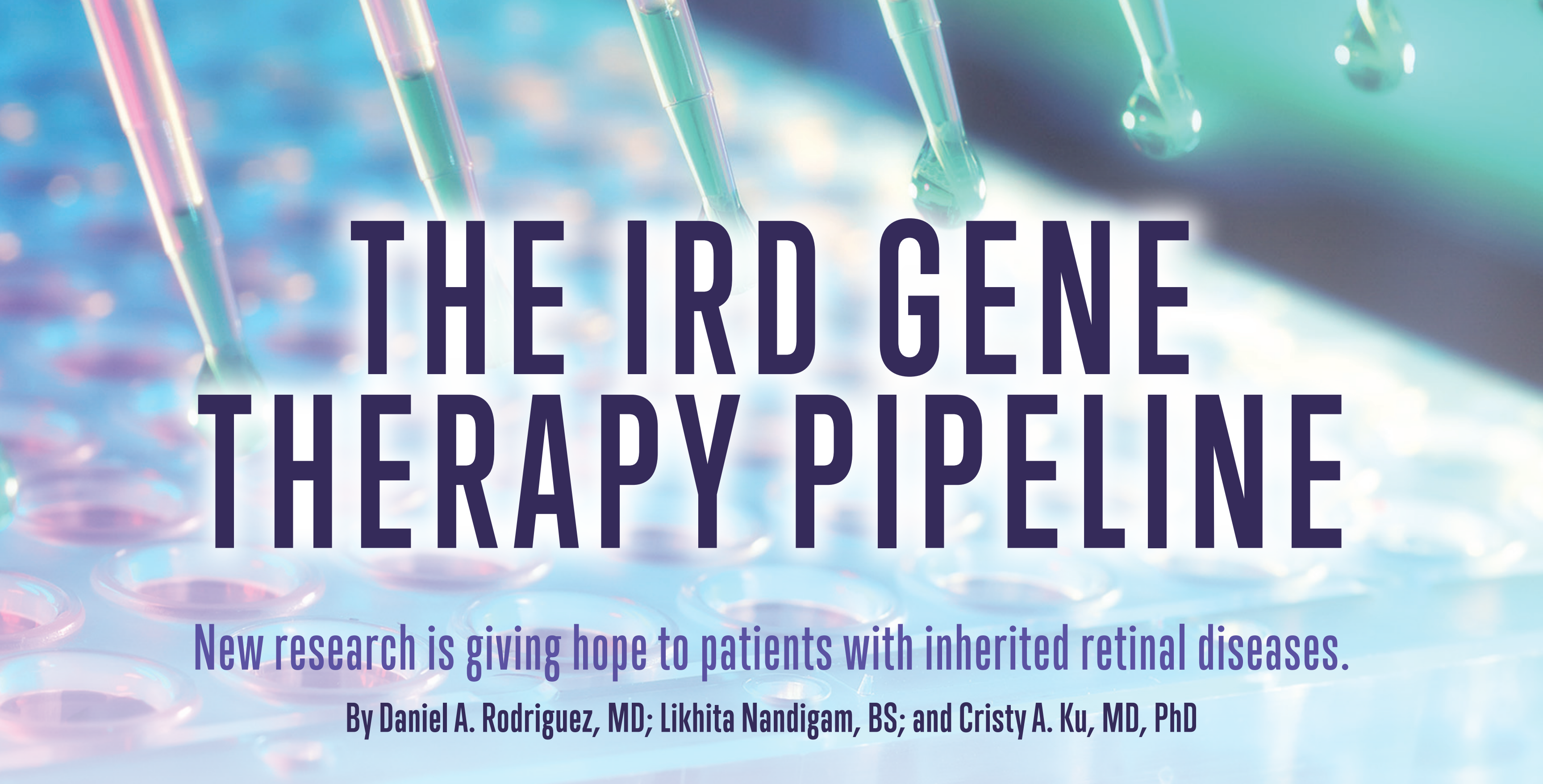

THE IRD GENE THERAPY PIPELINE

New research is giving hope to patients with inherited retinal diseases.

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Inherited retinal diseases (IRDs) are a heterogenous group of diseases characterized by dysfunction and degeneration of photoreceptors and/or the retinal pigment epithelium (RPE) stemming from defects in at least 349 genes.[1] Since the 2017 FDA approval of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics) for the treatment of *RPE65*-associated Leber congenital amaurosis (LCA), more than 30 gene therapies have entered the pipeline to address LCA, retinitis pigmentosa (RP), Stargardt disease, Usher syndrome, choroideremia, and achromatopsia (Table). Here, we highlight recent updates for many of these clinical trials.

LEBER CONGENITAL AMAUROSIS

More than 25 genes are associated with LCA,[2] and gene replacement of *GUCY2D* and *LCA5* is under investigation. The 12-month interim results from a phase 1/2 study (NCT03920007) of subretinal gene augmentation of *GUCY2D* (ATSN-101, Atsena Therapeutics) report safety and improvements in dark-adapted full-field stimulus testing (FST), multi-luminance mobility testing, and BCVA in patients receiving the highest dose.[3-5]

Preliminary reports on the first three adults treated with gene replacement of *LCA5* with OPGx-LCA5 (Opus Genetics) showed safety and early signs of biological activity (NCT05616793), with expected treatment of the next escalation dose in mid-2024.[6]

Mutations in *CEP290* are associated with an estimated 10% to 30% of LCA cases,[7,8] making it an important target. Rather than attempting replacement of this extremely large gene (~7.5 kB), RNA and gene editing have been employed to target the common intronic mutation, c.2991+1655A>G, that is present in at least one allele in 77% of patients.[9]

Sepofarsan (ProQR Therapeutics) is an antisense oligonucleotide that binds *CEP290* mRNA transcript to block aberrant splicing. In the phase 1b/2 dose-escalation study (NCT03140969), five of 11 patients showed a clinically meaningful improvement in BCVA and FST.[10,11] Longer-term analysis of a young patient treated in the contralateral eye in the extension study (NCT03913130) demonstrated a peak biologic response at 3 months, which lasted 3 years, across multiple measures in anatomy and visual function. Further development of sepofarsen, however, is on pause.[12]

CRISPR-Cas9 gene editing has also been used to remove the *CEP290* c.2991+1655A>G intronic mutation.[13] While the

AT A GLANCE

- There are more than 30 gene therapies in the pipeline to treat inherited retinal diseases (IRDs).
- Therapeutic strategies for IRDs include gene augmentation and replacement, RNA and gene editing, CRISPR-Cas9 gene editing, and optogenetics.
- Challenges remain in adequate timing of intervention and expectations in meeting outcome measures, which may differ in each disease.

phase 1/2 study (NCT03872479) is currently paused, interim results showed promising improvements in FST and an average of 0.21 logMAR BCVA improvement with clinically significant improvement over 0.3 logMAR in four patients.[14]

RETINITIS PIGMENTOSA

RP is the most common IRD with a prevalence of one in 4,000 and is associated with more than 100 genes.[15] X-linked RP generally shows a more severe phenotype compared with other inheritance patterns. More than 70% of X-linked RP is caused by the *RP3* gene encoding for the RP GTPase regulator (RPGR) protein, in which males show severe vision loss by the third to fourth decade of life.[16]

Subretinal AAV5-hRKp-*RPGR* (MGT009, MeiraGTx/Janssen) demonstrated overall safety and improvement in perimetry in phase 1/2 trials, although three patients on the highest dose showed inflammatory responses and/or a decrease in retinal sensitivity (NCT03252847).[17] The phase 3 study (NCT04671433) is administering the low and intermediate doses with an extension study for a subgroup randomly assigned to delayed treatment (NCT04794101).

rAAV2tYF-GRK1-*RPGR* (AGTC-501, Beacon Therapeutics) uses adeno-associated virus (AAV) 2 with three tyrosine-to-phenylalanine capsid mutations designed to improve transduction efficiency.[18] The 12-month interim results from the phase 2 study (NCT04850118) show promising improvements in microperimetry, FST, and mobility testing.[19]

4D Molecular Therapeutics developed a proprietary R100 AAV capsid variant to widely transduce all retinal layers, including photoreceptors to intravitreally deliver gene replacement of *RPGR*. The active phase 1/2 clinical trial is testing two doses of 4D-125 (NCT04517149).

Gene replacement for *PDE6A*-associated RP (STZ Eyetrial) is currently active in a phase 1/2 trial (NCT04611503). However, initial findings showed that two of nine treated patients had moderate to severe vision loss with foveal thinning, and another five had temporary decreases in vision.[20]

Gene replacement of *PDE6B* (EyeDNA/Coave Therapeutics) is recruiting in a phase 1/2 trial (NCT03328130) with positive results at 5 years—eyes treated with the low dose showed a 12-letter difference compared with untreated eyes. The 2-year results of six patients with less advanced disease receiving the higher dose showed stability of vision loss and improvements in FST and foveal anatomy.[21]

Gene replacement of *RLBP1*, currently in a phase 1/2 trial in Sweden, used a self-complementary AAV8 capsid (scAAV8-*RLBP1*) that has been shown in preclinical models to have greater transduction efficacy than other vectors.[22]

To target autosomal-dominant RP caused by mutations in *RHO*, a dose-escalation phase 1/2 trial administered intravitreal antisense oligonucleotides (QR-1123, ProQR Therapeutics) to block transcription of the common *P23H-RHO* mutation (NCT04123626). Preliminary results reported safety and improvements in perimetry, with repeated dosing planned in the phase 2 trial.[23]

Gene-agnostic strategies expressing neurotrophic factors and modifier genes are being evaluated. One trial is exploring subretinal SPVN06 (SparingVision) to express *rod-derived cone viability factor*, which promotes cone photoreceptor survival (NCT05748873). Expression of *NR2E3* (Ocugen), a nuclear hormone receptor that modulates retinal homeostasis, has been found to rescue retinal degeneration in RP mouse models. A phase 1/2 trial (NCT05203939) is recruiting for RP associated with *RHO* and *NR2E3* mutations and LCA associated with *CEP290* mutations[24]; a phase 3 trial is recruiting for RP associated with *RHO* and any other gene (NCT06388200).

X-LINKED RETINOSCHISIS

Two phase 1/2 trials are investigating gene therapy for X-linked retinoschisis. VegaVect is exploring intravitreal gene replacement with AAV8-scRS-IRBP-*hRS* (NCT02317887), and Atsena Therapeutics is looking at subretinal gene replacement with AAV.SPR-hGRK1-*hRS1syn* (ATSN-201; NCT05878860).

STARGARDT DISEASE

Stargardt disease, associated with autosomal-recessive mutations in *ABCA4*, has an incidence of one in up to 10,000.[25]

A gene-agnostic strategy (Ocugen) is currently underway with AAV5 expressing *human retinoic acid receptor-related orphan receptor alpha*, thought to regulate lipid metabolism, oxidative stress, and inhibition of the complement system. A phase 1/2 trial is enrolling with safety reported in the phase 1 dose-escalation cohort (NCT05956626).[26]

An optogenetics approach is ongoing (NCT05417126) with intravitreal injection of AAV2 expressing multi-characteristic opsin (MCO-010, Nanoscope) under the mGluR6 promoter for patients with Stargardt disease associated with *ABCA4*, *PROM1*, and *ELOVL4* mutations. Preliminary phase 2a results showed clinically significant improvements in BCVA and a 3 dB gain in mean sensitivity in perimetry.[25,27]

Gildeuretinol acetate (ALK-001, Alkeus Pharmaceuticals), designed to reduce the dimerization of vitamin A, is showing promise as an oral therapy for patients with Stargardt disease caused by a mutation in *ABCA4*. Preliminary data from TEASE-3 (NCT02402660) demonstrated that treated patients showed no progression and remained asymptomatic during therapy (between 2 and 6 years).[28]

USHER SYNDROME

Usher syndrome, an autosomal-recessive condition, leads to deafness and retinal degeneration. *USH2A* is the most common cause of syndromic and non-syndromic RP, and two mutations in exon 13, c.2299delG and c.2276G>T,

TABLE. ACTIVE GENE THERAPY TRIALS FOR INHERITED RETINAL DISEASE					
Gene	Treatment Agent (Sponsor)	Treatment Strategy	Trial ID	Phase	End Date
Leber Congenital Amaurosis					
GUCY2D	AAV8-GRK1-*GUCY2D* (ATSN-101, Atsena Therapeutics)	Gene replacement	NCT03920007	1/2	05/2023
LCA5	AAV8-*hLCA5* (OPGx-LCA5, Opus Genetics)	Gene replacement	NCT05616793	1/2	08/2024
CEP290	EDIT-101 (Editas Medicine)	Alter splicing error	NCT03872479	1/2	05/2025
CEP290	Sepofarsen (QR-110, ProQR Therapeutics)	Alter splicing error	NCT03913143	2/3	01/2022
Retinitis Pigmentosa/Rod-Cone Dystrophy					
RPGR	AAV.R100-*hcoRPGR* (4D-125, 4D Molecular Therapeutics)	Gene replacement	NCT04517149	1/2	06/2026
RPGR	AAV5-hRKp.*RPGR* (MeiraGTx/Janssen)	Gene replacement	NCT04671433	3	09/2024
			NCT04794101	3	09/2029
RPGR	rAAV2tYF-GRK1-*RPGR* (AGTC-501, Beacon Therapeutics)	Gene replacement	NCT06333249	1/2	04/2023
			NCT03316560	1/2	11/2023
			NCT04850118	2/3	08/2025
RPGR	AAV8-*RPGR* (BIIB112, Biogen/NightstaRx)	Gene replacement	NCT03584165	3	06/2024
PDE6A	rAAV.*hPDE6A* (STZ Eyetrial)	Gene replacement	NCT04611503	1/2a	07/2027
PDE6B	AAV2/5-*hPDE6B* (EyeDNA/Coave Therapeutics)	Gene replacement	NCT03328130	1/2	12/2029
RLBP1	scAAV8-*RLBP1* (CPK850, Novartis)	Gene replacement	NCT03374657	1/2	05/2026
RHO	Antisense oligonucleotide (QR-1123, ProQR Therapeutics)	Reduce mutant P23H protein	NCT04123626	1/2	06/2022
Gene agnostic: *RHO, PDE*	AAV-RdCVF-*RdCVFL* (SPVN06, SparingVision)	Overexpression of *rod-derived cone viability factor*, a cone neurotrophic factor	NCT05748873	1/2	03/2025
Gene agnostic	OCU400-301 (Ocugen)	Overexpression of *NR2E3*	NCT06388200	3	06/2025
Gene agnostic	AAV2-*ChR2* (RST-001, AbbVie)	Optogenetics	NCT02556736	1/2	06/2020
Gene agnostic	rAAV2.7m8-CAG-ChrimsonR-tdTomato (GS030-DP/-MD, GenSight Biologics)	Optogenetics and visual interface stimulating glasses	NCT03326336	1/2a	12/2022
Gene agnostic	AAV2-CAG-ChronosFP (BS01, Bionic Sight)	Optogenetics	NCT04278131	1/2	12/2024
Stargardt Disease					
ABCA4	EIAV-*ABCA4* (SAR422459, Sanofi)	Gene replacement	NCT01736592	1/2	08/2023
ABCA4	AAV5-*hRORA* (OCU410-ST, Ocugen)	Regulate pathways in oxidative stress/lipofuscin formation	NCT05956626	1/2	10/2025
ABCA4	Gildeuretinol acetate (ALK-001, Alkeus Pharmaceuticals)	Reduce the dimerization of vitamin A	NCT02402660	2	03/2025
Usher Syndrome					
USH2A	Antisense oligonucleotide (QR-421a, ProQR Therapeutics)	Induce skipping of exon 13	NCT05158296	2/3	12/2024
Choroideremia					
CHM	AAV R100 (4D-110, 4D Molecular Therapeutics)	Gene replacement	NCT04483440	1	06/2024
Achromatopsia					
CNGA3	AAV8.*hCNGA3* (STZ Eyetrial)	Gene replacement	NCT02610582	1/2	06/2027
CNGA3	rAAV2tYF-PR1/7-*hCNGA3* (AGTC-402, AGTC)	Gene replacement	NCT02935517	1/2	08/2022
CNGB3	rAAV2tYF-PR1.7-*hCNGB3* (AGTC-401, AGTC)	Gene replacement	NCT02599922	1/2	06/2022

constitute approximately 35% of pathogenic allele-causing disease.[29] One clinical trial is investigating the efficacy of an intravitreal antisense oligonucleotide (QR-421a, ProQR Therapeutics) to induce in-frame skipping of exon 13.[30] A phase 1b/2 study of 14 treated patients showed improvements in BCVA, perimetry, and ellipsoid zone architecture.[31] The phase 2/3 study is evaluating two different loading doses, followed by maintenance dosing at 3 months and every 6 months thereafter. Although further development is on pause,[12] Théa recently acquired this program.[32]

CHOROIDEREMIA

Choroideremia is an X-linked recessive chorioretinal degenerative disease caused by mutations in *CHM*, which encodes the REP1 protein. It has a prevalence of one in 50,000 to 100,000 and presents with nyctalopia in childhood or early adolescence.[33] Despite early-onset severe chorioretinal degeneration, small irregular islands of relatively preserved retina remain throughout the disease process.

The phase 1/2 trial of subretinal rAAV2.REP1 (University of Oxford) revealed surgical complications of foveal damage, which led to the use of an automated injection system, intraoperative OCT, and the subretinal saline pre-bleb technique to limit retinal stretch and reflux into the vitreous space.[34-36] To decrease the risk of retinal damage from surgical intervention, 4D Molecular Therapeutics is exploring an intravitreal delivery of REP1 (4D-110) in a phase 1 dose-escalation study (NCT04483440) using the same AAV R100 capsid variant technology employed in targeting *RPGR*.[37]

ACHROMATOPSIA

Achromatopsia is an autosomal recessive disease with an estimated 70% to 80% of cases associated with *CNGA3* or *CNGB3*, encoding for the subunits of cone cyclic nucleotide-gated channels.[38] The 3-year outcomes of gene replacement of *CNGA3* in the STZ Eyetrial (NCT02610582) reported no serious adverse events, although no statistical significance was reached between treated and untreated eyes, given improvements also observed in the untreated eye.[39]

Treatment of *CNGA3* with AGTC-402 (AGTC) in the phase 1/2 clinical trial (NCT02935517) was halted due to lack of consistent biological improvement and three cases of severe inflammation.[40] The phase 1/2 trial targeting *CNGB3* (NCT02599922) showed promising results, although the program has since stopped due to a sponsorship change.

CHALLENGES AHEAD

While the IRD clinical trial landscape expands, challenges remain in adequate timing of intervention and expectations in meeting outcome measures, which may differ in each disease. With developments in intravitreal antisense oligonucleotides, further research is needed to evaluate treatment durability and balance potential adverse effects. Lastly, novel gene-agnostic strategies are emerging, which may better encompass treatment for these rare diseases. ■

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