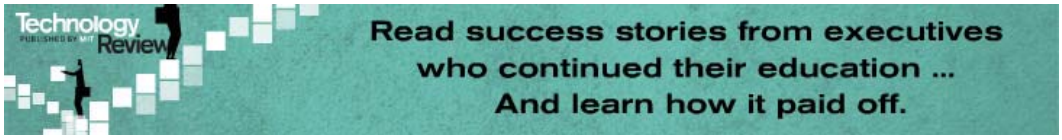

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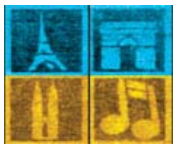

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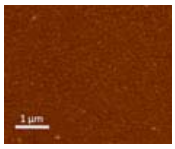

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