

Testing Gene Therapy Treatment Options



Surveying the landscape of gene therapy trials for inherited retinal diseases.

BY BENJAMIN BAKALL, MD, PhD

Inherited retinal diseases (IRDs) are rare, blinding conditions caused by genetic variations. Although effective treatment strategies to arrest or reverse progression of these diseases have been difficult to achieve, this has begun to change as a result of the revolution in understanding of the human genome. Successful identification of the causative genes for IRDs has led to initiation of clinical trials for treatments with the potential to mitigate disease progression and possibly improve vision in patients with IRDs.

In December, the US FDA approved the first gene therapy for the treatment of patients with retinal dystrophy caused by biallelic mutations in the *RPE65* gene and with viable retinal cells as determined by their treating physician. This approval of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) will hopefully facilitate the approval process for other gene therapies using similar technology. This article focuses on the strategies used in several current and upcoming clinical trials on gene therapy for IRDs.

HOW WE APPROACH THE TREATMENT OF IRDs

Specific treatment for IRDs is dependent on the molecular disease mechanism for each condition and the stage of the disease. For recessive genetic diseases caused by loss of gene function, addition of the normal gene can be a sufficient treatment. IRDs with an autosomal dominant inheritance pattern may have a dominant negative effect, and a combined approach, with suppression of expression of the abnormal gene plus addition of a normal gene, may be required.

Certain IRDs are caused by mutations that alter the gene splicing and disrupt the coding sequence for the translated

protein. Gene editing with the novel technique known as *clustered regularly interspaced short palindromic repeats* (CRISPR) has great treatment potential.¹

The most common approach for retinal gene therapy, however, is delivery of the normal gene with a viral vector designed not to proliferate or cause cellular damage.

Viral Vectors

The adeno-associated virus (AAV) has high retinal affinity and tolerability and is the most widely used retinal gene therapy vector for genes up to about 5 kb in size.²

AT A GLANCE

- ▶ Specific treatment for IRDs is dependent on the molecular disease mechanism for each condition and the stage of the disease.
- ▶ Successful identification of the causative genes for IRDs has led to initiation of clinical trials for treatments with the potential to mitigate disease progression.
- ▶ The current standard of care for patients with IRDs is to recommend genetic testing, genetic counseling, and possible treatment or participation in a gene therapy treatment trial.

TABLE. GENE THERAPY CLINICAL TRIALS FOR INHERITED RETINA DISEASES*

DISEASE	GENE	VECTOR	DELIVERY	SPONSOR(S)
Phase 3 Complete, Approved by US FDA				
LCA and RP	<i>RPE65</i>	AAV	Subretinal	Spark Therapeutics
Current Clinical Trials				
Achromatopsia	<i>CNGA3</i>	AAV	Subretinal	AGTC, Tübingen Hospital
Achromatopsia	<i>CNGB3</i>	AAV	Subretinal	AGTC, MeiraGTx
Choroideremia	<i>CHM</i>	AAV	Subretinal	Spark Therapeutics, Nightstar Therapeutics, Tübingen Hospital
LCA	<i>CEP290</i>	N/A	Intravitreal	ProQR
LCA and RP	<i>RPE65</i>	AAV	Subretinal	MeiraGTx
RP	<i>MERTK</i>	AAV	Subretinal	King Khaled Eye Specialist Hospital
RP	<i>PDE6B</i>	AAV	Subretinal	Horama
RP (Optogenetic)	<i>Chr2</i>	AAV	Intravitreal	Allergan
RP (Optogenetic)	<i>ChrimsonR</i>	AAV	Intravitreal	GenSight Biologics
Stargardt disease	<i>ABCA4</i>	EIAV	Subretinal	Sanofi
Usher syndrome type 1	<i>MYO7A</i>	EIAV	Subretinal	Sanofi
X-linked RP	<i>RGPR</i>	AAV	Subretinal	AGTC, Nightstar Therapeutics, MeiraGTx
X-linked retinoschisis	<i>RS1</i>	AAV	Intravitreal	AGTC, NEI

* The most advanced completed, currently active, or soon-to-be-activated gene therapy treatment trials for retinal dystrophies registered in the online database clinicaltrials.gov.

Abbreviations: AAV, adeno-associated virus; AGTC, Applied Genetic Technologies Corporation; EIAV, equine infectious anemia virus; LCA, Leber congenital amaurosis; N/A, not applicable; NEI, National Eye Institute; RP, retinitis pigmentosa

Retinal gene therapies for larger genes, up to 9 kb, use the lentiviral equine infectious anemia virus (EIAV) vector.³ Two ongoing trials for relatively large genes, including the *ABCA4* gene for Stargardt disease and the *MYO7A* gene for Usher syndrome type 1, use the EIAV vector.

More than 75% of all identified retinal dystrophy genes are relatively

small and can fit into one of these viral vectors.⁴ To deliver the gene to the retina, the vector is injected either into the vitreous cavity or into the subretinal space after surgical vitrectomy to improve transfection of outer retinal cells. Options for delivering larger genes to the retina include a dual AAV vector system, with each vector containing half of the gene,⁵ or attaching

the gene to nanoparticles.

IRDs caused by genetic mutations altering the gene splicing can be treated with allele-specific oligonucleotides that normalize the gene expression. These RNA molecules are injected into the vitreous cavity without any vector. The latter strategy is used in patients with Leber congenital amaurosis (LCA) caused by the *CEP290* gene.

Most retinal gene therapy treatments to date require the patient to have viable remaining photoreceptor cells. Optogenetics is a disease gene-independent technology that can be used in conditions with significant photoreceptor loss. In this approach, the remaining retinal neurons are converted to photosensitive cells by expression of bacterial rhodopsin genes. In a trial sponsored by Allergan, channelrhodopsin is being transfected to retinal cells, and in another trial conducted by GenSight Biologics the ChrimsonR photopigment is used in combination with a portable medical device.

There are several completed, ongoing or upcoming clinical trials involving viral vectors for the treatment of IRDs (Table). The diseases targeted in these trials are discussed briefly below.

RPE65 Gene-Related Retinal Dystrophy

Mutations in the *RPE65* gene can cause LCA and, in some cases, retinitis pigmentosa (RP). The *RPE65* protein is an important visual cycle enzyme that contributes to the activation of the chromophore 11-cis-retinal.

After successful treatment of small and large animal models, including rodents and dogs,⁶ the first human trials of the therapy that eventually became voretigene were initiated in 2007. Multiple competing early-phase clinical trials used variations of AAV vector-based delivery of the *RPE65* gene to the subretinal space.⁷⁻¹³

A recent phase 3 trial demonstrated safety and efficacy of the treatment for the primary outcome, a novel standardized multiluminance mobility test of the ambulatory vision in different levels of light encountered in daily life.¹⁴ In addition, investigators observed significant improvement of light sensitivity and kinetic visual field testing after treatment. The traditional study outcome, visual acuity, which is dependent on cone photoreceptors, was improved, but the change did not reach statistical significance in this rod photoreceptor-mediated condition.

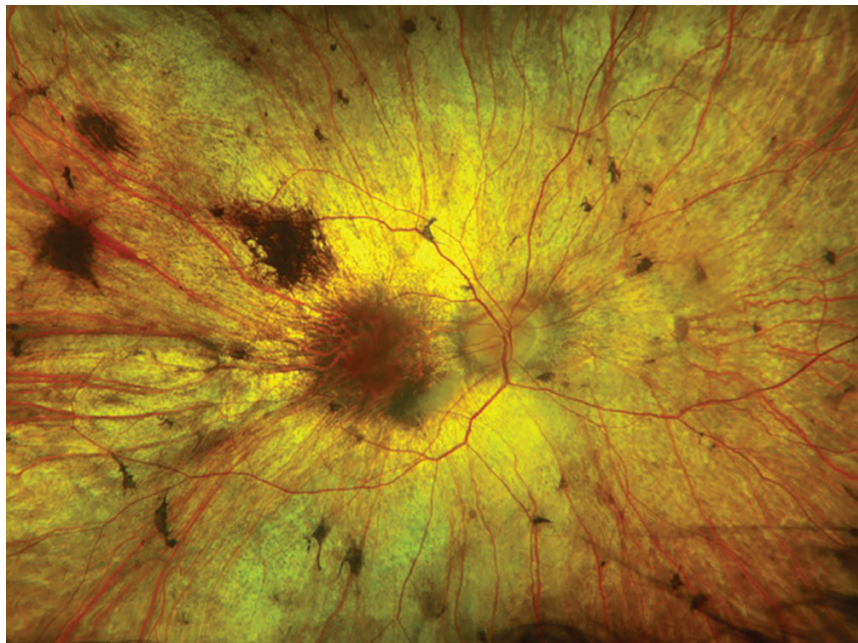


Figure 1. Fundus widefield photo of the right eye of a man with choroideremia caused by a hemizygous mutation in the *CHM* gene. There is extensive peripheral retinal dystrophy with preservation of the central macula and scattered areas in the periphery.

Treatment durability of at least 3 years has recently been reported for voretigene.¹⁵ Examples of reported visual improvements include patients seeing clouds in the sky for the first time and no longer requiring a white cane for ambulation.

Choroideremia

Progressive patchy chorioretinal dystrophy with night blindness is caused by mutations in the *CHM* gene, an X-linked condition, and mainly affects men (Figure 1).¹⁶ Early phase clinical trials indicate that visual acuity improved in treated individuals.¹⁷ The active competing clinical trials can be found in the Table.

Stargardt Disease

The most common macular dystrophy, with hallmarks of lipofuscin accumulation and macular atrophy, is autosomal recessive Stargardt disease. A current clinical trial is using subretinal injection of a lentiviral vector that was shown to express the *ABCA4* gene in a mouse model. The rationale for the trial is based on the success of this strategy in reducing lipofuscin in animal models.¹⁸

Retinitis Pigmentosa

The most common retinal dystrophy is RP, which can be caused by more than 60 different genes and which affects 1 in 3,000 individuals in the United States. RP can be nonsyndromic or syndromic, in which case other organs are affected. For example, hearing loss is present in patients with Usher syndrome. Multiple organs are often affected in patients with Bardet-Biedl syndrome. Current gene therapy trials target nonsyndromic RP genes, including the *RPGR* gene for X-linked RP (Figure 2).

For two genes causing autosomal recessive RP, a *PDE6B* gene trial is ongoing in France, and a trial for the *MERTK* gene has been performed in Saudi Arabia. Syndromic RP in Usher syndrome type 1, caused by the *MYO7A* gene, is currently being treated in another trial.

Achromatopsia

Severe light sensitivity and decreases in central vision and color vision are characteristics of achromatopsia, which is caused by mutations in specific cone photoreceptor

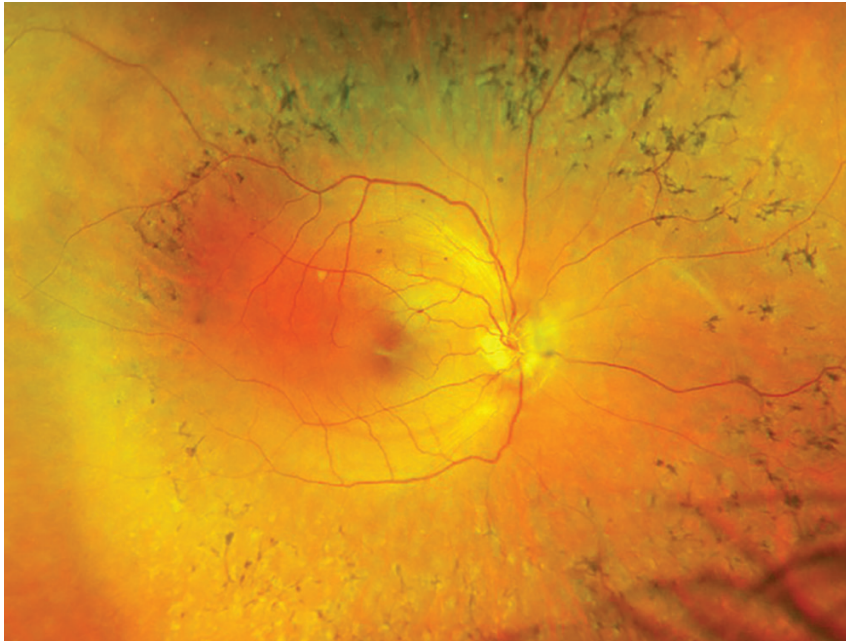


Figure 2. Fundus widefield photo of the right eye of a man with X-linked retinitis pigmentosa caused by the *RPGR* gene. The optic disc is tilted consistent with myopia, and the arterioles are attenuated. Retinal dystrophy and bone spicule-like pigmentation are shown in the midperiphery.



Figure 3. Fundus photo of the right eye of a boy with juvenile X-linked retinoschisis with a mutation in the *RS1* gene. The retinal examination shows radial cysts in the central macula and a metallic sheen in the periphery.

genes. Gene therapy targeting the *CNGA3* and *CNGB3* genes successfully improved vision in large animal models, leading the way to current human clinical trials.¹⁹

X-Linked Retinoschisis

X-linked juvenile retinoschisis, caused by variants in the *RS1* gene,

results in separation of the retinal layers in the central macula with peripheral schisis and increased risk of retinal detachment (Figure 3).²⁰ In two trials of competing therapies, AAV vector expressing the *RS1* gene is being delivered via intravitreal injection to reduce the risk of retinal detachment.

CHANGING STANDARDS AND OUTCOMES

Thanks to recent developments in treatments for retinal dystrophies, the new standard of care for patients with these diseases is to recommend genetic testing for an accurate diagnosis, to offer genetic counseling, and to consider treatment or patient participation in a gene therapy treatment trial. ■

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BENJAMIN BAKALL, MD, PHD

- Clinical Assistant Professor, University of Arizona College of Medicine, Phoenix, Arizona
- Retina specialist, Associated Retina Consultants, Phoenix, Arizona
- bbakall@gmail.com
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