

UPDATE ON GENE THERAPY FOR THE TREATMENT OF HEREDITARY RETINAL DISEASES

Retinal gene therapy is on the brink of clinical reality.

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Genetic defects in more than 200 known genes are associated with hereditary retinal disorders, and there are no approved treatments for most of these inherited disorders. Gene therapies being developed for many of these conditions may soon improve vision or slow disease progression in patients who, until now, have had limited or no therapeutic options.

In gene therapy, a functional copy of a gene is introduced into a patient's own cells to treat a genetic defect. Normal protein that is produced from a functional gene has the potential to correct the underlying cause of a disease and induce a long-lasting therapeutic effect. Engineered viruses, or viral vectors, are used to deliver genes into cells.

Viral vectors have been optimized for use as gene delivery vehicles by removing pathogenic elements and severely impairing the viruses' ability to replicate. Viruses used for this purpose include lentivirus, herpes virus, adenovirus, and adeno-associated virus (AAV).

AAV is particularly well suited for use in gene therapy and is straightforward to work with from a gene engineering perspective. AAV is a small, simple, nonenveloped virus with only two native genes, and vectors made with AAV have the capacity to carry gene sequences up to approximately 4,000 base pairs in length.¹ Gene delivery with AAV vectors does not alter a patient's native DNA. AAV vectors have no viral genes remaining, reducing the possibility that viral genes will cause an adverse event. AAV usually elicits a weak immune response and has not been shown to cause disease in humans.¹

This article provides a review of gene therapies being investigated for the treatment of various hereditary retinal diseases. The status of gene therapies for inherited retinal diseases is depicted in the Figure on page 67.

GENE THERAPIES FOR THE RETINA

Leber Congenital Amaurosis

Leber congenital amaurosis (LCA) is an inherited, early-onset retinal dystrophy caused by mutations in any of at

least 16 genes. Approximately 6% of LCA cases are caused by mutations in the *RPE65* gene and are classified as LCA type 2 (LCA2).^{2,3} *RPE65* encodes an enzyme required to reset the phototransduction cascade, converting *trans*-retinal back to *cis*-retinal after photoisomerization.

Multiple clinical trials have evaluated the safety, tolerability, and efficacy of a single subretinal injection of an AAV vector expressing human *RPE65* in patients with LCA2. Four phase 1/2 trials have supported the safety and therapeutic potential of AAV-*RPE65* gene therapy, and results from a completed phase 3 trial (NCT00999609) show improvements in functional vision and light sensitivity without adverse events related to the AAV vector or a deleterious immune response.⁴⁻⁸

X-linked Retinoschisis

X-linked retinoschisis (XLRS) is an inherited retinal disease characterized by schisis, or splitting, of the retinal layers and reduced visual acuity. A hallmark of XLRS is selective reduced b-wave amplitude on scotopic bright-flash combined rod-cone electroretinogram, which often



AT A GLANCE

- In gene therapy, engineered viruses, or viral vectors, are used to deliver a functional copy of a gene into a patient's cells to treat a genetic defect.
- Adeno-associated virus vectors have no viral genes remaining, reducing the possibility that viral genes will cause an adverse event.
- The first commercially available gene therapy product was approved in Europe in 2012, and the FDA is expected to review multiple gene therapies for potential approval this year, including the first candidate for treatment of a retinal disease.

	Sponsor Registry Number	Single or multicenter	Trial phase	Intraocular Delivery	Capsid	Promoter and functional gene	Current status of trial		
						promoter functional gene	enrolling	trial ongoing	trial complete
LCA2	U. College London NCT00643747		1/2		AAV-2	RPE65 RPE65			
	Spark Therapeutics NCT00999609		3		AAV-2	CBA RPE65			
	U. Pennsylvania, NEI NCT00481546		1		AAV-2	CBA RPE65			
	Spark Therapeutics NCT00516477		1		AAV-2	CBA RPE65			
	AGTC NCT00749957		1/2		AAV-2	CBA RPE65			
XLRS	AGTC NCT02416622		1/2		AAV-2YF	CBA RS1			
	NEI NCT02317887		1/2		AAV-8	RS1 RS1			
ACHM	B3 AGTC NCT02599922		1/2		AAV-2YF	PR1.7 CNGB3			
	A3 U. Tübingen, LMU Munich NCT02610582		1/2		AAV-8	Arr3 CNGA3			
	AGTC NCT02935517		1/2		AAV-2YF	PR1.7 CNGA3			
Stargardt	Sanofi NCT01367444		1/2			CMV ABCA4			
Usher 1B	Sanofi NCT01505062		1/2			CMV MYO7A			
Choroideremia	U. Oxford (NightstaRx) NCT01461213		1/2		AAV-2	CBA CHM			
	U. Alberta (NightstaRx) NCT02077361		1/2		AAV-2	CBA CHM			
	Spark Therapeutics NCT02341807		1/2		AAV-2	CBA CHM			
	Bascom Palmer (NightstaRx) NCT02553135		2		AAV-2	CBA CHM			
	U. Tübingen NCT02671539		2		AAV-2	CBA CHM			
	U. Oxford (NightstaRx) NCT02407678		2		AAV-2	CBA CHM			
LHON	Huazhong U. NCT01267422		not listed		AAV-2	CMV ND4			
	GenSight Biologics NCT02064569		1/2		AAV-2	CMV ND4			
	NEI, Bascom Palmer NCT02161380		1		AAV-2	smCBA ND4			
	GenSight Biologics NCT02652780		3		AAV-2	CMV ND4			
Optogenetics	RetroSense Therapeutics NCT02556736		1		AAV-2	CBA Chr2			

Figure. Snapshot of clinical trials of gene therapy for hereditary retinal diseases, in progress and completed. Key features and status of all active or completed gene therapy clinical trials, including trials that are enrolling but have not initiated treatment. Abbreviations: ACHM, achromatopsia; LCA2, Leber congenital amaurosis type 2; LHON, Leber hereditary optic neuropathy; XLRS, X-linked retinoschisis

results in a “negative” electroretinogram (b-wave to a-wave amplitude ratio of less than 1).⁹

XLR5 is caused by mutations in the *RS1* gene, which encodes the retinoschisin protein.¹⁰ Retinoschisin is expressed and secreted primarily from photoreceptor and bipolar cells, and the monomeric protein forms octamers that bind strongly and specifically to the surface of most cell types in the retina. Mutated forms of retinoschisin are unable to bind, which results in splitting of the nerve fiber layer, the inner nuclear layer, the outer nuclear layer, and the outer plexiform layer.

Preclinical studies in a knockout mouse model and safety findings in rabbits and nonhuman primates have supported the advancement of gene therapy product candidates for XLR5 to clinical trials.^{11–15} Two phase 1/2 clinical trials are evaluating the safety and tolerability of an intravitreal injection of an AAV vector expressing human *RS1* in patients with XLR5. Applied Genetic Technologies Corporation (AGTC) is conducting a multicenter, open-label, two-stage dose-escalation trial (NCT02416622). The second stage will evaluate a maximum tolerated dose determined during the first stage. The vector evaluated in this trial contains a functional *RS1* gene coupled to a strong ubiquitous promoter and packaged into an AAV capsid that has been optimized for enhanced delivery to photoreceptors (AAV2tYF). The National Eye Institute (NEI) is conducting a single-center, open-label, single-stage dose-escalation trial (NCT02317887). The vector evaluated in this trial contains a functional *RS1* gene controlled by the *RS1* promoter and packaged into an AAV8 capsid. Both trials are active, and enrollment is ongoing.

Achromatopsia

Achromatopsia primarily affects the cone photoreceptors and is characterized by severe sensitivity to light, reduced visual acuity, and loss of color discrimination. Achromatopsia is caused by mutations in any of at least six genes identified to date, all of which are involved in phototransduction. About 75% of achromatopsia cases are caused by mutations in either the *CNGB3* or *CNGA3* genes, which encode subunits of the cyclic nucleotide-gated ion channel that depolarizes or hyperpolarizes the photoreceptor membrane as part of the phototransduction cascade.^{16,17}

For *CNGB3* achromatopsia, preclinical studies in mouse and dog models and safety findings in mice and nonhuman primates have led to *CNGB3* gene therapy clinical trials.^{18–21} AGTC is conducting a phase 1/2 open-label, two-stage dose-escalation trial (NCT02599922) to evaluate the safety and tolerability of a subretinal injection of an AAV vector expressing human *CNGB3* in patients with *CNGB3* achromatopsia. The second stage will evaluate a maximum tolerated dose determined during the first stage.

For *CNGA3* achromatopsia, preclinical studies in mouse and natural occurring sheep models have supported the advancement to *CNGA3* gene therapy clinical trials.^{22–24} Two

trials, one active and one planned, will evaluate the safety and tolerability of a subretinal injection of an AAV vector expressing human *CNGA3*.

University Hospital Tübingen and Ludwig Maximilian University of Munich are conducting a phase 1/2 single-center, open-label, single-stage dose-escalation trial (NCT02610582). The vector used in this trial contains a functional *CNGA3* gene packaged into an AAV8 capsid.

AGTC is planning a phase 1/2 multicenter, open-label, two-stage dose-escalation trial (NCT02935517). The second stage will evaluate a maximum tolerated dose determined during the first stage. The vector evaluated in this AGTC trial will contain a functional *CNGA3* gene controlled by a promoter (PR1.7) that was engineered to drive robust and specific expression in all three types of cone photoreceptors.²⁵ The functional *CNGA3* gene with PR1.7 promoter is packaged into an AAV2tYF capsid.

X-linked Retinitis Pigmentosa

Roughly 10% to 20% of retinitis pigmentosa (RP) cases are X-linked, and more than 70% of X-linked cases are caused by mutations in the *RPGR* gene.^{26–29} *RPGR* X-linked RP (XLRP) is one of the most severe forms of RP, characterized by early onset of night blindness and rapid progressive peripheral visual loss, leading in most cases, to near total blindness by middle age.

The *RPGR* gene encodes a protein required for the transport of proteins along the cilium that connects the inner and outer segments of photoreceptors. About 60% of *RPGR* mutations occur in a unique 3 prime (3') region of the *RPGR* gene called ORF15.³⁰

Preclinical findings from dog models of XLRP have favored the advancement of *RPGR* gene therapy clinical trials. Pending the results of additional preclinical studies, AGTC has reported plans to conduct a phase 1/2 multicenter, open-label, two-stage dose-escalation trial to evaluate the safety and tolerability of a subretinal injection of an AAV vector expressing human *RPGR*.³¹

Stargardt Disease

Stargardt disease is an inherited macular dystrophy characterized by the presence of yellow-white flecks in the perifoveal region and macular atrophy resulting in reduced visual acuity that may begin in late childhood. Stargardt disease is caused by mutations in the *ABCA4* gene, which encodes a protein transporter required to clear excess all-*trans*-retinal after photoexcitation.³² In the absence of clearance, all-*trans*-retinal will accumulate and form deposits in photoreceptors and retinal pigment epithelium (RPE) cells.

Preclinical studies in a knockout mouse model and safety findings in rabbits and nonhuman primates have led to gene therapy trials.^{33,34} Sanofi is conducting a phase 1/2 open-label dose-escalation trial (NCT01367444) to evaluate the safety and tolerability of a subretinal injection of a lentiviral vector

TAKING OPTOGENETICS A STEP FURTHER

Recently Applied Genetic Technologies Corporation (AGTC) and Bionic Sight announced a strategic collaboration to develop a new optogenetic therapy that leverages AGTC's experience in gene therapy and ophthalmology and Bionic Sight's neuroprosthetic device and algorithm for retinal coding. AGTC president and CEO Sue Washer spoke with *Retina Today* to better explain the concept of optogenetics and to comment on the collaboration.

Ms. Washer explained that optogenetics is the use of gene therapy to deliver a unique protein that can be activated with a light signal to the eye.

"This is important in ophthalmology because some people with degenerative diseases lose their photoreceptors, which are cells that recognize light and turn it into an electrical signal that the brain understands," Ms. Washer said. "Without photoreceptors, your eye cannot transmit the signals that the brain uses to create visual images." She noted that optogenetics delivers genes to other, nonphotoreceptor cells in the eye and makes them light-sensitive, allowing signaling to the brain to take place even in the absence of functional photoreceptors.

Where does Bionic Sight enter the equation? Ms. Washer said that preclinical models have shown that the combination of making cells light-sensitive and using the mathematical algorithm in Bionic Sight's device results in activation of the new light-sensitive proteins in a way that allows the brain to understand images more completely.¹ The device and the gene therapy work together. "If you just had the device and no light-sensitive cells there would be no vision, and if you just had the

light-sensitive cells but no device you might have some vision, but it would not be as clear and comprehensible to the brain," Ms. Washer noted. "The two components working together are important for providing patients with improved outcomes."

What is the current status of this innovation? Ms. Washer said that Bionic Sight's device will need to be evolved because it is currently being tested as a prototype. "In parallel to developing the gene therapy, or optogenetics, portion, [AGTC] will be working with Bionic Sight in transforming the prototype into something more user-friendly." As far as what patient groups this therapy would target, Ms. Washer said, "It is agnostic to any underlying cause of visual problems; however, we are going to begin the initial safety and efficacy work in patients with advanced retinitis pigmentosa."

Basic groundwork such as initial toxicology and biodistribution studies, a phase 1 safety trial in humans, and planning how to iterate the device prototype still must be completed, but Ms. Washer said all of those activities are work with which both companies are familiar. Research led by Sheila Nirenberg, PhD, founder of Bionic Sight, has demonstrated in an in-vitro model that the company's retinal device can nearly replicate the visual firing pattern normally created by photoreceptor cells in creating the electrical signals the brain uses to recognize an image.

According to Ms. Washer, AGTC and Bionic Sight plan to file an investigational new drug application for the combination treatment program in 2018.

1. Nirenberg S, Pandarinath C. Retinal prosthetic strategy with the capacity to restore normal vision. *Proc Natl Acad Sci USA*. 2012;109(37):15012-15017.

based on an equine infectious anemia virus (EIAV) expressing human *ABCA4* in patients with Stargardt disease.

Usher Syndrome Type 1B

Usher syndrome type 1 is associated with profound congenital deafness and early-onset retinitis pigmentosa. More than half of Usher syndrome cases are type 1B and are caused by mutations in the *MYO7A* gene.³⁵⁻³⁷ The *MYO7A* gene encodes a myosin motor that transports molecules along the actin cytoskeleton of cells in the retina and inner ear.

Based on preclinical studies in a mouse model,³⁸ Sanofi is conducting a phase 1/2 open-label dose-escalation trial (NCT01505062) to evaluate the safety and tolerability of a subretinal injection of an EIAV-based lentiviral vector expressing human *MYO7A*.

Choroideremia

Choroideremia is an X-linked retinal disorder caused by mutations in the *CHM* gene, characterized by atrophy of the choriocapillaris and RPE leading to progressive constriction

of vision and eventual total blindness. *CHM* encodes Rab escort protein 1, which is required for the intracellular trafficking of proteins and organelles.³⁹

Preclinical findings in a knockout mouse model have led to clinical trials.⁴⁰ Six clinical trials are under way or complete, each evaluating the safety, tolerability, and therapeutic potential of a subretinal injection of an AAV vector expressing human *CHM*.

The trial that is complete was a phase 1/2 multicenter, open-label, dose-escalation trial led by the University of Oxford (NCT01461213); a further ongoing phase 2 clinical trial (NCT02407678) at the same institution is planned. Long-term results with follow-up to 3.5 years have demonstrated efficacy.⁴¹

Other trials are ongoing with completed enrollment: a phase 1/2 single-center, open-label, single-arm study at the University of Alberta (NCT02077361); a phase 1/2 multicenter, open-label, dose-escalation trial sponsored by Spark Therapeutics (NCT02341807); a phase 2 single-center, open-label, single-arm study at Bascom Palmer Eye Institute (NCT02553135); and a phase 2 single-center, open-label, single-arm trial at University Hospital Tübingen (NCT02671539).

Leber Hereditary Optic Neuropathy

Leber hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease associated with central vision loss and characterized by degenerated retinal ganglion cells. More than 90% of cases are caused by mutations in one of three mitochondrial genes—*ND1*, *ND4*, and *ND6*—each of which is required for the process of oxidative phosphorylation that converts oxygen and simple sugars into energy for the cell.^{42,43} More than half of all LHON cases are caused by the same single base-pair substitution in the *ND4* gene.^{42,43}

Fueled by favorable preclinical findings from studies in an *ND4* mouse model,⁴⁴ trials are evaluating the safety, tolerability, and therapeutic potential of an intravitreal injection of an AAV vector expressing human *ND4* in patients with *ND4* LHON.

Two trials have been completed: a phase 1/2 single-center, open-label, dose-escalation trial sponsored by GenSight Biologics (NCT02064569) and a single-center, open-label trial at Huazhong University (NCT01267422). Results from the latter trial showed that *ND4* gene therapy for LHON was safe and suggested visual improvement in some patients.⁴⁵

Two additional trials are active with ongoing enrollment, including a phase 3 multicenter, double-masked, controlled trial by GenSight Biologics (NCT02652780) and a phase 1 single-center, open-label, dose-escalation trial supported by the NEI and conducted at Bascom Palmer Eye Institute (NCT02161380). Initial results from the latter study reported no serious adverse events in the first five patients.⁴⁶

Blue Cone Monochromacy

Blue cone monochromacy (BCM) is an inherited X-linked retinal disorder characterized by severely abnormal or absent long- and medium-wavelength cone function but normal short-wavelength cone function. BCM is caused by mutations in or around the X-linked *OPN1LW/OPN1MW* gene cluster that encodes the L and M opsin proteins, respectively.⁴⁷ Clinical manifestations of BCM are similar to achromatopsia, including severe light sensitivity, reduced visual acuity, and loss of color discrimination.

Imaging studies suggest that cone photoreceptors persist in the central retinas of patients with BCM, supporting the potential value of gene therapy.⁴⁸ Preclinical studies of gene therapy for BCM and other color vision disorders are ongoing.

OPTOGENETIC THERAPY

Optogenetic therapy is an emerging gene therapy-based technology in which light sensitivity is introduced into cells that do not normally detect or respond to light. Current efforts in the retina field are focused on delivering the light-sensitive green algae protein channelrhodopsin 2 (ChR2) into retinal ganglion cells.⁴⁹ Optogenetic therapy has the potential to treat patients with late-stage retinal dystrophies, when most photoreceptors have been irreparably damaged or lost, regardless of any specific disease-causing mutations.

One clinical trial is evaluating the safety and tolerability of an AAV vector expressing ChR2, administered by intravitreal injection. RetroSense Therapeutics and the Retina Foundation of the Southwest are conducting a phase 1/2 single-center, open-label, dose-escalation trial of this therapeutic approach in patients with advanced RP (NCT02556736).

See “Taking Optogenetics a Step Further” on page 69 for additional information on optogenetic therapy.

FUTURE OUTLOOK

Gene therapy has never been closer to becoming a reality for patients. The first commercially available gene therapy product, Glybera (uniQure), for the treatment of patients with familial lipoprotein lipase disease who experience severe or multiple pancreatitis attacks, was approved by the European Medicines Agency (EMA) in 2012.⁵⁰ In May 2016, the EMA approved Strimvelis (GlaxoSmithKline), an ex-vivo stem cell gene therapy for the treatment of patients with the rare but debilitating immunodeficiency ADA-SCID (severe combined immunodeficiency due to adenosine deaminase deficiency).⁵¹ The US Food and Drug Administration is expected to review multiple gene therapies for potential approval this year, including the first candidate for the treatment of a retinal disease. The development of gene therapy is rapidly accelerating and we are racing toward a future in which we will be able to improve or maintain sight in more patients than ever before. ■

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