

# A Retinal Research Nonprofit Paves the Way for Commercializing Gene Therapies

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AN EMERGING, vision-restoring gene therapy for a devastating retinal disease is poised for Food and Drug Administration (FDA) approval. If it gets the regulatory nod, it will be the first gene therapy to receive FDA approval for the eye or an inherited condition.

The story of this groundbreaking treatment began with discovery of the gene *RPE65* nearly 25 years ago at the National Eye Institute,<sup>1</sup> and continued when the Foundation Fighting Blindness (FFB), the world's leading private funding source for inherited retinal disease (IRD) research, invested \$10 million in studies that linked mutations in *RPE65* to blindness,<sup>2</sup> and advanced an *RPE65* gene therapy into clinical trials.

On October 12, 2017, the FDA's Cellular, Tissue and Gene Therapies Advisory Committee unanimously recommended marketing approval for the investigational treatment, voretigene neparovec (LUXTURNA), for people with vision loss from biallelic mutations in *RPE65*. Defects in the gene lead to certain forms of Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP). Affecting 1,000–2,000 people in the United States, these conditions cause devastating vision loss in childhood, including night blindness and loss of visual acuity and color perception. Eventually, nearly all patients with biallelic *RPE65* mutations go completely blind.

During the Advisory Committee's hearing, representatives from Spark Therapeutics, the therapy's commercial developer, reviewed impressive Phase 3 clinical trial results for 32 participants, some as young as 4 years of age. The company reported

clinically meaningful and statistically significant vision improvements in participants' functional vision, light sensitivity, and visual function. Results were durable for up to 3 years—the longest reported patient follow-up. The safety profile was consistent with vitrectomy and subretinal injections, which are frequently performed for the treatment of other retinal conditions.

Most compelling was testimony from patients for whom the treatment was life changing (Fig. 1). After a single subretinal injection to each eye, many reported putting away their navigational canes, seeing facial expressions for the first time, enjoying a world of vibrant color, and even observing stars in the night sky.

"I didn't realize stars were little dots that twinkled," said Misty Lovelace, a young woman at the hearing who received the *RPE65* gene therapy in 2012. She also told the Committee that she was able to see her mother's face clearly for the first time shortly after receiving the treatment.

For the impassioned group of families who founded FFB in 1971, this was a moment they had been waiting for. But little did they know it would take more than 46 years to reach it. While it was clear in the early 1970s that virtually no research was underway to even understand how these retinal conditions occur, no one, not even the top retinal experts, had any idea how complex and diverse the diseases actually were. No one knew the formidable challenge that lay ahead. But at no point did anyone ever think of ever giving up the fight to overcome them. Through its persistent and tenacious family of

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**Figure 1.** Eleven-year-old Cole Carper (*right*), the youngest speaker at the Food and Drug Administration hearing for LUXTURNA, said he loves playing with Lego now that he has better vision thanks to the gene therapy. His 13-year-old sister, Caroline (*not pictured*), who was also in Spark's Phase III study, now enjoys reading print books instead of Braille. She's also preparing for a role in the play "Shrek"—something her mom, Ashley (*left*), said would have been very difficult before treatment.

donors, FFB has raised more than \$725 million toward its mission to become the world's largest private funding source for IRD research.

### THE FIGHT FOR VISION BEGINS

FFB's story began when Eliot Berson, MD, at the Massachusetts Eye and Ear Infirmary (MEEI),

brought two families together to fund the creation of the first-ever laboratory to study retinal degenerations. One family, Gordon and Lulie Gund (Fig. 2), had just returned from Russia after a failed, last-ditch effort to find a cure for Gordon's advancing RP. The condition, affecting about 100,000 people in the United States, progressively constricts the patient's visual field to the point where there's only a pinhole of vision left—or nothing at all. By the time Gordon and Lulie went to Russia, he had virtually no vision left.

"My wife, Lulie, and I, who were alone in this frantic search, went all over this country pursuing paths that led to dead ends," said Gordon. "Shortly after my central vision closed in, I travelled to Russia with the hope of finding a cure. That trip also led to a dead end and eventually to a commitment by Lulie and me to turn our frustration into something positive."

Ben and Beverly Berman were also trying to find answers for their two young daughters, Mindy and Joanne, who both had RP. Like the Gunds, they too were frustrated by the lack of knowledge of the disease that was slowly robbing their daughters' vision.

Dr. Berson brought the Gunds and Bermans together, and they established the RP Foundation with the MEEI's Berman-Gund Laboratory for the Study of Retinal Degenerations as its first project. The nonprofit was renamed the Foundation Fighting Blindness in 1995 to reflect its commitment to eradicating the entire spectrum of these vision-robbing retinal conditions.

While in those early days retinal disease experts knew that RP and other related conditions ran in families, it took 18 years from FFB's inception for



**Figure 2.** Gordon and Lulie Gund, co-founders of The Foundation Fighting Blindness.

researchers to find the first gene associated with RP or any IRD. Identified in 1989 by an FFB-funded team at Trinity College Dublin, the gene was *RHO*,<sup>3</sup> which, when mutated, can cause autosomal dominant RP. The gene expresses rhodopsin, a light-sensitive protein in rod photoreceptors that, when exposed to light, initiates the biochemical process that makes vision possible in dimly lit settings.

Since that discovery, more than 260 genes have been associated with myriad IRDs, including Usher syndrome, which causes combined deafness and blindness; Stargardt disease, a form of inherited macular degeneration causing central vision loss; and LCA. The discovery of most IRD genes was made by FFB-funded investigators.

While IRDs are Mendelian conditions, their genetic diversity is daunting. For example, more than 80 genes, when mutated, can each cause RP. Furthermore, not all IRD genes and mutations have been identified. Most genetic testing laboratories report they can identify IRD-causing mutations in at least 60% of patients. With the advent and reduced cost of powerful, next-generation sequencing technologies such as whole-exome and whole-genome sequencing, geneticists continue to find the more elusive genes and mutations every year, enabling experts to diagnose more patients and identify new treatment targets.

## THE ROAD TO THE CLINIC

The vision for gene therapy for IRDs began in earnest in 1990, when a 4-year-old girl with adenosine deaminase deficiency, a condition that results in severe compromise of the immune system, received gene therapy in an FDA-authorized clinical trial. The milestone study inspired Jean Bennett, MD, PhD, and Albert Maguire, MD—a wife and husband team of clinical researchers who met at Harvard Medical School—to consider the possibility of gene therapies for RP and other IRDs.<sup>4</sup>

They saw IRDs as a clear and compelling target for gene therapy for several reasons:

- Patients have defects in a single gene—compensating for the mutated gene with a functional gene would directly address the primary disease pathway.
- The retina is a small and accessible target—transfecting a critical mass of cells (*e.g.*, photoreceptors) to achieve a therapeutic effect would be more feasible than delivering genes to other larger organs and systems.
- The treatment's efficacy—that is, changes in visual function—could be measured non-invasively.

- The eye is immune privileged, reducing the chance of rejection.
- Most humans and animals have two retinas, so one could serve as a control.

In 1991, Dr. Bennett received an FFB career development award, which enabled her and Dr. Maguire to begin developing *in vivo* gene therapy techniques. Data from those studies were used to obtain a larger National Eye Institute grant to develop gene therapies for retinal diseases.

Subsequent FFB-funded breakthroughs made by Andreas Gal, MD, PhD—he identified *RPE65* mutations as a cause of LCA, as well as a Briard canine model of the condition—would ultimately attract the attention of Drs. Bennett and Maguire for developing an *RPE65* gene therapy. Furthermore, despite severe vision loss in early childhood, *RPE65* patients usually retain viable photoreceptors for several years. *RPE65* expresses an enzyme that metabolizes vitamin A to make photoreceptors light sensitive—the protein doesn't play a role in photoreceptor development.

The pivotal laboratory breakthrough for *RPE65* gene therapy came in 2000 when an FFB-funded team from the University of Pennsylvania (Bennett, Maguire, Jacobson, Aguirre, and Cideciyan), Cornell (Acland), and the University of Florida (Hauswirth) bestowed vision to Briards born blind from LCA.<sup>5</sup> The investigators used an adeno-associated virus (AAV) to deliver healthy copies of *RPE65* safely to the canines' retinal pigment epithelium, a single layer of support cells in which *RPE65* is expressed.

The dramatic results for the Briards—including Lancelot, the most charismatic of them all—were presented to the U.S. Congress and featured by a plethora of international television, newspaper, and radio outlets. The breakthrough in canines provided strong proof of principle for vision restoration in people and set the stage for the *RPE65* gene therapy clinical trial that would launch in 2007 at Children's Hospital of Philadelphia (CHOP), led by Drs. Bennett and Maguire. Two other *RPE65* gene therapy trials would begin about the same time—one at the Universities of Pennsylvania and Florida and the other at Moorfields Eye Hospital in London.

## STRONG MOMENTUM FOR COMMERCIAL DEVELOPMENT

Since the launch of the *RPE65* gene therapy clinical trials in 2007, there's been a tremendous surge in both clinical trials and commercial investment for IRDs. Nearly 20 human studies for IRD gene therapies are underway around the world, and many new IRD gene therapy biotechs are springing up.

Spark was established in 2013—a spin-off of CHOP with Dr. Bennett as a scientific co-founder. The company is developing gene therapies for IRDs (choroideremia is their next target in the clinic) and other genetic conditions, such as hemophilia and Batten disease. Spark has attracted more than \$500 million in investments.

With \$8.5 million in preclinical funding from FFB, the biotech Applied Genetic Technology Corporation (AGTC) has launched gene-therapy clinical trials for achromatopsia, an IRD causing day blindness, and X-linked retinoschisis, a devastating IRD, which results in splitting of the retina's inner and outer layers. The company recently submitted an investigational new drug application for an X-linked RP gene therapy. AGTC has garnered \$265 million in investments.

William Hauswirth, PhD, a world leader in AAV vector development for IRDs at the University of Florida, is one of AGTC's scientific co-founders. "We as an organization would not be here today without FFB and Dr. Hauswirth," said Sue Washer, AGTC's chief executive officer, at FFB's 2017 Investing in Cures Summit in Chicago. "And that all started with the work that was funded by the Foundation in Bill's lab at the University of Florida."

Major pharmaceutical and biotechnology companies have entered the IRD gene therapy business as well. Biogen, for example, has made investments in retinal gene therapy development at the University of Pennsylvania and AGTC. Sanofi is also conducting gene therapy clinical trials for Usher type 1B and Stargardt disease.

In 2016, Allergan acquired the startup RetroSense, which is developing a novel, optogenetic technology—a gene therapy that produces channelrhodopsin-2, a protein expressed in algae, to bestow light sensitivity to blind RP patients who have lost all of their photoreceptors. Unlike gene replacement, the treatment works independent of the recipient's IRD-causing gene.

FFB launched its Clinical Research Institute (CRI), an independent subsidiary, in 2004 to accelerate clinical advancement of gene therapies and other promising treatments by: (1) forming partnerships with big pharma, biotechs, and

startups; (2) funding translational projects with strong therapeutic potential; (3) conducting natural history studies to identify participants and outcome measures for clinical trials; and (4) building a global registry of patients with IRDs—[www.MyRetinaTracker.org](http://www.MyRetinaTracker.org)—for clinical trial recruitment and other research activities.

Most recently, FFB-CRI committed to an investment of up to \$7.5 million in Nacuity, a Dallas-based startup developing N-acetylcysteine amide, a potent antioxidant for the retina showing vision-saving potential for RP. The molecule was developed through FFB-funded studies by Peter Campochiaro, MD, at Johns Hopkins University.

In addition, FFB-CRI is investing up to €7 million in SparingVision, a Paris-based biotech advancing a neuroprotective protein known as rod-derived cone viability factor for saving vision in people with RP and potentially other IRDs. That emerging therapy came from more than a decade of FFB-funded research by José Sahel, MD, and Thierry Léveillard, PhD, at the Institut de la Vision.

## WE'VE ONLY JUST BEGUN

LUXTURNA, if FDA approved, will be the first of hopefully many IRD gene therapies to come.

But gene replacement therapy won't be the answer for everyone with an IRD—at least for now. Developing such treatments for each of the 260+ IRD genes is a daunting task from technical, financial, and regulatory standpoints. Many patients, depending on their disease-causing gene mutation and stage of vision loss, may be better candidates for stem-cell treatments or small molecules that work independent of the gene defect. These approaches are also a major part of FFB's grant portfolio.

But from a clinical development standpoint, gene therapies are leading the way for saving and restoring vision. Because the retina is neural tissue, an extension of the brain, scientists are eager to take what they are learning in the clinic from IRD gene therapies to apply them to other devastating neurodegenerative conditions.

Visit [www.FightBlindness.org](http://www.FightBlindness.org) to learn more about FFB and the latest news in IRD research.

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