Gene therapy improves vision in patients with congenital retinal disease

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In a clinical trial at The Children's Hospital of Philadelphia, researchers from The University of Pennsylvania have used gene therapy to safely restore vision in three young adults with a rare form of congenital blindness. Although the patients have not achieved normal eyesight, the preliminary results set the stage for further studies of an innovative treatment for this and possibly other retinal diseases.

An international team led by The University of Pennsylvania, The Children's Hospital of Philadelphia, the Second University of Naples and the Telethon Institute of Genetics and Medicine (both in Italy), and several other American institutions reported their findings today in an online article in the *New England Journal of Medicine*.

"This is the first gene therapy trial for a nonlethal pediatric condition," said Albert M. Maguire, M.D., Associate Professor, Department of Ophthalmology, University of Pennsylvania School of Medicine and a physician at The Children's Hospital of Philadelphia. Maguire, together with his wife, Jean Bennett, M.D., Ph.D., Professor of Ophthalmology at Penn and Senior Investigator at the F.M. Kirby Center for Molecular Ophthalmology at Penn's Scheie Eye Institute, have been researching inherited retinal degenerations such as Leber congenital amaurosis (LCA), for 18 years. LCA is a group of inherited blinding diseases that damages light receptors in the retina. It usually begins stealing sight in early childhood and causes total blindness during a patient's twenties or thirties. Currently, there is no treatment for LCA.

“Patients’ vision improved from detecting hand movements to reading lines on an eye chart,” Maguire added. In 2001, Bennett and Maguire were part of a team which reported successfully reversing blindness using gene therapy on dogs affected by the same naturally occurring form of congenital blindness.

The current study is sponsored by the Center for Cellular and Molecular Therapeutics at The Children’s Hospital of Philadelphia, directed by Katherine A. High, M.D. High, a study leader and an Investigator of the Howard Hughes Medical Institute, has been a pioneer in translational and clinical studies of gene therapy for genetic disease, and in 2005 initiated a collaboration with Bennett and her group to translate their exciting animal findings into a clinical study.

The scientists used a vector, a genetically engineered adeno-associated virus, to carry a normal version of the gene, called RPE65, that is mutated in one form of LCA. Three patients, ages 19, 26 and 26, received the gene therapy via a surgical procedure performed by Maguire between October 2007 and January 2008 at The Children’s Hospital of Philadelphia, where the gene vector was manufactured at the hospital’s Center for Cellular and Molecular Therapeutics (CCMT).

Starting two weeks after the injections, all three patients reported improved vision in the injected eye. “Standard vision tests showed significantly improved vision in the patients,” said Alberto Auricchio, M.D., a study leader from the Telethon Institute of Genetics and Medicine and University of Naples Federico II. The researchers also reported that each injected eye became approximately three times more sensitive to light, and each was improved compared to the uninjected, previously better functioning eye.

The LCA gene therapy vector showed no signs of causing inflammation in the retina or other toxic side effects. One of the three patients had an

adverse event, a hole in the retina that did not affect eyesight and may have been surgery-related, rather than related to biological effects of the therapeutic gene or the vector used to carry it.

The patients enrolled in the study to date were identified at the Department of Ophthalmology at the Second University of Naples, an institution with long-standing experience in collecting and studying patients with inherited retinal diseases, under the supervision of Francesca Simonelli, M.D.

Testing continued over a period of six months following the gene therapy vector administration. One patient was better able to navigate an obstacle course compared to before the injection. The patients also had less nystagmus, an involuntary movement of the eyes that is common in LCA. In the patient who experienced better vision even in the uninjected eye, the researchers suggest that the reduced nystagmus benefited both eyes.

“The current clinical trial will continue with more patients and with ongoing follow-up to monitor results,” said Bennett. “We expect improvements to be more pronounced if treatment occurs in childhood, before the disease progresses.”

“This result is important for the entire field of gene therapy,” notes High, a past president of the American Society of Gene Therapy. “Gene transfer has been in clinical trials for over 15 years now, and although it has an excellent safety record, examples of therapeutic effect are still relatively few. The results in this study provide objective evidence of improvement in the ability to perceive light, and thus lay the groundwork for future studies in this and other retinal disorders,” said High.

The pace of moving from pre-clinical discoveries into clinical trials has typically been slow in the field of gene therapy due to the breadth of

expertise required, ranging from in-depth knowledge of the disorder to detailed understanding of vector design, manufacture, and pre-clinical evaluation. The complexities of regulatory oversight at both the federal and local levels also present challenges. Through the Center for Cellular and Molecular Therapeutics, The Children's Hospital of Philadelphia has developed concentrated expertise and substantial resources to facilitate the "bench to bedside" translation of gene therapy.

Source: University of Pennsylvania School of Medicine