THERAPIES FOR IRDS:

Moving Beyond Single-Gene Solutions

Emerging gene-agnostic strategies target shared pathways and offer options for IRD patients without mutation-specific therapies.

By Aykut Demirkol, MD; Rajvir Solanky; Jayvin Hernandez-Reyes; İlay Demirkol; and Kuzey Soydas. Reviewed by Stephen H. Tsang, MD, PhD

Inherited retinal diseases (IRDs) are a genetically and clinically heterogeneous group of disorders caused by pathogenic variants in more than 250 genes.[1,2] Mutation-specific gene augmentation and gene editing have transformed care for a small subset of patients, yet the sheer genetic diversity and cost of developing "one therapy per gene" mean that most individuals with an IRD still lack an approved treatment.[1,2] As a result, gene-agnostic strategies may broaden treatment options by targeting shared downstream pathways rather than individual mutations.[3-5] These broader therapeutic approaches aimed at preserving or restoring vision are gaining increasing attention.[1,6] For retina specialists, understanding these modalities is increasingly important when counseling patients about trial opportunities and realistic expectations.[1]

WHAT GENE-AGNOSTIC MEANS IN PRACTICE

Gene-agnostic therapies are designed to benefit patients regardless of the specific mutation, offering a unified approach across diverse IRD genotypes.[1] Rather than correcting a single faulty gene, they either preserve the viability of remaining cells, replace cells that have been lost, or rewire surviving retinal circuitry to regain light sensitivity.[1,6] A recent review grouped these strategies into

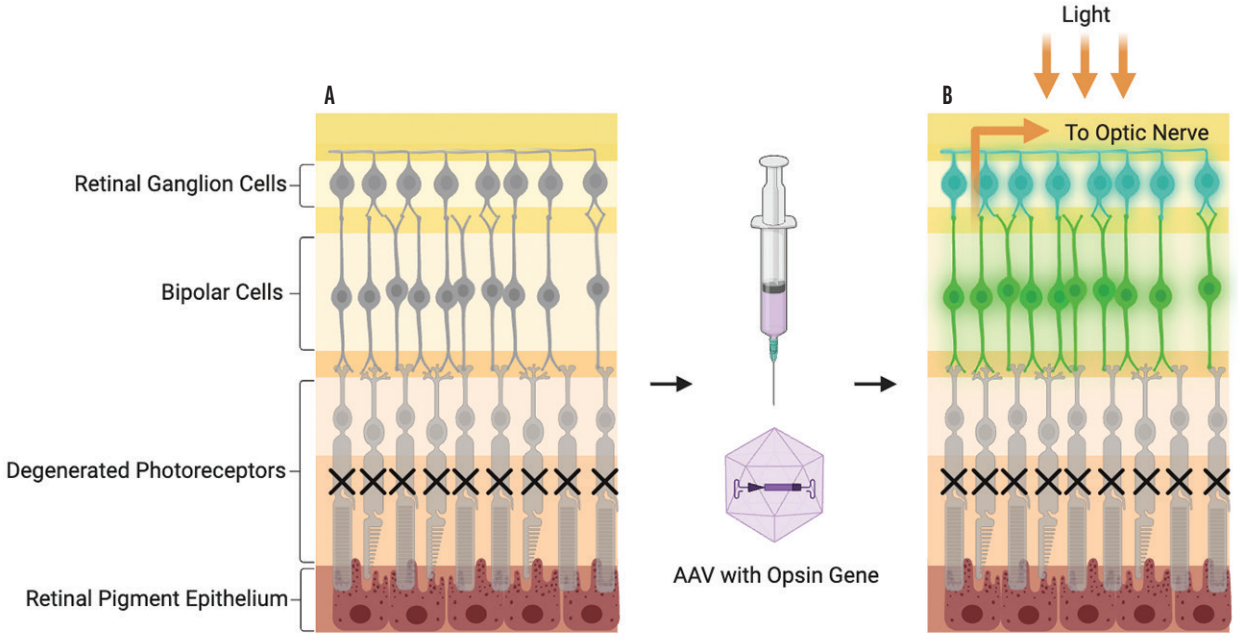

Figure 1. A simplified diagram of optogenetic therapy shows an untreated retina (A) and the AAV-mediated delivery of opsin to bipolar or ganglion cells, leading to the restoration of light-driven output (B). Created in BioRender. Solanky R. 2026. BioRender.com/ukztdxr

several categories: neurotrophic and metabolic support, immune modulation, retinal cell replacement or reprogramming, and optogenetics.[1] Because these interventions target common final pathways of degeneration, they can be applied across broad phenotypes such as rod-cone dystrophy or macular dystrophy, even when the underlying genetics are unknown or complex.[1,2]

Optogenetics: Restoring Light to a Silent Retina

Optogenetic approaches are attractive for patients with end-stage disease in whom photoreceptors are severely depleted but inner retinal neurons remain relatively intact.[7] Adeno-associated viral (AAV) vectors deliver microbial or engineered opsin genes into bipolar or ganglion cells, conferring de novo light sensitivity to the surviving neurons (Figure 1).[7] These strategies have generated visually evoked responses in preclinical models and early human studies, even when traditional photoreceptor-based vision is no longer possible.[7]

Clinical trial data from several candidates suggest optogenetic treatment can improve mobility, object recognition, and functional vision tasks in select patients with advanced retinitis pigmentosa (RP), although sample sizes remain small and visual acuity gains are modest.[8] Practical challenges include optimizing light delivery (often via light-enhancing goggles), balancing sensitivity and temporal resolution, and determining the ideal disease stage at which enough inner retinal architecture persists to benefit from treatment.[7,8]

Leading optogenetic candidates in this space include the following therapies:

- **MCO-010 (Nanoscope Therapeutics):** phase 2b/3 RESTORE trial (NCT04945772) in RP, rolling biologics licensing agreement underway[9]
- **RTx-015 (Ray Therapeutics):** phase 1 ENVISION dose-escalation study in RP/choroideremia (NCT06460844)
- **BS01 (Bionic Sight):** phase 1/2 open-label dose-escalation trial in advanced RP (NCT04278131)
- **GS030 (GenSight Biologics):** phase 1/2 PIONEER first-in-human optogenetic trial in late-stage RP (NCT03326336)

KEY TAKEAWAYS

- Gene-agnostic therapies aim to treat inherited retinal diseases by targeting shared downstream pathways such as photoreceptor loss, metabolic stress, inflammation, and circuit dysfunction.
- Optogenetics, cell replacement, and modifier gene or metabolic reprogramming approaches are progressing through clinical trials.
- Treatment selection is increasingly stage-dependent: Neuroprotective approaches are best suited for early disease, cell-based therapies for intermediate stages, and optogenetics for advanced disease.

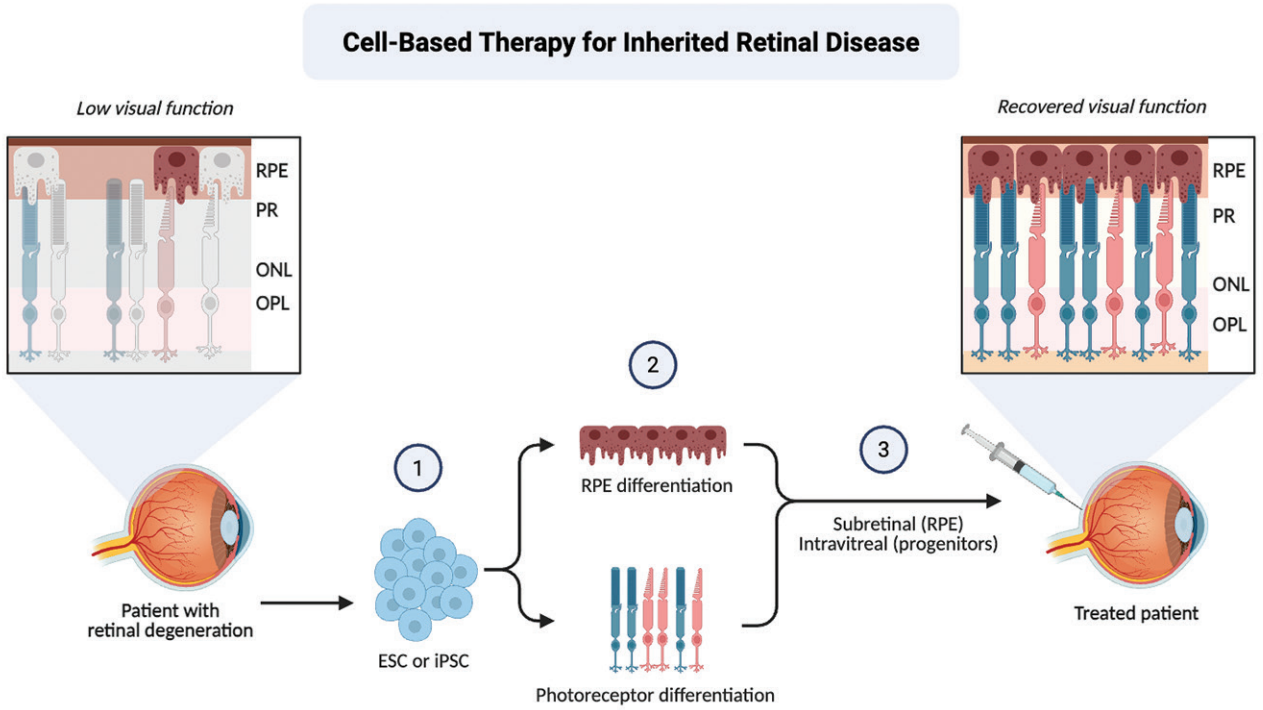

Figure 2. This diagram shows the steps of RPE monolayer transplantation and photoreceptor/progenitor cell delivery. Created in BioRender. Solanky R. 2026. BioRender.com/enz30p9

Cell Replacement: RPE and Photoreceptor Transplantation

Cell-based therapies aim to replace dysfunctional retinal pigment epithelium (RPE) and photoreceptors or provide trophic support through transplanted progenitor cells and organoids (Figure 2).[1,6] RPE transplantation has progressed from experimental macular relocation procedures to trials using human embryonic stem cell-derived or induced pluripotent stem cell-derived RPE monolayers for conditions such as AMD and Stargardt disease.[10,11] Early-phase studies of embryonic stem cell-derived RPE injected subretinally in patients with AMD or Stargardt disease reported that most participants experienced stabilized or modestly improved visual acuity with acceptable safety profiles.[10,11]

Photoreceptor replacement has developed in parallel, leveraging advances in retinal organoids and donor photoreceptor enrichment.[5,12] Recent reviews describe how transplanted photoreceptor precursors can integrate into host outer nuclear layers in animal models or at least transfer cytoplasmic material that partially restores function, although achieving robust synaptic integration and long-term survival remains challenging.[12,13]

Intravitreal or subretinal delivery of allogeneic retinal progenitor cells has entered early human trials for IRDs such as RP, with data showing dose-related mean BCVA improvements with patient-reported gains in light sensitivity and reading ability.[14]

Leading cell-based, gene-agnostic candidates include the following therapies:

- **Famzeretcel (jCell, jCyte):** phase 2 JC02-88 trial in RP (NCT06912633)
- **hRPC (ReNeuron):** phase 1/2 trial in RP (NCT02464436)
- **RG6501 (OpRegen, Lineage/Genentech/Roche):** phase 1/2 trial for geographic atrophy secondary to dry AMD (NCT02286089)
- **CNS10-NPC (Cedars-Sinai):** phase 1 trial in RP (NCT04284293)

Modifier Gene Therapy and Metabolic Reprogramming

Modifier gene therapy occupies an interesting middle ground between classic gene replacement and fully gene-agnostic neuroprotection.[1,2] Rather than correcting a single mutated gene, modifier therapies introduce a gene—often a transcription factor or regulator—that can rebalance dysfunctional networks across multiple IRD genotypes.[1,2] For example, OCU400 (Ocugen) is an AAV-based modifier gene therapy delivering NR2E3, a nuclear hormone receptor involved in photoreceptor development, metabolism, and survival.[15] The phase 3 liMeliGhT trial, which completed enrollment, is a broad, gene-agnostic trial enrolling patients with RP due to a diverse array of gene mutations.[15]

In parallel, several groups (including our own) have focused on gene-agnostic metabolic reprogramming in preclinical models of RP.[16-18] CRISPR editing of the prolyl hydroxylase domain protein 2 (PHD2/EGLN1), initially an anti-anemia drug target, was shown to reprogram the aerobic glycolysis node in rod photoreceptors. It was able

to rescue both rod and cone survival across divergent autosomal recessive and dominant RP models, independent of the underlying rod-specific gene mutation.[17,19]

Separately, ablation of von Hippel-Lindau in rod photoreceptors elevated hypoxia-inducible factor activity, enhanced glycolysis, and slowed degeneration of both rods and cones in RP models, while inducing reciprocal changes in RPE glycolytic flux, underscoring the importance of metabolic crosstalk between photoreceptors and the RPE.[18,20]

Targeting microRNA-mediated pathways offers another gene-agnostic strategy: Modulation of miR-181a/b in the RPE was recently shown to improve RPE morphology, reduce aerobic glycolysis, and slow photoreceptor degeneration in a mouse RP model, highlighting microRNAs as tunable regulators of retinal metabolism.[18,21]

Together, these studies support the broader concept that metabolic and transcriptional reprogramming can act as gene-agnostic interventions to prolong photoreceptor survival across multiple IRD genotypes.[1,16-18,22]

In addition to OCU400, other gene-agnostic or mutation-independent candidates include the following:

- **SPVN06 (SparingVision):** phase 1/2 PRODYGY trial in rod-cone dystrophy (NCT05748873)
- **KIO-301 (Kiora Pharmaceuticals):** phase 2 ABACUS-2 trial in late-stage RP (NCT06628947)
- **ACDN-01 (Ascidian Therapeutics):** phase 1/2 STELLAR trial for *ABCA4*-related Stargardt disease and other *ABCA4* retinopathies (NCT06467344)
- **Sepofarsen (Sepul Bio):** phase 3 HYPERION trial in *CEP290*-associated Leber congenital amaurosis type 10 (NCT06891443)
- **Ultevursen (Sepul Bio):** phase 2b LUNA trial for *USH2A* exon 13-related RP and Usher syndrome (NCT06627179)

ENABLING TOOLS AND CLINICAL ENDPOINTS

As gene-agnostic approaches move toward the clinic, sensitive structural, functional, and metabolic endpoints are essential for detecting treatment effects.[2,23] Stable isotope-resolved metabolomic protocols have been developed to quantify retinal and RPE glucose metabolism, providing a framework to evaluate how candidate therapies alter glycolytic and tricarboxylic acid-cycle flux in preclinical models.[22]

On the clinical side, chromatic full-field stimulus testing (FST) has emerged as a practical psychophysical endpoint to quantify residual rod- and cone-mediated sensitivity in IRD cohorts.[24] In a recent study comparing patients with rod-cone versus cone dystrophies, standardized chromatic FST using white, red, and blue stimuli showed high feasibility and moderate discriminative accuracy; blue-red threshold differences helped differentiate patterns of dysfunction but required interpretation alongside genetic testing and multimodal imaging.[24]

Such tools complement established outcome measures such as BCVA, microperimetry, ellipsoid zone integrity on OCT, and patient-reported outcomes, and they will be increasingly important in trials evaluating optogenetic therapies, cell-based interventions, and metabolic modifiers.[2,20,21]

PRACTICAL CONSIDERATIONS FOR THE RETINA SPECIALIST

Several themes are relevant when counseling patients about gene-agnostic therapies.[1,2] First, these approaches do not eliminate the value of precise molecular diagnosis; knowing the genotype remains important for eligibility in mutation-specific trials, prognosis, and family counseling, even if the therapy itself is gene-independent.[1,2]

Second, timing is critical; neuroprotective or cone-preserving strategies such as cone-viability factor–based therapies and certain cell therapies are likely to be most effective when sufficient photoreceptor structure remains. Optogenetic interventions may be reserved for advanced disease with minimal residual outer retina but preserved inner retinal circuitry.[6-8,14] This therapeutic window paradigm highlights the critical need to align the chosen therapeutic approach with the patient's specific clinical stage.

Third, patients should understand that most of these interventions are currently in early-phase trials, with primary goals of establishing safety and appropriate dosing; functional benefits, while promising in some reports, are still being defined and may be modest or variable.[6-8,14,15]

Regulatory designations such as orphan status and expedited pathways may accelerate the development of gene-agnostic treatments, but widespread clinical availability is still several years away.[15] In the interim, retina specialists must stay current with active trials, referring eligible patients, and setting balanced expectations that emphasize both the hope and the uncertainties inherent to first-in-class therapies.[1,23] ■

Author acknowledgement: Stephen H. Tsang, MD, PhD, is gratefully acknowledged for his mentorship and for facilitating this invitation.

AI disclosure: ChatGPT, version 4.0, OpenAI, was used to assist with language editing and manuscript organization. All content was reviewed, verified, and revised by the authors, who assume full responsibility for the accuracy and integrity of the manuscript. The AI tool was not used for data analysis, interpretation, or drawing scientific conclusions.

1. John MC, Quinn J, Hu ML, Cehajic-Kapetanovic J, Xue K. Gene-agnostic therapeutic approaches for inherited retinal degenerations. *Front Mol Neurosci.* 2023;15:1068185.
2. Igoe JM, Lam BL, Gregori NZ. Update on clinical trial endpoints in gene therapy trials for inherited retinal diseases. *J Clin Med*. 2024;13(18):5512.
3. Rao RC, Arduini BL, Borden S, et al. Safety and tolerability of RPESC-RPE transplantation in patients with dry age-related macular degeneration: Low-dose clinical outcomes. *Cell Stem Cell*. 2025;32(11):1659-1670.e4.
4. Temple S. Modeling, targeting and healing: stem cell strategies to combat neurodegeneration in the brain and eye. Presented at ARVO 2026; Denver, Colorado; May 7, 2026.
5. Temple S. From stem cell discovery to the clinic: Developing a therapy for age-related macular degeneration. Presented at the New York Stem Cell Club Meeting; New York, New York; June 12, 2026.

(Continued on page 44)

(Continued from page 37)

6. Long J, Xu Z, Hu P, Ye Y, Long D. Stem cell therapy for inherited retinal diseases: Trends and insights from 2000 to 2024. *Cell Transplant*. 2025;34: 09636897251400835.
7. McClements ME, Staurenghi F, MacLaren RE, Cehajic-Kapetanovic J. Optogenetic gene therapy for the degenerate retina: recent advances. *Front Neurosci*. 2020;14:570909.
8. Tsang S, Crago SM, Stevenson S. AAO 2025: Early optogenetic therapy shows promise for patients with inherited retinal diseases. Ophthalmology Times. October 22, 2025. Accessed May 14, 2026. tinyurl.com/5n7zvs9v
9. Nanoscope Therapeutics announces durable 3-year vision improvements from REMAIN study of MCO-010 in retinitis pigmentosa [press release]. Nanoscope. October 22, 2025. Accessed May 27, 2026. tinyurl.com/3s4ckbts
10. Chen Q, Zhang T, Chen Z, et al. Retinal pigment epithelium transplantation in retinal disease: clinical trial development, challenges, and future directions. *Biomolecules*. 2025;15(8):1167.
11. Schwartz SD, Hubschman JP, Heilwell G, et al. Embryonic stem cell trials for macular degeneration: a preliminary report. *Lancet*. 2012;379(9817):713-720.
12. Klymenko V, González Martínez OG, Zarbin MA. Recent progress in photoreceptor cell-based therapy for degenerative retinal disease. *Stem Cells Transl Med*. 2024;13(4):332-345.
13. Du Y, Shen Y. Progress in photoreceptor replacement therapy for retinal degenerative diseases. *Cell Insight*. 2024;4(1):100223.
14. jCyte announces publication of Phase I/IIa safety study of retinal progenitor cell therapy for retinitis pigmentosa [press release]. jCyte. August 25, 2025. Accessed May 14, 2026. www.jcyte.com/news/press/2025-aug-25
15. Ocugen announces phase 3 liMeliGhT enrollment completion for OCU400, a novel modifier gene therapy for retinitis pigmentosa [press release]. Ocugen. March 2, 2026. Accessed May 14, 2026. tinyurl.com/4cuu53u6
16. Nolan ND, Cui X, Robbings BM, et al. CRISPR editing of anti-anemia drug target rescues independent preclinical models of retinitis pigmentosa. *Cell Rep Med*. 2024;5(4):101459.
17. Caruso SM, Cui X, Robbings BM, et al. Ablating VHL in rod photoreceptors modulates RPE glycolysis and improves preclinical model of retinitis pigmentosa. *J Clin Invest*. 2025;135(7):e185796.
18. Costa BLD, Quinn PMJ, Wu WH, et al. Targeting miR-181a/b in retinitis pigmentosa: implications for disease progression and therapy. *Cell Biosci*. 2024;14(1):64.
19. Tsang SH. Retinitis pigmentosa: mitigating retinal degeneration with CRISPR technology. NYP/Columbia Advances in Ophthalmology. June 4, 2024. Accessed May 14, 2026. tinyurl.com/3f7zk4vs
20. Hurley JB. Retina metabolism and metabolism in the pigmented epithelium: a busy intersection. *Annu Rev Vis Sci*. 2021;7:665-692.
21. Alrawi DDM, Farhan SR, Alkhathami AG, et al. MicroRNA-mediated metabolic control in HCC: From molecular networks to therapy. *Exp Cell Res*. 2026;454(2):114853.
22. Komissarov G, Pandey K, Nolan ND, et al. Protocol to assess retinal metabolic flux of mice via stable isotope-resolved metabolomics. *STAR Protoc*. 2026;7(1):104252.
23. Heaps NM, Kong MD, Demirkol A, Tsang SH, Scott IU. Stem cell therapies for retinal de-generations. *Retinal Physician*. 2025;22(May):16-18.
24. Demirkol A, Sahli E, Hou B, et al. Diagnostic role of chromatic full-field stimulus test in rod-cone versus cone dystrophies. *Biomedicines*. 2026;14(2):377.

AYKUT DEMIRKOL, MD
- Postdoctoral Research Scientist, Department of Ophthalmology, Columbia University Irving Medical Center, New York
- Assistant Professor of Ophthalmology, Uskudar University, Istanbul, Turkey
- ademirkol79@hotmail.com
- Financial disclosure: None

RAJVIR SOLANKY
- Research Assistant, Harkness Eye Institute, Department of Ophthalmology, Columbia University Irving Medical Center, New York
- rms2285@columbia.edu
- Financial disclosure: None

JAYVIN HERNANDEZ-REYES
- Student, City College of New York, New York
- Research Student, Tsang Lab, Columbia University Irving Medical Center, New York
- jhernan053@citymail.cuny.edu
- Financial disclosure: None

İLAY DEMIRKOL
- Intern, Tsang Lab, Columbia University Irving Medical Center, New York
- Financial disclosure: None

KUZEY SOYDAS
- Student, Koç School, Istanbul, Turkey
- Financial disclosure: None