Developing Gene Therapy to Fight Blindness

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An international team of scientists and clinicians from the United States and Saudi Arabia are working to develop gene therapy for treating a rare, hereditary retinal disease. The therapy has been shown to restore lost vision in animal models of retinitis pigmentosa (RP). Their work is being funded in part by a $1.5 million grant from the Prince Salman Center for Disability Research in Saudi Arabia, where the recessive gene mutation that leads to the eye disease RP has been found in children from several families.

The study is being led by Kang Zhang, MD, PhD, professor of ophthalmology at the University of California, San Diego School's Shiley Eye Center and director of the UCSD Institute for Genomic Medicine, and Fowzan Alkuraya, MD, senior clinical scientist and head of developmental genetics unit at King Faisal Specialist Hospital and Research Center, Saudi Arabia.

RP is a type of hereditary retinal dystrophy, a group of inherited disorders in which abnormalities of the photoreceptor rods and cones lead to progressive visual loss. Rods and cones are specialized light-sensitive nerve cells that line the retina. They collect light and then send nerve signals that the brain interprets as vision. Rods facilitate black and white vision and are used mainly at night. During the day, humans depend on cones for color vision.

In people with the genetic mutations that cause RP, rods and cone cells die. Affected individuals first experience defective dark adaptation or "night blindness," followed by reduction of the peripheral visual field known as tunnel vision, sometimes followed by loss of central vision late in the course of the disease. RP affects one in 3,000 to 4,000 people in the United States.

The planned clinical approach of this research trial involves a receptor protein called MERTK that is expressed in the retinal pigment epithelium, the pigmented cell layer just outside the retina that closely interacts with photoreceptors in the maintenance of visual function. Patients with loss of MERTK function have a defect in phagocytosis - a mechanism used to remove pathogens and cell debris. As a result of this defect, debris accumulates between the photoreceptors and retinal pigment epithelium, resulting in death of photoreceptors and loss of vision.

The researchers plan to deliver the *MERTK* gene in a viral vector - a carrier commonly used to deliver genetic material to treat these cells in order to restore function of photoreceptors. Using a rodent model of RP with a similar *MERTK* mutation, the researchers have demonstrated in proof-of-concept studies that viral vector delivery of *MERTK* corrects the mutant gene and restores vision.

The eye is an ideal place for gene therapy because it's an "immune-privileged site," meaning that the eye is able to tolerate the introduction of foreign cells with a minimal, if any, inflammatory immune response, according to Zhang.

The research team's next step is to show that such gene therapy is safe in further animal studies, to be conducted in China, along with additional rat studies that will be conducted at UC San Diego and at the University of Florida.

Once safety for the procedure has been shown, the team hopes to proceed to a human clinical trial in seven patients identified in Saudi Arabia, perhaps as early as spring of 2010.

The same type of vector has been successfully tested in both animals and humans for a similar type of early-onset retinal degeneration called Leber's congenital amaurosis.

Additional investigators include William Hauswirth, PhD, at the University of Florida, Gainesville; SriniVas Sadda, MD, at Doheny Eye Institute, University of Southern California; Emad Abboud, MD, and Hisham Alkuraya, MD, at King Khaled Eye Specialist Hospital, Saudi Arabia; and Peiquan Chao, MD, PhD, Department of Ophthalmology, Shanghai Jiaotong University.

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