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Gene Therapy Improves Vision in Small Clinical Trial

Six months after the launch of a clinical trial evaluating the safety of gene therapy for a rare but severe form of retinal degeneration, vision has improved in all three patients who received the treatment.

Based on those findings, physicians will proceed with additional clinical trials to investigate the treatment for Leber congenital amaurosis (LCA), an inherited disease that causes severe visual impairment at birth and progresses to complete blindness by the time patients reach their thirties or forties.

The study was led by Katherine High, a Howard Hughes Medical Institute investigator and the director of the Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia, where the clinical trial took place. The findings were published online April 27, 2008, in the *New England Journal of Medicine*. The other senior author was Jean Bennett of the University of Pennsylvania. A second paper also published in the *New England Journal of Medicine* on April 27, 2008, reports similarly encouraging findings from an LCA gene therapy trial conducted in London.

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- Edwin M. Stone

The researchers say their findings suggest that their gene therapy technique — which uses a viral vector to introduce a corrective gene into the eye — might also be used to treat related forms of retinal degeneration.

Researchers have had some success in using gene therapy to treat other diseases, but these treatments have required patients' cells to be removed, genetically manipulated outside the body, and then reintroduced into the patient. "However, what people have always wanted in gene therapy is,

essentially, a medicine in a bottle, where you can inject a medicine into the patient and get a response,” High said.

The results of the new trial represent a success with this type of *in vivo* gene therapy, in which a viral vector carries a gene directly into a patient's cells to correct a genetic abnormality. In the past, the therapeutic effects of this type of approach have been undermined by patients' immune responses to the virus.

High has worked for years to develop gene therapies for multiple diseases, and has encountered this frustration in her own work. “Our previous *in vivo* gene therapy, for hemophilia, showed temporary success, but there was an immune response to the virus that abrogated the effect,” she said. “However, this therapy for LCA2 involved introducing the viral vector into the eye, a relatively ‘immunoprivileged’ site like the rest of the central nervous system. What is exciting about this work is that it demonstrates an *in vivo* gene therapy that seems to work,” she said. High and one of her co-authors, Edwin Stone at the University of Iowa, who both conduct patient-oriented research, were named Howard Hughes Medical Institute investigators in 2002.

Mutations in twelve different genes have been found to cause different forms of LCA, all of which are untreatable. With their treatment, High and her colleagues targeted LCA2, which is caused by mutations in a gene called *RPE65*. *RPE65* encodes a protein that the eye needs to produce rhodopsin, which helps convert light into an electrical signal.

To treat LCA2, High and her colleagues engineered a virus called adeno-associated virus to carry a corrective gene for RPE65 into the retina. Prior to testing the therapy in patients, the researchers injected the vector behind the retina of RPE65-deficient dogs and found that the animals' vision was restored. More than seven years after a single treatment, these animals have retained their vision.

In the initial clinical trial, designed to test the safety of the treatment, the researchers injected the vector into one eye in each of three patients who are 19-26 years old. They performed two kinds of tests of eye function before and after administering the corrective gene. One set of tests comprised standard vision tests, such as asking patients to read an eye chart or navigate an obstacle course. The other physiological test measured the reflexive reaction of the pupil to light.

“The visual acuity tests showed that all three of the patients reported improved vision,” said High. “Also, in all three cases, the injected eyes were more effective in driving the pupillary response to light. These were very exciting findings,” she said.

HHMI investigator Edwin Stone, a co-author of the paper, said “these results are very encouraging that gene replacement therapy will ultimately prove to

be an effective therapy for RPE65-associated LCA.” However, he cautioned, “we need to remember that only a few patients have been treated thus far and that these patients have only been followed for a few months.” Stone specializes in studying inherited eye diseases.

High concurs, adding, “We know what happens after six months, but we don’t know what happens after ten years. There is always that unknown element. Will it persist? Will it be associated with any long term complications? We don’t know that.”

The only complication the researchers have observed thus far is that one patient developed a “macular hole,” a small break in the center of the retina, which was probably a result of the surgical procedure. The hole did not affect the patient’s vision, High said, since the patient had no vision in the macula.

High pointed out that the disease progresses as patients age, so they would like to include younger patients in subsequent trials. “The younger the subject, the better the chance of response,” she said. “Eventually, we would like to treat children as young as possible after they are diagnosed, because that would offer the maximum chance of effectiveness.”

According to Stone, the results suggest that the same therapeutic approach might be used to treat related diseases. “There are a number of heritable retinal diseases that are similar to RPE65-associated LCA in that the structure of the retina is relatively normal and the visual defect results from the loss of function of a single protein,” he said. “Many of these diseases should be amenable to treatment using an approach that is similar to the one taken in this study.”