

FIRST GENE THERAPY FDA-APPROVED FOR AN INHERITED RETINAL DISEASE



The approval has stimulated research into gene therapies for other IRDs.

BY MEGHAN J. DEBENEDICTIS, MS, LGC, MED, AND ALEKSANDRA V. RACHITSKAYA, MD

The idea of gene therapy has been discussed in the medical literature since as early as the 1970s. In 1972, Friedman and Roblin proposed that it was theoretically possible to introduce “good” DNA to replace defective DNA.¹ Over the years, a number of gene therapy clinical trials emerged in efforts to treat genetic diseases of inborn errors of metabolism, all with varying degrees of success.

The basic principle of gene therapy is to put corrective genetic material into cells to treat genetic disease. Several gene therapy approaches, including replacement gene therapy, optogenetics, addition of a growth factor, suppression gene therapy, and gene editing, have been proposed in attempts to treat various ophthalmologic conditions.

Optogenetics focuses on creating artificial photoreceptors to restore photosensitivity. This is accomplished by gene delivery of light-activated optogenetic tools (channels or pumps) to surviving cells, such as ganglion cells, that remain intact in the retinal circuit in various diseases.² It has been posited that genetically added growth factor proteins, such as adenovirus-expressed endostatin and angiostatin gene products, could have anti-VEGF properties.³ Short-interfering RNAs could be used for down-regulation of gene expression, resulting in functional inactivation of the targeted genes.⁴ Finally, technologies such as CRISPR (standing

for *clustered regularly interspaced short palindromic repeats*) could allow editing of one or several sites within the mammalian genome.⁵

The most common type of gene therapy is replacement gene therapy, which involves replacing a mutated gene that causes disease with a healthy copy of that gene. It is first necessary to identify the causative mutated gene. This technology works best in autosomal recessive biallelic disease with loss-of-function mutations. A vector is then created to carry a wild-type copy of the gene into the cell of interest. The transfected gene is not incorporated into the host DNA but is expressed, resulting in production of a protein with normal function.

Scientists and companies have spent decades perfecting the use of vectors for genetic material and identifying ways to deliver them to increase therapeutic efficacy and treatment duration. Early investigations used viruses that delivered genes to every cell in the body, which triggered a massive immune response that could lead to organ failure. More recently designed vectors deliver specific genes to specific cells.

TARGET: IRDs

With the eye’s unique immunologic privilege, inherited retinal diseases (IRDs) have become one of the leading targets in gene therapy research over the past 15 years. Successful treatment and restoration of vision

AT A GLANCE

- The most common type of gene therapy is replacement gene therapy, in which a mutated gene that causes disease is replaced with a healthy copy of that gene.
- *RPE65* gene mutations account for up to 10% of autosomal recessive Leber congenital amaurosis and early-onset retinal dystrophy cases.
- The positive results of gene therapy clinical trials for *RPE65*-mediated retinal dystrophy led to the first US regulatory approval of a gene therapy in January 2018.



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in vivo was first achieved in canine models with *RPE65*-related retinal degeneration.⁶ The successful delivery of a wild-type *RPE65* gene using a recombinant adeno-associated virus (AAV), with positive results, paved the way for human clinical trials.

In healthy eyes, *RPE65* is expressed in the retinal pigment epithelium (RPE) and encodes an RPE-specific 65 kD protein, all-trans retinyl ester isomerase, an enzyme crucial to the retinoid cycle. The enzyme plays an essential role in the visual cycle. *RPE65* is responsible for the conversion of all-trans retinyl esters to 11-cis retinol during phototransduction. The 11-cis retinol is converted to 11-cis retinal and is used in visual pigment

regeneration in photoreceptor cells.⁷

However, despite the inability of the RPE cells to provide sufficient 11-cis retinal to the photoreceptors in *RPE65*-related retinal degeneration, the photoreceptors degenerate slowly, so that phenotypic recovery is possible through restoration of the missing enzyme to the RPE.⁸ *RPE65*-mediated retinal dystrophy is an autosomal recessive disease that occurs due to biallelic loss-of-function mutations in the *RPE65* gene, making it an attractive condition for gene replacement therapy.⁷

RPE65 gene mutations account for up to 10% of autosomal recessive Leber congenital amaurosis and early-onset retinal dystrophy cases.⁹ Patients

with this condition have an early-onset retinal dystrophy phenotype with profound night blindness from birth but residual cone-mediated vision and often mild, if any, nystagmus. The disease usually manifests in childhood.

CLINICAL TRIAL RESULTS

Initially restricted to adults and involving treatment of only one eye, *RPE65* gene therapy trials have since expanded to include children and bilateral treatment. The results of a phase 3 *RPE65* gene therapy clinical trial, published last year, showed improvement in functional vision in treated patients, in comparison with untreated control participants, at 1 year.⁸

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DYSTROPHIES HAS EXPLODED.

Eligible participants for this trial included patients aged 3 years or older with best corrected visual acuity of 20/60 or worse in each eye or visual field of less than 20°. The primary outcome of the study was multiluminance mobility testing (MLMT). Patients were required to follow a maze at different illumination (lux) levels ranging from a brightly lit office environment to a moonless night.

At 1 year, there was a statistically significant difference in improvement in mean bilateral MLMT favoring the intervention group. Moreover, 13 (65%) of 20 intervention participants, but no control participants, passed MLMT at the lowest luminance level tested (1 lux), demonstrating the maximum possible improvement. The authors reported no product-related serious adverse events or deleterious immune responses. Improvements in both navigational abilities and light sensitivity were evident within the first 30 days after subretinal delivery and remained stable for 1 year, as they have for at least 3 years in participants in the previous phase 1 trial.⁸

REGULATORY APPROVAL

This groundbreaking work and the results of these *RPE65* gene therapy trials led to regulatory approval of this therapy by the US Food and Drug Administration in January. Voretigene neparvovec-rzyl

(Luxturna; Spark Therapeutics) is approved for the treatment of patients with confirmed biallelic *RPE65* mediated IRD. It is the first directly administered gene therapy approved in the United States that targets a genetic disease caused by mutations in a single gene.

Voretigene is administered via subretinal injection in both eyes separately and on separate days. The surgery, which is performed by a vitreoretinal surgeon, requires pars plana vitrectomy and subretinal injection of a total volume of 0.3 mL. The recommended site of injection is located along the superior vascular arcade, at least 2 mm distal to the center of the fovea.¹⁰ Given the small number of patients who qualify for this specific gene therapy, there are a few dedicated sites across the country that are offering the treatment. The cost of treatment is currently \$425,000 per eye.¹¹

MORE TO COME

With the pivotal success and US Food and Drug Administration approval of voretigene for treatment of biallelic *RPE65*-mediated IRD, ongoing research in other IRDs has exploded. Gene therapy research is being conducted at various stages for choroideremia, X-linked juvenile retinoschisis, Stargardt disease, achromatopsia (*CNGB3* and *CNGB3*), gyrate atrophy, retinitis pigmentosa (*RPGR*, *RLBP1*, *PDE6A*, and *PDE6B*),

Leber hereditary optic neuropathy, and Usher syndrome (*MYO7A* and *USH2A*).

Advances in the field of gene therapy make the accurate diagnosis of hereditary retinal dystrophies more important than ever. Genetic testing is crucial to identify the underlying cause of disease in this patient population and to allow potential intervention with gene therapy and other novel therapies. The burgeoning field of gene therapy provides hope to patients who previously had no hope of preserving or regaining vision. ■

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