Gene Therapy Trial Update: A Primer for Vitreoretinal Specialists

by Cristy A. Ku, MD, PhD; Mark E. Pennesi, MD, PhD

Medical history was made in fall 2015 when Spark’s SPK-RPE65 phase 3 U.S. Food and Drug Administration (FDA) registration trial showed gains in functional vision and light sensitivity in certain patients with inherited retinal dystrophies (IRDs) such as Leber congenital amaurosis and retinitis pigmentosa. After more than a decade of work, the results represent the first successful randomized, controlled trial ever completed in gene therapy for a genetic disease. If FDA approved, hope will be provided to those patients suffering from IRDs due to an RPE65 mutation.

For this column, Mark E. Pennesi, MD, PhD, and Cristy A. Ku, MD, PhD, from the Casey Eye Institute in Portland, OR, provide an overview of this complex topic. There are more than 20 ongoing clinical trials investigating gene therapies for various retinal diseases. They will discuss innovations, the role of vitreoretinal specialists in managing these patients, and clinical versus genetic characterization of disease.

Our community should acknowledge the contributions of the trial participants and families, as well as the investigators and all who contributed to this groundbreaking accomplishment in medicine. The ability to carefully and precisely target disease using a one-time administration of a gene therapy and have a meaningful impact on the lives of patients suffering from debilitating IRDs is historic. Furthermore, the knowledge gained opens doors to develop treatments for other diseases like choroideremia.

We are grateful to Drs. Pennesi and Ku for generously sharing their extensive knowledge on this topic with our community. I am certain we will all find this primer very educational, and that it will allow us to better inform our patients, their caregivers, and our community.

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INNOVATIONS IN GENE THERAPY

IRDs are a clinically diverse group of diseases affecting one in 3,000 people that involve mutations in more than 200 genes. Despite their genetic diversity, IRDs can be thought of in two broad categories requiring differing gene therapy strategies. The most common approach is gene replacement, which replaces an absent or functionally null gene product. Current trials replace null genes associated with autosomal recessive LCA, Stargardt disease, and Usher syndrome type 1B (Table 1). Gene replacement of RS1 and CHM treats X-linked diseases, X-linked retinoschisis, and choroideremia, respectively.

In contrast, gene suppression is required to treat many autosomal dominant (AD) retinal degenerations, such as rhodopsin mutations associated with autosomal dominant retinitis pigmentosa. This strategy works to mitigate a dominant negative or toxic gain of function causing visual dysfunction and degeneration. Gene suppression through RNA interference (RNAi) can decrease expression of both mutant and normal gene copies, requiring subsequent gene replacement. Alternatively, site-specific correction at the nucleotide level can be conducted with zinc finger nucleases, TALEN, or CRISPR/Cas gene editing tools. Although still in preclinical studies, these methods may potentiably correct a wide range of dominant or recessive mutations.

When no genetic mutation is identified, or when the gene remains untouched, mutation-independent strategies become necessary. Viral vectors can be used as a general platform for the delivery or addition of genes into retinal cells that provide therapeutic effects. For example, expression of agents such as rod-derived cone viability factor, which promote cone photoreceptor cell survival, may mediate neuroprotection regardless of the underlying genetic mutation. A second strategy is optogenetics, which aims to induce light sensitivity in residual inner retinal cells following complete loss of the outer retina. Light-sensitive proteins, similar to rhodopsin, are instead expressed in retinal ganglion or bipolar cells. Expression of channelrhodopsin-2, derived from Chlamydomonas reinhardtii algae, recently marked the first entry of optogenetics in clinical trials (Table 1). Viral vectors are also being utilized to express the chimeric vascular endothelial growth factor receptor-binding agents, sFLT01, or two anti-angiogenic proteins, endostatin and angiostatin (RetinoStat; Oxford BioMedica, Oxford, UK), for treating neovascular AMD (Table 1).

VITREORETINAL SPECIALISTS IN FIRST-LINE MANAGEMENT OF IRD PATIENTS

Vitreoretinal specialists are often the gateway for IRD patients into clinical trials. They play a vital role in the preliminary diagnosis, referral, and patient education. Despite varying diagnostic resources available, a patient’s history may help to generate a broad phenotype, such as rapid early onset diseases like LCA versus slower-progressing, later-onset retinal dystrophies, such as RP. Subjective symptoms, such as loss of color discrimination or night vision, may distinguish macular cone dystrophies from rod dystrophies, which can be objectively confirmed through multifocal and full-field electroretinography. We provide resources to aid vitreoretinal specialists in preliminary differential diagnoses of IRDs (Table 2) to assist referral of patients with suspected IRDs to specialty centers conducting clinical trials (Table 1). Rapid referral of young infants and children who require examination and diagnostic testing under anesthesia is also appropriate. Early intervention often offers the best therapeutic effects in IRDs, particularly in AIPL1-LCA and MYO7A-Usher patients.

Vitreoretinal specialists may also facilitate discussions in diagnosis, treatment, and treatment limitations to establish patient expectations prior to lengthy workup. Expectations in diagnoses should be made explicit, with complexities in molecular diagnostics potentially leading to inconclusive results. Despite an expanding number of gene targets, a majority of patients also may not be gene candidates in current trials.

Limitations in gene therapy itself should be discussed, as it does not restore vision to that of a normal-sighted person, but more likely aims to slow disease progression. For example, treated RPE65-LCA patients had minimal gains in visual acuity, but did achieve subjective visual improvement and gains in more sensitive visual tests. A delicate balance exists between providing accurate and realistic information and conveying optimism for the immense potential that ophthalmic gene therapy holds. We have compiled resources to provide to patients for understanding retinal degenerations, the process of genetic testing and
<table>
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<tr>
<th>Disease (Gene)/(Vector)</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Status</th>
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<th>Retinitis Pigmentosa – Optogenetics</th>
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**Age-Related Macular Degeneration**

| sFLT01 / (AAV2) | Genzyme/Sanofi                     | I/II | Active, not recruiting | Retina Consultants of Arizona; Johns Hopkins University; Ophthalmic Consultants of Boston; U. Mass, Worcester; Retina Consultants of Houston | 01024998 |
| sFLT01 / (AAV2) | Lions Eye Institute, Perth Australia | I/II | Active, not recruiting | Lions Eye Institute, Nedlands Australia | 01494805 |
| Endostatin, Angiostatin / (EAV) | Oxford BioMedica | I | Active, not recruiting | U. Iowa; Johns Hopkins University; OHSU | 01301443 |
| Endostatin, Angiostatin (EAV) | Oxford BioMedica | I | Recruiting, by invitation | Johns Hopkins University; OHSU | 01678872 |

RPE65 = retinal pigment epithelium-specific protein 65kDa; MERTK = MER proto-oncogene tyrosine kinase; ABCA4 = ATP-binding cassette, sub-family A, member 4; MYO7A = myosin VIIA; CHM = choroideremia, rab escort protein 1; RS1 = retinoschisin 1; sFLT01 = soluble fms-related tyrosine kinase 1; AAV = adeno-associated virus; EIAV = equine infectious anemia virus; U. = University of; CHOP = Children’s Hospital of Philadelphia; OHSU = Oregon Health & Science University; UCL = University College London; NEI = National Eye Institute; NIH = National Institutes of Health

clinical trial participation, and clinical trial registries that keep patients updated in recruitment (Table 3).

**CLINICAL AND GENETIC DIAGNOSIS OF INHERITED RETINAL DISEASES**

Much like glaucoma, the diagnosis of a specific IRD stems from the gestalt of findings from patient history, numerous subjective and objective testing modalities, and genetic testing. Since these diseases have historically been untreatable, extensive workups have been deferred in the past. With the potential for treatment, the paradigm is now shifting to determining the underlying genetic etiologies.

In clinical diagnostic testing, patients should expect to undergo detailed imaging, visual function, and electrophysiological testing. The low visual acuity of IRD patients often also requires specialized visual function testing, such as microperimetry and full-field stimulus testing. A molecular diagnosis serves multiple roles in patient management. It confirms clinical diagnosis if a mutation is found in a gene associated with the suspected IRD. Most importantly, identification of the causative gene is now a prerequisite in determining treatment options. Knowledge of mutation and inheritance may also aid in early diagnosis of siblings or influence family planning. Beyond individual patient care, it provides the basis for genotype-phenotype studies. Such studies demonstrated the therapeutic potential in RPE65-LCA patients and may influence future gene target selection.

Historically, Sanger sequencing of a single or small group of suspected genes was the sole means of mutation identification. The relatively low diagnostic yield tremendously increased with the current standard of next-generation sequencing (NGS). NGS sequences numerous genes in parallel, such as LCA panels testing about 20 genes and large IRD panels testing more than 100 genes. With increased detection rates, data filtering of true genetic mutations from population gene variants is first required. Parental testing and segregation analysis also help delineate unknown variants from causative mutations. Lastly, clinical correlation from IRD literature is necessary. Resources for vitreoretinal specialists to learn more about genetic testing, genetic counseling, and molecular diagnostic techniques and the laboratories conducting them are provided (Table 2).
TABLE 2
Informational Resources for Ophthalmologists and Vitreoretinal Specialists

**Diagnosis of IRDs**
- GeneReviews
- Clinical Gene Utility Cards
  Available for choroideremia, Usher syndrome, achromatopsia, and BEST1-related dystrophies.
- Reviews:
  - Hamel et al., 2006
  - Hamel et al., 2007

- Textbooks:
  - *Inherited Chorioretinal Dystrophies: A Textbook and Atlas*
  - *Genetics for Ophthalmologists*
  - *New Insights into Retinal Degenerative Diseases*
  - *Retinal Degenerative Diseases and Experimental Therapy*
  - *Principles and Practice of Clinical Electrophysiology of Vision*

- Understanding Genetics of IRDs, Molecular Genetic Analyses, and Labs Conducting These Analyses
  - Genetic Testing Registry (GTR)
    *Searchable database of labs performing molecular analyses.*
  - eyeGENE
    [https://nei.nih.gov/eyegene/doctors_eyegene](https://nei.nih.gov/eyegene/doctors_eyegene)
    *Biorepository linking patient phenotypic and genotypic data.*
  - EuroGenTest:
    *Information on the validity and utility of genetic testing.*
    *European labs conducting clinical NGS genetic testing.*
    *Information on NGS testing, genetic counseling guidelines, patient pamphlets on the process of molecular diagnostic testing.*

**Clinical Trials Information**
- ClinicalTrials.gov: [https://clinicaltrials.gov](https://clinicaltrials.gov)
- Orphanet: [http://www.orpha.net](http://www.orpha.net)
  *European clinical trials database*

IRDs = inherited retinal degenerations; NGS = next-generation sequencing

With emerging technologies in molecular diagnostics, gene delivery and editing tools, and diverse vision rescue strategies, the potential of gene therapy for treatment of IRDs continues to climb. The evolving role of vitreoretinal specialists will greatly contribute to this growing treatment pipeline. We hope to have provided a basis of understanding treatment strategies and molecular diagnoses as a starting point in patient education and management.
TABLE 3

Informational Resources for Patients

Understanding IRDs

- Foundation Fighting Blindness (FFB): http://www.blindness.org/newly-diagnosed
- Fighting Blindness: http://www.fightingblindness.ie/eye-conditions/
- American Foundation for the Blind: http://www.afb.org/info/living-with-vision-loss/eye-conditions/12
- Retina International: http://www.retina-international.org/eye-conditions/

Understanding Inheritance and Genetics of IRDs

- FFB: http://www.blindness.org/genetic-testing
- Fighting Blindness: http://www.fightingblindness.ie/eye-conditions/human-genetics-a-brief-insight/
- National Human Genome Research Institute: http://www.genome.gov/19016903

Clinical Trials Information

  General information on the process of participating in clinical trials
- NCRR – ResearchMatch: https://www.researchmatch.org/
  A user-friendly version of clinicaltrials.gov. Patients enroll and submit a profile to the registry, permitting researchers to contact them for trial participation
- ClinicalTrials.gov: https://clinicaltrials.gov

Clinical Trial Registries

- FFB and Choroideremia Research Foundation – MyRetinaTracker: https://www.myretinatracker.org
  Updates patients on relevant research and clinical trials. Clinicians may provide patients’ phenotypic data to aid in determining clinical trial eligibility.
- NCRR – ResearchMatch: https://www.researchmatch.org/
- Usher Syndrome Coalition: https://www.usher-registry.org/en
  Registry matching Usher patients to research studies and clinical trials recruiting patients.

IRD Specialists

- FFB: http://www.blindness.org/retinal-physicians

Support Groups

- RareShare: http://www.rareshare.org

IRDs = inherited retinal degenerations

REFERENCES


