Review Article

Therapeutic landscape for inherited ocular diseases: current and emerging therapies

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Abstract

Inherited ocular diseases comprise a heterogeneous group of rare and complex diseases, including inherited retinal diseases (IRDs) and inherited optic neuropathies. Recent success in adeno-associated virus-based gene therapy, voretigene neparvovec (Luxturna®) for *RPE65*-related IRDs, has heralded rapid evolution in gene therapy platform technologies and strategies, from gene augmentation to RNA editing, as well as gene agnostic approaches such as optogenetics. This review discusses the fundamentals underlying the mode of inheritance, natural history studies and clinical trial outcomes, as well as current and emerging therapies covering gene therapy strategies, cell-based therapies and bionic vision.

Keywords: Antisense oligonucleotides, cell replacement therapy, gene therapy, inherited optic neuropathy, inherited retinal diseases

INTRODUCTION

Hereditary ocular diseases encompass a broad spectrum of rare conditions either isolated to the eye or present with extraocular manifestations such as Stargardt disease and ocular cutaneous albinism. In recent years, inherited retinal diseases (IRDs) and inherited optic neuropathies have dominated discussions due to rapid evolution in the therapeutic landscape in gene and cell replacement therapies for these disease entities.

IRDs primarily arise from mutations in nuclear genes found in the photoreceptors (PRs) and/or retinal pigment epithelium (RPE). Depending on the causative gene, IRDs can disproportionately affect the rod or cone PRs, thus impacting peripheral or central visual fields, night or colour and daytime vision to different degrees. Most IRDs progress slowly, though marked variability in disease onset and severity exists depending on the underlying mutation. Retinitis pigmentosa (RP) is the most common form of IRD.

In inherited optic neuropathies, mutations are predominantly identified in the mitochondrial genome. Painless, subacute, central visual loss may occur unilaterally with sequential second eye involvement over days/weeks/months or simultaneously in both eyes. Leber hereditary optic neuropathy (LHON) is one of the most common mitochondrial disorders with an estimated prevalence ranging from 1 in 31,000 to 1 in 54,000.[1-6]

GENETICS AND INHERITANCE

More than 3 billion nucleotide base pairs residing in 23 pairs of chromosomes make up the human genome. Within each chromosome are hundreds to thousands of genes, each carrying specific instructions for protein synthesis. It is estimated that the human genome comprises up to 20,338 genes, each making an average of three proteins. Of these, 317 genes (281 mapped) are known to cause inherited retinal diseases and, to a lesser extent, inherited optic neuropathies (RetNet @ http://www.sph.uth.tmc.edu/RetNet/).[7]

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As diploid organisms, humans carry two alleles for each gene, one inherited from each parent. Hereditary diseases may arise from mutations in a single gene (monogenic) or chromosomal abnormalities. Common modes of Mendelian inheritance are autosomal dominant (AD), autosomal recessive (AR) and sex or X linked (XL).

AD disorders manifest from mutation in one allele of the disease gene. Offspring of an affected individual have a one in two chance of inheriting the mutant allele. Several molecular mechanisms underly AD disorders and these include the following:[8,9]

- *Haploinsufficiency*: mutation in one allele of the gene halves the gene dosage or expression, culminating in insufficient protein production to sustain physiological function. Aniridia (OMIM #106210) due to mutation in the *PAX6* gene (OMIM *607108), a regulatory paired box gene crucial to ocular development, is one such example. Haploinsufficient truncating mutations in the *PAX6* gene account for most cases of aniridia, but chromosomal rearrangements from deletions in the 11p13 region (WAGR region) are contributory.[10]
- *Dominant negative*: a mutation whereby activity of the wild-type protein is interfered with by the mutant protein.[11] An example is AD retinitis pigmentosa (ADRP) due to mutation in the rhodopsin gene (*RHO*, OMIM *180380). *RHO* was the first gene in which causative mutations were identified to cause RP.[12,13]
- *Dominant gain-of-function mutation*: a form of mutation whereby activity of the mutated protein is increased compared to that of the wild-type protein.[13] An example is the constitutive activation of retinal guanylate cyclase 1 in AD guanylyl cyclase-activating protein 1 (GCAP-1)-related AD cone dystrophy.[14,15]

AR disorders arise when both alleles of a gene are mutated, resulting in little or no protein production. Recessive mutations are more often associated with loss-of-function (LOF) mutation. Homozygotes have an identical mutation on both alleles, whereas compound heterozygotes have two different disease-causing sequences. Parents of a child with AR disease are carriers or heterozygotes.

XL disorders are caused by mutations in genes found on the X chromosome and can manifest in recessive or dominant (rare) forms. Male-to-male transmission is not possible. Affected males are hemizygotes and often develop more severe disease than females who may or may not manifest disease, the severity of which may also be variable due to lyonisation. Lyonisation, or X-inactivation, is a process by which one X chromosome is 'silenced' and rendered inactive. XL recessive IRDs include juvenile XL retinoschisis, XL retinitis pigmentosa (XLRP), choroideraemia and ocular albinism (OA). Multimodal imaging, particularly fundus autofluorescence, highlights distinctive mosaic retinopathy signatures in carriers of XLRP, choroideraemia and OA.[16,17]

In contrast to nuclear genes, the mitochondrial genome is inherited (almost) exclusively from the maternal lineage and expressed in thousands of copies in each nucleated cell. Mitochondria are vital, energy-generating organelles residing outside the nucleus of a cell. In mitochondrial disorders, heteroplasmy is a state where wild-type and mutant alleles coexist in varying proportions in different tissue types and may influence disease severity. LHON arises from missense point mutations in mitochondrial DNA (mtDNA) with m. 11778G>A in the *ND4* gene being the predominant form.[18] More recently, certain variants in the nuclear *DNAJC30* gene have been reported to cause autosomal recessive (ar) LHON.[19,20]

NATURAL HISTORY STUDIES AND DEFINING CLINICAL TRIAL OUTCOMES

The monogenic basis of most IRDs, accessibility of the retina for non-invasive functional testing and multimodal structural imaging, coupled with relative immune privilege of the eye, render the organ ideal for therapeutic intervention. Tight blood–retinal barrier limits or prevents systemic dissemination of injected viral vector, while the absence of retinal cell division and compensatory retinal neurogenesis mechanisms after birth limits any compromise on transgene expression.

Recent success in adeno-associated virus (AAV)-based gene therapy voretigene neparvovec (Luxturna®; Spark Therapeutics, Philadelphia, PA, USA and Novartis, Basel, Switzerland) for *RPE65*-related IRD[21] moved proof-of-concept gene therapies for IRDs from bench to bedside, opening the possibilities for modulating, halting or even partially reversing the degenerative process. With a pivot towards clinical trials for gene therapies, natural history studies for specific IRDs are crucial for detailed characterisation (both phenotyping and genotyping) of populations to better define eligibility criteria, optimal therapeutic window and appropriate primary and secondary efficacy endpoints for clinical trial design.

When designing a new clinical trial, the chosen efficacy endpoints must be meaningful and relevant for the targeted retinal disease. Evolution in medicine necessitates constant evaluation and updates on the existing standards for safety and efficacy outcomes for investigational therapeutic trials. Established endpoints from pharmacological trials for neovascular age-related macular degeneration[22-25] and diabetic macular oedema[26] may not be directly relevant to IRD. Most IRDs tend to have slow progression with wide range of vision ranging from 20/20 to ultra-low vision. Quantitative primary outcome measures based on improvement in functional (e.g. best-corrected visual acuity [BCVA]) and structural (e.g. central subfield thickness on macular optical coherence tomography) measures alone may not accurately reflect treatment efficacy in IRDs. Psychophysical tools such as automated or kinetic perimetry, microperimetry, pupillometry and electrophysiological tests

including electroretinography (ERG) are valuable, provided their application is based on cellular target structure. The full-field stimulus test (FST), although not a psychophysical equivalent of ERG, can be used to detect residual rod and cone sensitivity where ERG is undetectable.[27,28] Surrogate endpoints measuring the functional impact on daily activities may better reflect treatment efficacy in IRD.[29] An example is the multi-luminance mobility test (MLMT), an orientation and mobility (O&M) course evaluating the speed and accuracy at which a patient navigates through an obstacle course under various illumination levels. Pioneered in the voretigene neparvovec (Luxturna) trials,[21,30-32] the MLMT as a functional endpoint demonstrated meaningful correlation with patient's activities of daily living, which led to market approval of Luxturna. Since then, the MLMT has been adopted in various ongoing therapeutic interventional trials. Virtual reality (VR)-based O&M platforms provide promising alternatives pending further validation,[33] and a Phase 1 study evaluating a new VR mobility tool (clinicaltrials.gov identifier, NCT04289571) in IRD patients and healthy volunteers is underway. Established artificial systems for naturalistic test approximating daily activities, such as StreetLab® and Homelab®, are also available.[34]

In defining clinical endpoints, outcome measures from any new therapy must translate to meaningful change for patients. To this end, the Food and Drug Administration (FDA) designates importance on applying appropriate patient-reported outcome measures (PROM) in therapeutic trials, and PROMs are increasingly incorporated as outcome measures of visual function for gene therapy trials in IRD.[21,35-37] Despite some similarities in phenotype, the experience of living with a specific IRD is unique to each patient. Patient-reported outcomes (PROs) are equally valuable in capturing these individual experiences. Until recently, no validated PROM questionnaire, not even the well-established National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25), has been used as a primary endpoint for this specific purpose.[38] To address this need, the team at Kellogg Eye Centre (University of Michigan) derived psychometrically validated PROs, the Michigan Retinal Degeneration Questionnaire (MRDQ) and the Michigan Vision-Related Anxiety Questionnaire (MVAQ), both available for evaluation.[39,40] Similar requirements exist for paediatric IRD patients as adult PROMs may not be directly applicable. To accurately assess the impact of IRD and the effect of therapy on the paediatric cohort, paediatric-specific PROMs applying the appropriate language and relevant experience are required.[41]

THERAPEUTIC APPROACHES

Gene therapies

Gene therapy is broadly defined as the delivery of exogenous genetic material into target cells, leading to modification of gene expression in order to treat human diseases.[42] IRDs and inherited optic neuropathies can lead to devastating irreversible blindness and, up until recent times, have conventionally been accepted as untreatable. With the advent of gene therapy, patients with IRDs may now have a sustained and potentially curable modality of treatment.[43] Major advances in gene therapy technologies have generated tremendous industrial traction, which is a boon to IRD patients as the range of conditions with therapeutic trials continues to expand.

Genes can be modified at the genomic or post-genomic level to produce wild-type functional protein. Its various methods include gene supplementation, gene editing, RNA modulation using antisense oligonucleotides (ASOs) and optogenetics. To ensure therapeutic success, the choice of gene therapy must commensurate with the mode of inheritance and the stage of disease.

In gene therapy, a vehicle is required to deliver the transgene into host cells, using either viral or non-viral vectors. Adeno-associated viruses (AAVs) are the preferred method due to better long-term retinal transduction, low risk of immunogenicity, and low inflammatory and low retinal toxicity.[44,45] AAVs are limited by their transgene cargo capacity (4.7 kB) compared to lentiviruses (8 kB).[46] Non-viral vector alternatives include nanoparticles, liposomes or naked plasmid DNA.[47] Delivery can be approached in one of three ways: intravitreal, subretinal or suprachoroidal [Figure 1], each with its own advantages and disadvantages [Table 1].

Gene supplementation

Gene supplementation replaces the defective gene by delivering the wild-type gene (transgene) into host cells using viral vectors. This approach is amenable to LOF mutation in AR disorders and dominant IRDs caused by haploinsufficiency. The therapeutic window is critical as this approach requires viable retinal cells.

The AAV2-based voretigene neparvovec (Luxturna) received FDA (2017) and European Medicines Agency (2018) approval as the first ocular gene therapy for the

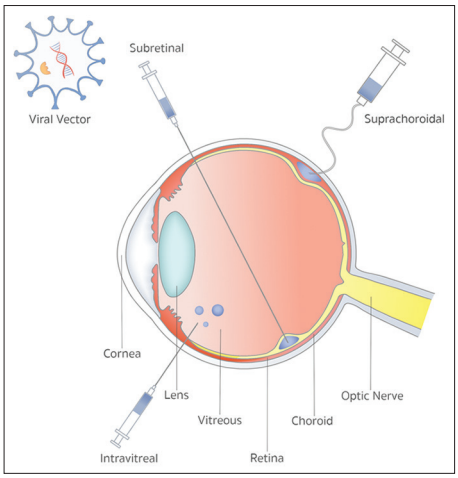

Figure 1: Diagram shows the routes of administration for retinal gene therapy. [Created using GNU Image Manipulation Program (GIMP)]

Table 1. Summary of advantages and disadvantages of the gene therapy delivery approaches.[54,55]

Approach	Subretinal	Intravitreal	Suprachoroidal[48-51]
Description	Delivered between PR and RPE	Delivered into vitreous	Delivered into SCS between choroid and sclera via catheters, needles or microneedles
Advantages	Concentration of therapeutics preserved Delivered directly into the target site of PR and RPE Relative immune privilege of subretinal space, minimising the risk of pre-existing NAbs against AAV	More accessible as it is performed in outpatient setting in adults No PPV or retinotomy-associated complications	More accessible as it is performed in outpatient setting using microneedle without sclerostomy[52] No PPV or retinotomy-associated complications Potentially greater spread of vectors
Disadvantages	Invasive procedure requiring PPV and retinotomy; examples of potential complications: macular hole, retinal detachment, endophthalmitis, foveal atrophy Limited spread of vectors subretinally Cost (e.g. OT, surgical consumables)	Dilution of therapeutics in vitreous Poorer transduction due to physical barrier of ILM impeding therapeutics reaching PR and RPE Exposure to NAbs against AAV inducing humoral response* and reducing treatment response[53]	AAV vectors need to traverse choroid to reach PR and RPE before potential rapid clearance via choriocapillaris Potential exposure to pre-existing NAbs as SCS is beyond blood-retinal barrier

*May be mitigated by 'directed evolution'. AAV: adeno-associated virus, ILM: internal limiting membrane, NAbs: neutralising antibodies, OT: operating theatre, PPV: pars plana vitrectomy, PR: photoreceptor, RPE: retinal pigment epithelium, SCS: suprachoroidal space

treatment of *RPE65*-related retinal dystrophy. A Phase 3 trial reported improved MLMT scores, FST values and Goldmann visual fields with sustained durability at year 3 and 4 post-treatment.[56] To better understand its long-term safety and efficacy profile in the real-word setting, the PERCEIVE study was conceived. To date, the interim 2-year data showed similar safety and efficacy profile to those reported in the clinical trials.[57]

In LHON, the RESCUE and REVERSE (GenSight Biologics, Paris, France) Phase 3 trials evaluated the efficacy of unilateral intravitreal lenadogene nolparvovec (LN; LUMEVOQ®), an AAV2 vector encoding the mitochondrial *ND4* protein (rAAV2/2-ND4), in patients with newly diagnosed (≤6 months, RESCUE; 6–12 months, REFLECT) ND4-LHON. The primary endpoint was not achieved, as the unexpected outcome of sustained improvement in BCVA in both the drug-treated and contralateral sham-treated eyes was observed.[58-60] A follow-up non-human primate study revealed viral vector DNA transfer to the contralateral eye, offering a plausible explanation for the unexpected bilateral improvement despite unilateral injection.[59] The REFLECT study (2018) comparing bilateral LN with bilateral LN/sham reported better average BCVA seen in the bilateral LN injection arm versus the unilateral LN arm, suggesting a dose effect.[61]

Gene editing

Gene editing is an emerging approach utilising the knockdown and replace method to repair dominant negative mutations. In certain AD IRDs such as rhodopsin (*RHO*)-associated ADRP, the mutated allele may exert a toxic dominant negative effect, rendering gene supplementation ineffective. In such instances, a gene knockdown and replacement approach would be ideal for functional and structural rescue.[62]

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 is a forefront gene editing technology involving a guiding RNA (gRNA) and a nuclease (genomic scissors) such as Cas9.[63] The CRISPR/Cas9 complex binds, cleaves and removes the target mutated gene, while a separate AAV vector simultaneously delivers the functional replacement gene precisely to the target site. CRISPR/Cas9-based therapies have been applied successfully in mouse models, such as in *RHO*-RP, using an 'ablate-and-replace' technique.[64] In post-mitotic retina, inactivation of the cleaved genomic locus using non-homologous end joining has been shown to be more efficient over precise corrections using homology-directed repair.[65]

BRILLIANCE is an ongoing Phase 1/2a study for the treatment of Leber congenital amaurosis 10 (LCA10). EDIT-101, a CRISPR-based drug, is used to target the frequent mutation c.2991+1655A>G in intron 26 (*IVS26*) of the *CEP290* gene to prevent insertion of the pseudoexon, exon X. Early efficacy data suggest improvement in FST, BCVA and navigation ability in a standardised course.[66]

In vivo base editing using adenine base editors has been successfully performed in LCA mouse models with *Rpe65* mutations, demonstrating increased cone survival and improved cone-mediated visual function. This novel proof of concept offers an exciting new alternative of gene editing.[67]

Antisense oligonucleotides

ASOs consist of small RNA molecules of 15–30 nucleotides in length that are able to hybridise with pre-messenger or messenger RNA (mRNA), thus exerting an effect on pre-mRNA processing or mRNA translation. ASOs can be designed to prevent aberrant splicing, block cryptic splice donor sites thus skipping of mutated exons, as well as knock down dominant negative allele. The use of ASOs as RNA therapy is a growing area of investigation within and beyond IRDs.

LCA10 is a childhood-onset blinding autosomal recessive retinal dystrophy arising from biallelic mutations in *CEP290*, and can also be associated with other syndromic ciliopathies

Table 2. Summary of bionic systems.

Prosthesis	Argus II[105-107]	IRIS II	OPTO-EPIRET[108]	Alpha AMS[109]	PRIMA[110]	Phoenix[99] Bionic[111]	Suprachoroidal Prosthesis[112]	Suprachoroidal transretinal stimulation device[113,114]	Orion[115]
Organisation	Second Sight Sylmar, CA, USA	Pixium Vision, Paris, France	Nanoretina Herzliya, Tel Aviv, Israel	Retina Implant AG, Reutlingen, Baden-Württemberg, Germany	Pixium Vision, France	University of Sydney, UNSW	Bionic Vision, Victoria, Australia	Osaka, Japan	Second Sight, USA
Site of implant	Epiretinal	Epiretinal	Epiretinal	Subretinal	Subretinal	Suprachoroidal	Suprachoroidal	Suprachoroidal	Cortical
Image acquisition	VPU	VPU	Intraocular sensor chips	Intraocular light-sensitive photodiodes	VPU	VPU	VPU	VPU	VPU
Outcome	Better accuracy localising test objects	Improved target and motion localisation, picture recognition and visual field	Good biocompatibility with rabbit eyes Pending clinical trials	Improved light perception, temporal resolution and light localisation in subjects	Improved light perception in atrophic zone Better letter recognition	Good biocompatibility with sheep eyes Pending clinical trials	Improved target localisation, function vision and observer-rated quality of life	Subjects able to detect phosphenes Demonstrated improvement in visual tasks	Ongoing clinical trials (clinicaltrials.gov identifier, NCT03344848)
Advantages	Able to overcome cornea/lens opacities	Able to overcome cornea/lens opacities	Simulates natural vision with eye movements and preserved microsaccades Does not require external parts	Simulates natural vision with eye movements and preserved microsaccades	Wireless and small-size implant allows for shorter and less-invasive surgery	Does not require vitrectomy	Does not require vitrectomy	Does not require vitrectomy	Directly stimulates visual cortex, and thus able to overcome optic neuropathy
Disadvantages	Requires vitrectomy	Requires vitrectomy Shortened lifespan possibly from microfractures	Limited by cornea/lens opacities Big array is difficult to implant, leading to risk of vitreous haemorrhage and retinal tears	Limited by cornea/lens opacities Requires vitrectomy	Requires vitrectomy	May require higher voltage due to increased distance between the implant and RGCs	May require higher voltage due to increased distance between the implant and RGCs	May require higher voltage due to increased distance between the implant and RGCs	Requires phosphene mapping to translate perceived phosphenes to functional vision

RGC: retinal ganglion cell, UNSW: University of New South Wales, VPU: external video camera and processing unit

such as Senior–Loken syndrome, Joubert syndrome, nephronophthisis, Bardet–Biedl syndrome and Meckel–Gruber syndrome.[68] The Illuminate trial evaluated the use of QR-110 or sepofarsen (ProQR Therapeutics NV, Leiden, The Netherlands), a 17-mer 2′-*O*-methyl modified phosphorothioate RNA aimed at restoring pre-mRNA splicing and ciliogenesis in *CEP290* c.2991+1655A>G by binding to the target pseudoexon region (between exons 26 and 27) and blocking the active cryptic splicing site. Despite statistically significant improvements in visual acuity and retinal sensitivity in the Phase 1/2 study, topline results from Phase 2/3 study did not meet the primary and secondary endpoints.[69] However, post hoc analyses of treatment effect demonstrated benefit in vision and retinal sensitivity, which was not observed in the sham-treated group and substantiated by PROs.[70]

Mutations in the *USH2A* gene can give rise to non-syndromic RP (nsRP) or syndromic RP associated with hearing loss (Usher syndrome type 2A). Two recurrent mutations within exon 13 of *USH2A*, c.2299delG and c.2276G>T, are responsible for up to a third of RP cases in some populations.[71] In the Phase 1/2 Stellar trial, intravitreal administration of ASO QR-421a (ProQR Therapeutics NV) in patients with nsRP demonstrated improvements recorded in BCVA, retinal sensitivity and perimetry with no safety signals. Based on these findings, ProQR announced plans for initiation of two Phase 2/3 multidose studies, Sirius and Celeste, for advanced and early to moderate USH2 populations, respectively.

Optogenetics

Optogenetic approaches offer a promising alternative in the setting of PR death. These aim to restore vision by introducing light-sensitive molecules to surviving cell types of the retina that enable light perception through the residual neurons.[72]

In the Phase 1/2a PIONEER study, Sahel *et al.*[73] described the use of an optogenetic vector in a patient with RP, where an AAV vector containing the light-sensing channelrhodopsin protein fused with a red fluorescein protein was administered into the worse seeing eye. Partial visual recovery was reported with better visual orientation and improved performance in visuomotor tasks.

Clinical trials by Nanoscope (Nanoscope Therapeutics, Inc., Bedford, TX, USA) are ongoing to investigate the safety and efficacy of vMCO-010, a virally carried multi-characteristic opsin, in RP (RESTORE trial, clinicaltrials.gov identifier, NCT04945772) and Stargardt disease (STARLIGHT trial, clinicaltrials.gov identifier, NCT05417126). Bionic Sight (AGTC, Alachua, FL, USA) is also conducting a Phase 1/2 trial to evaluate the safety and efficacy of BS01 (clinicaltrials.gov identifier, NCT04278131), a recombinant AAV vector expressing ChronosFP, delivered into the retinal ganglion cells of patients with RP. Early observations include markedly increased light sensitivity.[74] The safety and tolerability of RST-001 (clinicaltrials.gov identifier, NCT02556736; AbbVie Inc., North Chicago, IL, USA), administered intravitreally in patients with advanced RP is currently being investigated.

While current trials mainly target the retinal ganglion cells, it has been theorised that delivery of optogenetic molecules into diseased but viable cone PRs could better utilise post-PR retinal circuitry to gain higher quality vision. In a pre-clinical study where *Rcd1* canine models received a unilateral subretinal injection containing the enhanced halorhodopsin cDNA from *Natronomonas* fused to the yellow fluorescent protein reporter gene, partial visual restoration was observed with promising results showing improved ERG, visual-evoked potential responses and visual navigation.[75]

Cell therapies

Irreversible PR and RPE cell death occurs in end-stage retinal disease. As the retina has no intrinsic regenerative properties, stem cell therapy has been sought as a new means of regenerating the damaged retina.[76] In recent years, we have learned that rescue of host PR function arises from bidirectional cytoplasmic material exchange between the donor and host cells,[77-80] instead of donor cell integration, and successful transfer of material requires viable host PR cells.

Human embryonic stem cell (hESC)–derived RPE cell suspensions have been successfully transplanted subretinally into eyes with Stargardt disease, demonstrating survival, long-term safety and improved visual outcomes in Phase 1/2a clinical trials.[81-84] Despite the use of smaller gauge vitrectomy and cannula, epiretinal membrane formation from leaked RPE cells may cause macular or retinal traction, a known adverse event associated with the use of RPE suspension.[85-87] An alternative mode of transplantation using hESCs engineered into a monolayer RPE patch on a coated synthetic membrane, which better resembled native architecture as the cells were differentiated and polarised with established tight junction barriers, was used in age-related macular degeneration.[88]

Success in generating induced pluripotent stem cells (iPSCs) has offered a promising alternative to overcoming ethical concerns around the use of hESCs. Lingam *et al.*[89] described successful transplantation of iPSC-derived retinal PR precursor cells onto non-human primate models. At month 3 post-transplant, the cells had further developed into mature cone PRs, with optical coherence tomography showing restoration of the retinal ellipsoid zone.

Proof-of-concept studies using hESC/iPSC-derived retinas in end-stage retinal degeneration models demonstrated graft PR maturation, synapse formation between graft PR and bipolar cells, and light response in host retinal ganglion cells.[90-93] A safety study using allogenic iPSC-retinal sheets for patients with advanced RP is underway in Japan (trial ID: jRCTa050200027), with no safety concerns reported thus far for the first two patients. Tumourigenicity remains a major safety concern in stem cell-based therapy, necessitating rigorous

evaluation of genomic integrity for highly proliferative cells (such as progenitor cells) and cells of lower rate of proliferation (such as iPSC-derived RPE cells) that require at least *in vivo* tumourigenicity testing.[94] Human leukocyte antigens matching may mitigate safety concerns over tumourigenicity from undifferentiated iPSC and immunogenicity. Pluripotent stem cell-derived retinal organoid as a form of transplantation therapy offers exciting prospect.[95-101] Successful integration of retinal organoid-derived tissue with improved visual function has been demonstrated in several IRD models.[102]

Mesenchymal stem cells (MSCs) of different sources are currently being investigated for stem cell therapy in ongoing trials. In a Phase 1 trial, intravitreal injection of bone marrow-derived MSCs showed statistically significant improvement in BCVA, although this effect was not sustained and they returned to baseline by the 12-month mark.[103] Subtenon implantation of Wharton's jelly-derived MSCs in a Phase 3 trial demonstrated promising results with improvement in BCVA, visual field, outer retinal thickness, multifocal ERG and full-field flicker ERG up to 6 months.[104] This extraocular approach potentially provides a safer alternative for cell delivery, in contrast to intravitreal or subretinal injections.

Bionic systems

Retinal implants provide an innovative method of restoring sight in degenerative retinal diseases. Most of these implants are either sited epiretinally and tacked onto the retina, inserted subretinally or implanted in a suprachoroidal pocket. They receive information either from micro-electrode arrays connected to an external camera or through intraocular micro-photodiode arrays. Visual information is then transmitted directly to the retinal ganglion cells as electrical impulses, bypassing dysfunctional or degenerated PRs. Basic form and shape perception is what has been achieved in several clinical trials with these devices [Table 2].

Retinal prostheses made from foreign and synthetic materials may induce an inflammatory host response, causing fibrosis to form around the implant. The thickened fibrotic capsule induces a widening of the electrode–retina interface and increases perceptual thresholds, ultimately leading to decreased signal transmission.[116] Another hardware limitation is the need to ensure longevity of the implant, given the inaccessibility for maintenance.

Further studies are also ongoing to improve image resolution[117] and widen the visual field[118] to improve functional vision. The advent of retinal prostheses has truly offered a new and promising paradigm of treatment to patients with advanced retinal diseases.

CONCLUSION

The therapeutic landscape for inherited eye diseases is promising as new clinical trials and therapies continue to emerge. While overcoming challenges attributed to various gene therapy approaches, collaborative natural history studies are fundamental to refine understanding on specific IRDs and help define therapeutic strategies. Long-term safety and efficacy data will be pivotal in determining the future direction of gene therapy for both monogenic and polygenic eye diseases.

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Conflicts of interest

There are no conflicts of interest.

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