FOUNDATION FIGHTING BLINDNESS

LEBER CONGENITAL AMAUROSIS RESEARCH ADVANCES

Landmark Gene Therapy Restores Vision in Children and Young Adults

More than 100 children and young adults who were virtually blind have had some vision restored thanks to an innovative gene therapy to cure a severe form of retinitis pigmentosa known as Leber congenital amaurosis (LCA) caused by mutations in the RPE65 gene. The individuals are participating in clinical trials of the treatment at the Children's Hospital of Philadelphia (CHOP), Moorfields Eye Hospital in London, the Universities of Pennsylvania and Florida, and other centers around the world. One nine-year-old boy has put away his white cane and can now see the blackboard at school. A young woman was able to see fireflies for the first time after receiving the treatment. The CHOP clinical trial, sponsored by Spark Therapeutics, completed its final phase in which participants between the ages of 4 and 44 were better able to complete a mobility course after treatment. Thanks to these encouraging results, Spark will be seeking FDA approval for the gene therapy. If approved, it would be the first-ever FDA-approved gene therapy for the eye or an inherited disease. The Foundation funded much of the preclinical research that made these LCA gene-therapy clinical trials possible.

QLT's Clinical Trial for RP and LCA Treatment

The biopharmaceutical company QLT is conducting an international clinical trial for its synthetic retinoid treatment for people with LCA and retinitis pigmentosa (RP) caused by variations in the RPE65 or LRAT genes. Individuals with these genetic variations do not produce a retinoid critical for vision. QLT's treatment serves as a replacement for that missing retinoid. QLT announced impressive results for their Phase IB clinical trial for people with LCA and RP. Patients responded well to the seven-day treatment, reporting some gains in acuity and/or size of their visual field. The investigators were encouraged that the effect of the week-long oral treatment persisted for several months. In late 2016, QLT merged with Aegerion Pharmaceuticals to form Novelion Therapeutics.

Gene Therapy for LCA1 (GUCY2D Mutations)

Investigators from the Universities of Pennsylvania and Florida have demonstrated efficacy for gene therapy in two mouse models of LCA1 — one rich in cones, the other rich in rods. Based on an adeno-associated virus, the treatment provided profound improvement in

vision, which has persisted for eight months thus far. Patients with LCA1 have also been identified and characterized in preparation for a human study. Additional lab studies, including those for safety, are also planned to gain authorization from the U.S. Food and Drug Administration to launch a clinical trial. A partnership with the pharmaceutical company Genzyme has been established to advance the treatment.

Gene Therapy for LCA6 (RPGRIP1 Mutations)

A research team from Massachusetts Eye and Ear Infirmary is developing a gene therapy based on an adeno-associated virus for LCA caused by RPGRIP1 mutations. An earlier study showed that gene therapy rescued degenerating rods and cones in a mouse model of the condition. Forthcoming studies will determine if the therapy is effective for both early- and late-stage disease.

CRISPR Therapy in Development for CEP290 Mutations

The company Editas Medicines is developing a gene-editing therapy using a cut-and-paste technology known as CRISPR/Cas9 to correct defective copies of CEP290. (The long-hand for this technology is: Clustered, Regularly Interspaced Short Palindromic Repeats/ CRISPR-associated protein 9.) CRISPR, which comes from the immune system in strep bacteria, locates the region in the gene that needs correction. Cas9 is the molecular scissors that cuts out the mutation.

Gene Therapy for LCA Caused by RD3 Mutations Performs Well in Lab Study

A research team led by Robert Molday, PhD, at the University of British Columbia in Vancouver, has moved a step closer to developing a gene therapy for people with LCA caused by mutations in the gene RD3. The investigators used an RD3 replacement gene therapy to restore photoreceptor function in mice with the condition and plan to test the treatment in canines with RD3 mutations. Results of their mouse study were published in the journal *Human Molecular Genetics*. The researchers noted that photoreceptors of the treated mice survived for seven months, which is considered a relatively long time for these animals.