NOVEL APPROACHES TO TREAT INHERITED RETINAL DISEASE

Gene-agnostic strategies may one day provide treatment options for patients with retinal degeneration.

By Ishrat Ahmed, MD, PhD, and Mandeep S. Singh, MD, PhD


In recent years, there has been significant progress in our understanding of the pathogenesis of inherited retinal diseases (IRDs). Variants in more than 300 genes have been identified; however, the molecular diagnosis remains unknown in approximately 30% to 50% of patients with an IRD.[1-3] As such, the development of therapeutic approaches that are gene-agnostic is essential to provide treatment options for all patients with an IRD, not just those with specific variants. Here, we provide an overview of select gene variant-agnostic approaches, including pharmacologic therapies, optogenetics, stem cell therapy, and retinal prosthesis.

PHARMACOLOGIC THERAPIES

Treatments that slow disease progression and promote cell survival are particularly attractive because they are gene variant-agnostic. Although promising for other retinal diseases, encapsulated cell technology releasing ciliary neurotrophic factor did not yield long-term improvements in functional outcomes in patients with IRDs.[4] There are several other neurotrophic factors being investigated, including pigment epithelium-derived factor and rod-derived cone viability factor.[5] There has also been interest in targeting pathways that promote cellular dysfunction. This includes N-acetylcysteine, which reduces oxidative stress and may improve cone photoreceptor function; one therapeutic agent is currently in a phase 3 clinical trial (NCT05537220).[6]

THE PROMISE OF STEM CELLS

Stem cell therapy aims to restore vision through the release of neurotrophic factors and/or cell repair, regeneration, or replacement. Cell replacement requires proper

AT A GLANCE

- Stem cell therapy aims to restore vision in patients with inherited retinal diseases through the release of neurotrophic factors and/or cell repair, regeneration, or replacement.
- Optogenetics uses light-sensitive channels to enable remaining retinal circuitry to respond to light stimuli.
- Retinal prosthesis involves an implantable device that converts light into electrical signals that are transmitted to the remaining retinal circuitry.

alignment and integration of donor photoreceptors with the remaining neuronal circuitry of the recipient retina. Induced pluripotent stem cells (iPSCs) have significantly advanced the field of stem cell therapy by providing a renewable therapeutic cell source. iPSCs are derived from the trans-differentiation of somatic cells using a set of pluripotency transcription factors.[7,8] Using stepwise protocols, these cells can be differentiated into retinal progenitor cells followed by rod and cone photoreceptors.[9-11]

Photoreceptor transplantation in preclinical models has demonstrated successful integration of donor photoreceptors within the recipient retina, and, crucially, cone transplantation has gained traction as a possible treatment for foveal atrophy in AMD (Figure).[12] Studies in preclinical models also demonstrated the transfer of cytoplasmic material from donor to recipient photoreceptors,[13] and the therapeutic implications of this mechanism across multiple genetic variants is being studied. Several challenges remain, including graft rejection and inflammatory manifestations. Gene editing of autologous iPSCs or gene editing of HLA haplotype resulting in an immunocompatible iPSC line would potentially bypass concerns for graft rejection.[14]

REDIRECTING LIGHT

Optogenetics uses light-sensitive channels to enable the remaining retinal circuitry to respond to light stimuli.[15] This requires transfecting existing neurons (ie, bipolar or retinal ganglion cells) with genes encoding light-sensitive channels. Since viable photoreceptors are not absolutely necessary for optogenetics-based therapies, this approach can be used for advanced disease stages. Delivery approaches being studied include adeno-associated virus and nanoparticles.

GENE-DEPENDENT APPROACHES: AN UPDATE

Voretigene neparvovec-ryzl (Luxturna, Spark Therapeutics), which targets biallelic *RPE65*-associated retinal dystrophy with viable retinal cells, was the first FDA-approved gene therapy for IRD.[1] Initial functional improvement was noted following the subretinal delivery of voretigene neparvovec-ryzl, but questions arose regarding the degree of long-term therapeutic effect.[2-5] A subset of patients also developed progressive post-treatment chorioretinal atrophy, although these lesions have not generally been associated with vision loss.[5] Adeno-associated virus-mediated inflammation and direct toxicity are hypothesized to contribute to chorioretinal atrophy.

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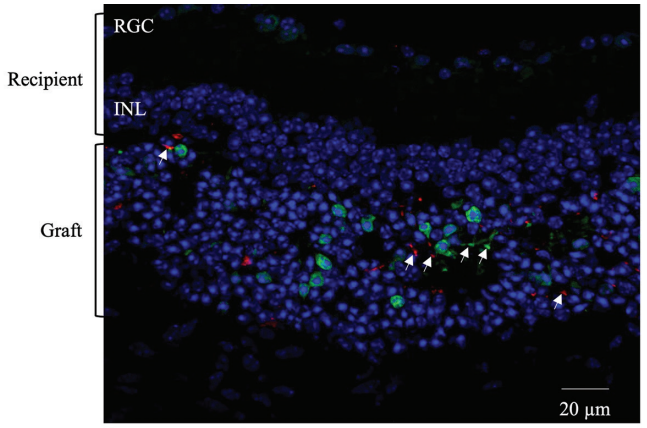

Figure. Cone photoreceptor cells were collected from a cone-rich donor mouse strain and transplanted into the subretinal space of an immunodeficient recipient mouse in an allogeneic approach.[12] Three months post-transplantation, numerous donor cones survived and elaborated key cellular structures, including cone outer segments (arrows). Abbreviations: INL, inner nuclear layer; RGC, retinal ganglion cell. *Data (unpublished) from Kang Li, Ying Liu, and Singh M at Wilmer Eye Institute, Johns Hopkins University.*

In 2021, Sahel et al published a case report of a blind patient treated with ChrimsonR-based optogenetics, demonstrating object recognition and improved performance on psychophysical tests and electroencephalography.[16] ChrimsonR, which is activated with red-shifted wavelengths, requires lower light intensities and is thought to reduce light-mediated retinal damage.[17] This technology requires goggles to detect changes in light intensity and project them as red-shifted (595 nm) light pulses onto the retina in real time. Optogenetics clinical trials include several types of opsins: ChrimsonR (GenSight Biologics), ChR2 (AbbVie), ChronosFP (Bionic Sight), and MCO-010 (Nanoscope Therapeutics).[15]

Retinal prosthesis involves an implant that converts light into electrical signals that are transmitted to the remaining retinal circuitry. Various implant designs include epiretinal, subretinal, suprachoroidal, optic disc, and cortical.[18] The Argus II device (Second Sight Medical) was approved by the FDA in 2013. Briefly, visual signals from a camera are converted into a brightness map that is transmitted wirelessly to the implant, which then transmits these signals to functioning neurons as pulse amplitudes. Five-year follow-up data show persistent improvement on functional vision assessment tasks, such as locating objects or directionality of motion.[19] However, visual gains were modest, and patients required intensive vision rehabilitation. Of note, the best visual acuity attained with the Alpha AMS retinal prosthetic device (Retina Implant AG) was 1.39 LogMAR and 20/500 or 6/150 Snellen.[20] Future directions include the use of AI to improve the implant and visual processing algorithms.[21]

THE WAY FORWARD

There has been a rapid advance in clinical trials encompassing both variant-dependent and variant-independent

therapeutic strategies for IRDs. With exciting variant-independent therapeutics in the pipeline, we can envision a future when every IRD patient, regardless of the causal gene variant, will have at least one treatment option to consider. In addition to enabling molecular diagnosis, providing heredity information to families, monitoring progression, and addressing ocular comorbidities and systemic associations, retina specialists may soon be able to create active therapeutic partnerships with their patients with IRD. ■

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ISHRAT AHMED, MD, PHD
- Assistant Professor of Ophthalmology, Retina Division, Johns Hopkins Genetic Eye Diseases Center, Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore
- iahmed2@jhmi.edu
- Financial disclosure: None

MANDEEP S. SINGH, MD, PHD
- Andreas C. Dracopoulos Professorship of Ophthalmology; Associate Professor of Ophthalmology and Genetic Medicine, Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore
- mandeep@jhmi.edu
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