THE LATEST IN GENE THERAPY CLINICAL TRIALS FOR IRD

Many investigational drugs for inherited retinal disease have made it to phase 2; a few are even in phase 3.

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The number of clinical trials aiming to preserve or restore vision for patients with an inherited retinal disease (IRD) has exploded in recent years.[1] Identification of disease-causing gene mutations is now part of routine clinical care, thanks to the low cost and widespread availability of gene panel testing. As more therapeutic interventions are developed, treatment opportunities should be included in our standard approach to the care of patients with an IRD.

In this article, we highlight some of the latest ongoing phase 2 and 3 gene therapy trials to help retina specialists provide their patients with every available option (Table).

RETINITIS PIGMENTOSA

Botaretigene sparoparvovec (MGT009 [formerly AAV-RPGR], MeiraGTx/Janssen) targets loss of function mutations in the *retinitis pigmentosa (RP) GTPase regulator* (*RPGR*) gene. The gene therapy relies on a stable deletion mutant of the *RPGR* isoform that is missing 126 amino acids but is sufficient to rescue the *RPGR* gene function.[2] Expression is driven by the human rhodopsin (RHO) kinase promoter, and it is packaged into the adeno-associated viral (AAV) 2/5 vector serotype.

A phase 1/2 trial (NCT03252847) compared subretinal injection of low, intermediate, and high doses in patients with X-linked RP (XLRP).[3] The overall safety profile was favorable, and patients in the low- and intermediate-dose cohorts demonstrated improved retinal sensitivity and functional vision at 1 year. Patients receiving the high dose had a decrease in retinal sensitivity, and two of the three patients had inflammatory responses that were steroid responsive. The phase 3 LUMEOS (NCT04671433) trial is currently underway and actively recruiting to enroll 96 patients.

Laruparetigene zosaparvovec (AGTC-501, Beacon Therapeutics) also aims to restore *RPGR* gene function in patients with XLRP and consists of a cone-specific PR1.7 promoter driving expression of a codon-optimized human *RPGR* coding sequence. It is packaged in an AAV2 capsid containing three tyrosine-to-phenylalanine mutations that improve transduction efficiency.[4] The phase 1/2 SKYLINE study (NCT03316560) included 29 patients with XLRP who received one subretinal injection, with the first nine treated in the periphery to test for safety and the subsequent patients treated centrally.[5] The microperimetry sensitivity improved at 1 year in all centrally dosed patients. A phase 2/3 study, VISTA (NCT04850118), is planned with randomization to low- or high-dose AGTC-501 or untreated control with an estimated enrollment of 63 patients.

Cotoretigene toliparvovec (BIIB112, Biogen) is designed to rescue *RPGR* gene function using an RHO kinase promoter to drive full-length human codon-optimized *RPGR* expression. Viral particles are generated using AAV8 capsids and delivered by subretinal injection. A phase 1/2 dose-escalation study, XIRIUS (NCT03116113), did not meet the primary endpoint of ≥ 7 dB improvement from baseline at five or more central microperimetry points at 1 year.[6] However, positive trends were observed across several secondary endpoints, including low luminance visual acuity. Patients

AT A GLANCE

- Several therapies for X-linked retinitis pigmentosa are in phase 2/3 or phase 3 trials, including MGT009 (MeiraGTx/Janssen), cotoretigene toliparvovec (BIIB112, Biogen), and laruparetigene zosaparvovec (AGTC-501, Beacon Therapeutics).
- The phase 2/3 trial of QR-421a (ProQR Therapeutics) for the treatment of patients with Usher syndrome with advanced vision loss is active but not recruiting.
- Optogenetic approaches can be used to make bipolar or retinal ganglion cells sensitive to light, bypassing the need for functional photoreceptor cells.

exiting the trial have been offered enrollment in a separate phase 3 trial, SOLSTICE (NCT03584165), that will monitor long-term outcomes over a 5-year period.

4D-125 (4D Molecular Therapeutics) is in a phase 1/2 trial, EXCEL (NCT04517149), for the treatment of patients with XLRP. This gene therapy uses a proprietary AAV capsid variant developed by the company, R100, to deliver a functional copy of the *RPGR* gene to the photoreceptors. In phase 1, patients were treated with one of two doses: 3E11 vg/eye or 1E12 vg/eye; in the phase 2 expansion portion, patients are treated with the latter dose. The therapy received FDA fast track designation, and the trial is active.[7]

TABLE. GENE THERAPY TRIALS FOR INHERITED RETINAL DISEASES

Gene	Mutation	Treatment (Sponsor)	Pharmacologic Agent	Mechanism	Delivery	Trial ID	Phase	Primary Completion
Leber Congenital Amaurosis								
GUCY2D	Loss of function	ATSN-101 (Atsena Therapeutics)	AAV8-GRK1-GUCY2D	Restores functional protein	Subretinal	NCT03920007	1/2	May 2023
CEP290	c.2991+1655A>G	AGN-151587 (Allergan)	AAV5-GRK1-Cas9	Genome editing	Subretinal	NCT03872479 (BRILLIANCE)	1/2	May 2025
		EDIT-101 (Allergan/Editas)	EDIT-101	Eliminates mutation		NCT03872479		
Choroideremia								
CHM	Loss of function	4D-110 (4D Molecular Therapeutics)	AAV.R100-hcoREP1	Restores functional protein	Subretinal	NCT04483440 (CHORUS)	1/2	June 2024
X-Linked Retinitis Pigmentosa (RP)								
RPGR	Loss of function	Botaretigene sparoparvovec (MeiraGTx/Janssen)	AAV5-RhoK-RGPRdel	Restores functional protein	Subretinal	NCT04671433 (LUMEOS)	3	March 2024
		Laruparetigene zosaparvovec (Beacon Therapeutics)	rAAV2tYF-GRK1-RPGR			NCT04850118 (VISTA)	2/3	January 2024
		4D-125 (4D Molecular Therapeutics)	AAV.R100-hcoRGPR			NCT04517149 (EXCEL)	1/2	June 2026
		BIIB112 (Biogen)	AAV8-RPGR			NCT03584165 (SOLSTICE)	3	June 2026
RP								
RHO	P23H	QR-1123 (ProQR Therapeutics)	antisense oligo	RNaseH mediated degradation	Intravitreal	NCT04123626 (AURORA)	1/2	June 2022
PDE6b	Loss of function	CTx-PDE6b (Coave Therapeutics)	AAV2/5-hPDE6B	Restores functional protein	Subretinal	NCT03328130	1/2	January 2023
Leber Hereditary Optic Neuropathy								
NADH dehydrogenase	G11778A ND4	GS010 (Gensight Biologics)	rAAV2/2-ND4	Restores functional protein	Intravitreal	NCT03293524	3	June 2024
Usher Syndrome								
USH2A	Exon 13	QR-421a (ProQR Therapeutics)	antisense oligo	Induces exon skipping	Intravitreal	NCT05158296 (SIRIUS)	2/3	August 2022
Optogenetics								
Non-genotype specific (RP patients for trial)		BS01 (Bionic Sight)	AAV2-CAG-ChronosFP	RGC stimulus w/ headset pattern transformation	Intravitreal	NCT04278131	1/2	December 2024
		Sonpiretigene isteparvovec (Nanoscope Therapeutics)	AAV2-mGluR6-MCO1	Direct bipolar cell stimulation		NCT04945772 (RESTORE)	2	March 2023
		GS030 (Gensight Biologics)	rAAV2.7m8-CAG-ChrimsonR-tdTomato			NCT03326336 (PIONEER)	1/2	December 2022
Non-genotype specific (Stargardt patients for trial)		Sonpiretigene isteparvovec (Nanoscope Therapeutics)	AAV2-mGluR6-MCO1			NCT05417126 (STARLIGHT)	2	July 2023

AAV2/5-hPDE6B (CTx-PDE6b, Coave Therapeutics) is designed to deliver a functional copy of the *PDE6b* gene to the subretinal space to induce transgene expression and synthesis of functional PDE6b proteins in photoreceptive rods and cones. The ongoing phase 1/2 trial (NCT03328130) has enrolled 17 patients with *PDE6b*-associated RP randomly assigned to one of four dosing cohorts. The preliminary 12-month data suggest the drug is well tolerated, and a subgroup of six patients with early disease treated with the high dose experienced positive efficacy; based on microperimetry, the patients showed improved retinal sensitivity in treated eyes compared with untreated eyes.[8]

QR-1123 (ProQR Therapeutics) is an antisense oligonucleotide that reduces the expression of the P23H protein selectively while preserving the expression of the wild-type RHO protein. The phase 1/2 trial (NCT04123626) includes up to eight single doses and a repeat dose cohort in a total of 11 patients with autosomal dominant RP. Treated patients will be followed for 12 months to evaluate safety, tolerability, and efficacy. The trial is active but not recruiting.

LEBER CONGENITAL AMAUROSIS

SAR439483 (ATSN-101, Atsena Therapeutics) is a gene therapy under investigation in a phase 1/2 dose escalation study for the treatment of *GUCY2D*-associated Leber congenital amaurosis (LCA) 1. Preliminary 6-month data, presented at the 2023 Association for Research in Vision and Ophthalmology meeting, showed that the nine patients who received the high dose had a mean change in retinal sensitivity from baseline that was significantly higher than the change noted in untreated eyes at day 28 and beyond. Two of those high-dose patients demonstrated an improvement in corrected visual acuity greater than 0.3 logMAR (no treated eyes had a decrease in BCVA).[9]

EDIT-101 (AGN-151587, Allergan/Editas) targets the heterozygous or homozygous mutation involving c.2991+1655A>G in intron 26 in the *CEP290* gene implicated in LCA10. The phase 1/2 trial (NCT03872479) is investigating a single subretinal injection of one of five doses in patients with LCA10. The trial is fully enrolled with 34 patients.

USHER SYNDROME

QR-421a (ProQR Therapeutics) is intended to treat patients with Usher syndrome and nonsyndromic RP due to mutations in exon 13 of the *USH2A* gene.[10] A phase 1/2 trial, STELLAR (NCT05176717), enrolled 20 patients who received intravitreal injections of one of three dose levels.[11]

No serious adverse events or ocular inflammation were reported, although one patient had worsening of preexisting cystoid macular edema. Efficacy endpoints demonstrated improved visual acuity with a mean benefit of 6 letters at 6 months after a single injection and total retinal sensitivity improvement of up to 40 dB. The phase 2/3 SIRIUS trial (NCT05158296) for patients with advanced vision loss (baseline VA < 20/40) includes administration of QR-421a at baseline, 3 months, and every 6 months thereafter with 18 months of follow-up.

X-LINKED RETINOSCHISIS

Atsena Therapeutics recently received FDA clearance for its investigational new drug application for a phase 1/2 trial of **ATSN-201** for the treatment of X-linked retinoschisis. The gene therapy uses an AAV.SPR capsid to deliver *RS1* to photoreceptors in the central retina/fovea. The open-label, dose-escalation trial is evaluating the subretinal injection of ATSN-201 in male patients with X-linked retinoschisis caused by pathogenic or likely pathogenic mutations in *RS1*.[12]

LEBER HEREDITARY OPTIC NEUROPATHY

Lenadogene nolparvovec (Lumevoq, GenSight Biologics) uses a mitochondrial targeting sequence to allow for proper expression of a missing or mutated mitochondrial gene—*NADH dehydrogenase*, in the case of study patients with Leber hereditary optic neuropathy.[13]

The company released favorable topline data from its phase 3 REFLECT trial (NCT03293524) 3 years post-treatment. Of the patients who received bilateral intravitreal injections of the study drug, 73% experienced a clinically meaningful improvement of at least -0.3 LogMAR (+15 ETDRS letters) relative to their observed nadir (worst BCVA recorded from baseline).[13] The treatment was well tolerated with the main ocular adverse event being intraocular inflammation that was responsive to treatment.[14]

CHOROIDEREMIA

4D-110 (4D Molecular Therapeutics) is currently under investigation in a phase 1/2 trial (NCT04483440) for the treatment of patients with choroideremia related to mutations in the *CHM* gene. The therapy uses the intravitreal R100 vector to deliver the product to the retina, in the hopes that it will lead to transgene expression in all retinal layers and regions after a single dose. The trial is fully enrolled with 13 patients and is expecting preliminary data in June 2024.[15]

OPTOGENETIC APPROACHES

Optogenetics is the use of exogenous photosensitive proteins (opsins) to enable rapid and precise manipulation of neuronal activity in response to light stimulation.[16] Optogenetic approaches can be used to make bipolar or retinal ganglion cells sensitive to light, bypassing the need for functional photoreceptor cells. Thus, any IRD that causes photoreceptor death or dysfunction while sparing other retinal neurons should theoretically respond to this therapeutic strategy. Several companies have started clinical trials to determine if opsins can restore some level of vision in patients with advanced RP and Stargardt disease.

Sonpiretigene isteparvovec (MCO-010, Nanoscope Therapeutics) targets opsin expression to bipolar cells. It relies on the mGluR6 promoter-enhancer, which is active in ON bipolar cells, to drive expression of multi-characteristic opsin. This therapy is designed to be sufficiently active at ambient light levels, so that no specialized hardware is required to project images to the retina.[17] A phase 1/2 clinical trial (NCT04919473) recruited 12 participants with advanced RP and demonstrated safety of a single intravitreal injection of sonpiretigene isteparvovec.[18] Nine of 11 patients demonstrated 2 luminance level improvements in vision-guided mobility or a 0.3 logMAR gain in visual acuity. A separate phase 2 trial, RESTORE (NCT04945772), demonstrated similar improvements. Vision-guided mobility, shape discrimination, and visual acuity gains were evident in 14 of 18 treated patients compared with three of nine patients receiving a placebo. Another phase 2 trial, STARLIGHT (NCT05417126), is investigating the efficacy of sonpiretigene isteparvovec for Stargardt disease.

GS030 (Gensight Biologics) combines an AAV2-based gene therapy with the use of light-stimulating goggles for the treatment of end-stage RP. The phase 1/2 PIONEER (NCT03326336) trial is evaluating the safety and efficacy of therapy in nine patients who received a single injection of one of three GS030 doses, followed by training with the goggles 8 weeks after injection. Preliminary data of patients treated with the highest dose suggest that patients with light perception vision could locate and count objects 1 year after treatment. The trial will continue through 4 years of follow-up. An extension study is planned to recruit patients to be treated with the highest dose of GS030.[19]

BS01 (Bionic Sight) is a recombinant AAV vector that expresses an enhanced light-sensitive channelrhodopsin gene for the treatment of RP. The phase 1/2 dose-escalation trial (NCT04278131) is recruiting 20 patients with RP who will be randomly treated with one of four doses. Interim data suggest that the top four responders who received the highest dose have gained the ability to recognize shapes and objects, according to a company release. The patients' success rate for identifying objects was equivalent to guessing at baseline (25% with four choices) and ranged between 80% and 100% after treatment. The therapy pairs a one-time treatment with BS01 with the use of a device that sends signals to the light-sensitive ganglion cells.[20]

CHALLENGES AHEAD

Researchers have made remarkable progress, although several important challenges must be overcome to provide effective gene therapies. First, researchers must define which subset of viral serotypes and promoters are most effective for stable gene expression in particular retinal neurons. Second, regulators should consider streamlining the regulatory framework so that various AAV gene delivery platforms can be adapted to deliver custom treatments for rare mutations that are not present in enough patients to support clinical trials. Third, although the evidence of visual improvement has been inconclusive in some trials, intervention earlier in the course of retinal degeneration may prove more successful for the same or similar treatments. We are hopeful that these challenges will be met with the same level of commitment and enthusiasm that has put our field at the forefront of innovation in gene therapy. ■

1. Fenner BJ, Tan TE, Barathi AV, et al. Gene-based therapeutics for inherited retinal diseases. *Front Genet*. 2022;12:794805.
2. Pawlyk BS, Bulgakov OV, Sun X, et al. Photoreceptor rescue by an abbreviated human RPGR gene in a murine model of X-linked retinitis pigmentosa. *Gene Ther*. 2016;23(2):196-204.
3. MeiraGTx announces positive top-line data from the MGT009 phase 1/2 clinical study demonstrating safety and improvement in multiple domains of vision in x-linked retinitis pigmentosa patients treated with botaretigene sparoparvovec (AAV-RPGR) compared to untreated randomized control [press release]. MeiraGTx. June 28, 2022. Accessed May 25, 2023. bit.ly/3MUfWm2
4. Petrs-Silva H, Dinculescu A, Li Q, et al. High-efficiency transduction of the mouse retina by tyrosine-mutant AAV serotype vectors. *Mol Ther*. 2009;17(3):463-471.
5. Anand R, Birch D. Sub-retinal gene therapy drug AGTC-01 for X-linked retinitis pigmentosa phase 2 randomized, controlled, masked multicenter clinical trial (Skyline) interim safety results. Presented at ASRS 2022, New York City, New York; July 13-16, 2022.
6. von Krusenstiern L, Liu J, Liao E, et al. Changes in retinal sensitivity associated with cotoretigene toliparvovec in X-linked retinitis pigmentosa with RPGR gene variations. *JAMA Ophthalmol*. 2023;141(3):275-283. Erratum in: *JAMA Ophthalmol*. 2023;141(3):293.
7. 4D Molecular Therapeutics announces FDA Fast Track Designation granted to 4D-125 for the treatment of X-linked retinitis pigmentosa [press release]. 4D Molecular Therapeutics. January 10, 2022. Accessed May 30, 2023. bit.ly/43glo80
8. Coave Therapeutics announces positive 12-month data from ongoing phase 1/2 clinical trial of investigational RP drug [press release]. Eyewire+. May 31, 2023. Accessed May 31, 2023. bit.ly/3IMhCM5
9. Atsena Therapeutics announces positive 6-month data from ongoing phase i/ii clinical trial of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in GUCY2D (LCA1) [press release]. Atsena Therapeutics. April 25, 2023. Accessed May 25, 2023. bit.ly/3BYkO3e
10. Dulla K, Slijkerman R, van Diepen HC, et al. Antisense oligonucleotide-based treatment of retinitis pigmentosa caused by USH2A exon 13 mutations. *Mol Ther*. 2021;29(8):2441-2455.
11. ProQR announces positive results from clinical trial of QR-421a in Usher syndrome and plans to start pivotal trials [press release]. ProQR Therapeutics. March 24, 2021. Accessed May 25, 2023. bit.ly/428c9pL
12. Atsena Therapeutics receives FDA clearance of IND application for ATSN-201, an investigational gene therapy for the treatment of X-linked retinoschisis [press release]. Atsena Therapeutics. May 1, 2023. Accessed May 25, 2023. bit.ly/3ozvRgn
13. GenSight Biologics. Mitochondrial targeting sequence. Accessed May 25, 2023. bit.ly/45U7vP1
14. GenSight reports topline efficacy and safety results at 3 years post-treatment with Lumevoq [press release]. Eyewire+. March 14, 2023. Accessed May 26, 2023. bit.ly/4305IM5
15. 4D Molecular Therapeutics announces updates on clinical pipeline and additional preclinical programs [press release]. 4D Molecular Therapeutics. January 9, 2023. Accessed May 30, 2023. bit.ly/43aibY8
16. Deisseroth K. Optogenetics: 10 years of microbial opsins in neuroscience. *Nat Neurosci*. 2015;18(9):1213-1225.
17. Wright W, Gajjeraman S, Batabyal S, et al. Restoring vision in mice with retinal degeneration using multicharacteristic opsin. *Neurophotonics*. 2017;4(4):041505.
18. Nanoscope Therapeutics announces positive topline results from phase 2b RESTORE trial of MCO-010 for the treatment of retinitis pigmentosa [press release]. Nanoscope Therapeutics. March 30, 2023. Accessed May 25, 2023. bit.ly/3WwKjCo
19. GenSight Biologics announces 1 year safety data and efficacy signals from phase 1/2 trial of optogenetic treatment candidate for RP [press release]. Eyewire+. February 15, 2023. Accessed May 26, 2023. bit.ly/30FQimo
20. Bionic Sight reports meaningful vision improvements for RP patients receiving highest dose of its emerging optogenetic therapy [press release]. Foundation Fighting Blindness. April 21, 2023. Accessed May 30, 2023. bit.ly/45DbhfF

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