Gene therapy safety trial for childhood blindness under way

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Three decades have passed since gene therapy pioneer William W. Hauswirth, Ph.D., and his colleagues at the University of Florida began work on a virus that could safely deliver corrective genes into living animals.

It's been six years since a multi-university team used gene therapy to give sight to puppies born with a defect that causes blindness.

Now the gene-transfer technique is being tested for safety in people in a phase 1 clinical research study conducted by the University of Pennsylvania and the University of Florida with support from the National Eye Institute of the National Institutes of Health.

A young adult with a form of hereditary blindness called Leber congenital amaurosis type 2, or LCA2, received an injection of trillions of replacement genes into the retina of one eye this month, making the volunteer one of the first people in the world to undergo the procedure. Shalesh Kaushal, M.D., Ph.D., an assistant professor of ophthalmology at UF, performed the gene transfer.

The volunteer was discharged last week from the General Clinical Research Center at UF.

In all, six adults and then three children between the ages of 8 and 17 will undergo the gene-transfer procedure at UF over the next year or more before safety data are fully evaluated. Names are not being

disclosed for privacy reasons. Potential risks are discussed with prospective participants as part of an extensive screening and informed consent process.

“This is the first study of its kind to investigate inherited blindness,” said Barry J. Byrne, M.D., Ph.D., a professor of molecular genetics and microbiology and director of UF’s Powell Gene Therapy Center. “The accomplishment reflects a great deal of work and dedication on the part of Dr. Hauswirth, as well as many other scientists and physicians, including Samuel G. Jacobson, M.D. Ph.D., professor of ophthalmology of the University of Pennsylvania, and literally dozens of people who were involved in manufacturing and safety testing the gene transfer agent here at UF.”

Hauswirth and Jacobson — the trial’s principal investigator — were among a multicenter team of NEI-supported clinicians and scientists that first established proof-of-concept for gene transfer for LCA in rodent models of the disease and in a breed of vision-impaired dogs called Briards. Restoration of visual function in dogs occurred in 2001 and has been described as remarkable and long-lasting.

Six years have gone by since the Briard puppies — “Lancelot” was the breakout star, going on to shake paws with lawmakers on Capitol Hill — acquired sight.

“The idea of the therapy is simple,” said Hauswirth, UF’s Rybaczki-Bullard professor of ophthalmic molecular genetics. “If cells are missing a gene for a vital function, such as vision, the therapy is to replace that gene.”

After rigorous preclinical safety studies in animals, including demonstrating the safety of the procedure in non-human primates, the investigators began a human clinical trial.

The effort involved intense collaboration with several investigators playing major roles, according to Jacobson. A short list of the key clinicians and scientists from Penn includes Artur V. Cideciyan, Ph.D., a research associate professor, and Tomas S. Aleman, M.D., a research assistant professor, both from the department of ophthalmology.

In LCA-type diseases, photoreceptor cells are unable to respond to light. NEI and NEI-supported researchers have found that LCA2 is caused by mutations in the RPE65 gene, which produces a protein with the same name that is vital for vision. This trial will evaluate the use of a modified adeno-associated virus — an apparently harmless virus that already exists in most people — to deliver RPE65 to the retina.

“Viruses have evolved a way to get into cells very efficiently, more efficiently than anything else we know to deliver a piece of genetic material to a cell,” Hauswirth said. “So all we’re doing is using evolution to our advantage — in this case, to deliver our therapeutic gene.”

Instrumental in developing the first gene-carrying adeno-associated vectors were eminent scholar Nicholas Muzyczka, Ph.D., a professor of molecular genetics and microbiology at UF, and Kenneth Berns, M.D., Ph.D., director of the UF Genetics Institute. In 1992 Muzyczka and Berns patented a form of the adeno-associated virus capable of introducing foreign DNA into mammalian cells. Terence Flotte, M.D., former chairman of UF’s department of pediatrics and the current dean of the School of Medicine at the University of Massachusetts Medical School, was instrumental in the early organization of the trial. Byrne is the principal investigator at UF.

The actual medical technique used to transfer the gene is not unusual, said Kaushal, who directs the vitreoretinal service in the UF College of Medicine.

“The procedure involves two incisions that give the surgeon access to the surface of the retina,” Kaushal said. “Then, fluid containing the virus is injected with a syringe and it creates a bubble. The virus will then be taken up by the photoreceptor cells and the retinal pigment epithelial cells and will theoretically produce the protein that these patients are missing.”

LCA2 affects about 2,000 people in the United States and is one of several incurable forms of blindness collectively known as retinitis pigmentosa, which in turn affects about 200,000 Americans.

Children with LCA2 experience major visual disability that can lead to total vision loss in adulthood. Although vision loss is severe, the structure of the retina — including its connection to the brain — can remain relatively intact for decades before the photoreceptor cells degenerate.

Source: University of Florida