

Crossing the Valley of Death to Find Cures for Blindness

Moving from bench to bedside is hard enough for therapies treating common diseases. The hurdles only get higher for those with orphan indications.

BY JACQUE DUNCAN, MD

Every day, I see patients with orphan inherited retinal degenerative diseases (iRDs) such as Leber congenital amaurosis (LCA), retinitis pigmentosa (RP), and Stargardt disease. Such diseases are the focus of my practice, and I have the privilege of working with courageous and tenacious patients who, despite a prognosis of progressive vision loss leading to blindness or severe visual impairment, are eager to learn about possible treatments.

Any retina doctor working with patients with orphan diseases wants desperately to save their vision, but currently there are no approved treatments. A number of factors frustrate the research efforts of those investigating such treatments. An orphan disease is defined as one that affects fewer than 200,000 people in the United States, so therapies are targeted at small populations, attracting little interest from many pharmaceutical companies. Furthermore, iRDs are genetically and clinically heterogeneous; approximately 250 genes are associated with disease manifestation, and geneticists estimate a large number of these genes have yet to be discovered.

Eight years ago, a spotlight illuminated the iRD field. Researchers at the University of Pennsylvania, Children's Hospital of Philadelphia, and University College London reported that gene replacement therapy significantly improved vision in young adults and children with LCA (RPE65 mutations) participating in a clinical trial.¹⁻³ This breakthrough provided proof of concept in humans that iRDs were treatable.

ADDRESSING THE TRANSLATIONAL CHALLENGE

A few years earlier, anticipating the hurdles in advancing these therapies from the lab into clinical trials—doing what those in the orphan iRD field call crossing the Valley

of Death—the research nonprofit Foundation Fighting Blindness (FFB) established a clinical advancement subsidiary, known today as the FFB Clinical Research Institute (FFB-CRI). Its goal: to develop safe and effective therapies for orphan iRDs and get them to patients who need them as quickly as possible. Its strategy: to gain commercial interest by forming partnerships, sharing clinical development knowledge, and de-risking the technologies.

“We knew it wouldn't be easy to attract commercial and pharma interest in therapies for orphan retinal conditions,” said Patricia Zilliox, PhD, chief drug development officer at FFB-CRI. “But we also knew there was great opportunity because [these therapies] have the potential to work well, and the retina is a clear, accessible target for validating therapies for a variety of neurodegenerative conditions.”

Since joining FFB-CRI, Dr. Zilliox has formed a partnership with Sanofi, which is leading gene therapy clinical trials for Usher syndrome and Stargardt disease. She also forged a partnership with Shire to develop a small-molecule treatment for the autosomal dominant RP, a blinding condition for which there is no treatment approved by the US Food and Drug Administration (FDA).

At a Glance

- Researchers investigating treatments for orphan retinal degenerative diseases face a number of challenges, including lack of funding.
- Third-party organizations interested in facilitating clinical investigation of treatments for orphan diseases can provide financial and logistical support to researchers.

"We are excited to have Shire address this critical therapeutic need," said Stephen Rose, PhD, chief research officer at FFB. "Our collaborative approach leverages FFB-CRI's research expertise with Shire's clinical development resources and experience, giving us an excellent opportunity for success in moving the treatment out to the people who need it."

"The orphan disease market is now coming up on big pharma's radar because of development and marketing incentives provided by the FDA," Dr. Zilliox said. "But breakthroughs in genetic discovery are also giving us big pieces of the puzzle. We know how better to address these inherited conditions."

SIGNIFICANT COMMERCIAL INVESTMENTS

Due to the success of earlier laboratory research, including preclinical studies supported by FFB, gene therapy startups are attracting hundreds of thousands of dollars of venture-capital investments and initiating human studies. For example, Spark Therapeutics is conducting a phase 3 clinical trial of RPE65 gene therapy for LCA and recently launched a phase 1/2 study in choroideremia. Likewise, the biotech company AGTC is developing gene therapies for X-linked RP, X-linked retinoschisis, and achromatopsia.

"These companies are not only leveraging proof-of-concept lab studies funded by us over the years, they're also looking to FFB-CRI for guidance in navigating the regulatory pathway and designing clinical trials," Dr. Rose said. "Dr. Zilliox brings more than 3 decades of clinical development experience to the table. That knowledge has been invaluable in enabling these potential treatments to advance through development and, ultimately, become available to patients."

NEED FOR RELIABLE OUTCOME MEASURES

FFB-CRI is also addressing the need for clinical trial endpoints—another challenge in crossing the Valley of Death. With most iRDs, which vary greatly from patient to patient in their presentation and progression, standard measures such as visual acuity and visual field are not able to reliably capture changes in vision in a practical timeframe.

FFB-CRI launched a 12-site natural history study examining people with Stargardt disease to identify a clinical trial endpoint. ProgSTAR, the 250-person retrospective and prospective study, will cost more than \$5 million, but the investment will speed development of effective treatments.

"We believe that a reliable endpoint for Stargardt disease will attract companies to the field," Dr. Zilliox said. "It will give them much more confidence that they can design a clinical trial for therapies that have a good chance of getting approved." She noted that ProgSTAR will also aid in patient recruitment for future clinical trials.

FFB-CRI has supported research led by the Retina Foundation of the Southwest for a new clinical trial outcome measure for people with RP. Findings suggest that ellipsoid zone width, an endpoint that measures the band of viable photoreceptors remaining in a patient's retina, will provide a more reliable and expeditious measure of disease progression and therapy efficacy than traditional endpoints.

FRAMEWORK FOR SUCCESS

FFB-CRI's success in translating orphan disease therapies from the bench to the bedside provides important lessons for others pursuing treatments for rare conditions. It takes collaborations and partnerships. It requires knowledge of clinical development and regulatory processes. It mandates good science; after all, we need to develop therapies that are safe and effective. And none of it can be accomplished without funding. However, a sound clinical development plan has the potential to attract significant commercial investment, as FFB-CRI has demonstrated.

THE PATIENT'S ROLE

At this time, retina doctors cannot cure patients going blind due to orphan iRDs, but we can give them hope because therapies for saving and restoring vision are, or may soon be, in the clinical pipeline. The days of "there's nothing that can be done" are over. I encourage patients to get genetics tests so they can qualify for upcoming trials, and I strongly suggest they register with the FFB-CRI patient registry (MyRetinaTracker.org) so they can be aware of forthcoming studies for which they may qualify. ■

To learn more about the work of FFB and its CRI subsidiary, visit www.fightblindness.org.

Jacque Duncan, MD, is a professor of clinical ophthalmology at the University of California, San Francisco, specializing in retinal degenerative diseases. She serves as chair of the Foundation Fighting Blindness scientific advisory board. She is a consultant for Spark Therapeutics, AGTC, Shire, Ocugen, Okuvision, Sucampo AG, Isis Pharmaceuticals, jCyte, and the California Institute for Regenerative Medicine. Dr. Duncan may be reached at jacque.duncan@ucsf.edu.



The author wishes to acknowledge contributions to this article made by Ben Shaberman of the Foundation Fighting Blindness.

1. Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med*. 2008;358(21):2231-2239.
2. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. *N Engl J Med*. 2008;358(21):2240-2248.
3. Cideciyan AV, Aleman TS, Boye SL, et al. Human gene therapy for RPE65 isomerase deficiency activates the retinoid cycle of vision but with slow rod kinetics. *Proc Natl Acad Sci U S A*. 2008;105(39):15112-15117.