Retinal Gene Therapy

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Abstract

Introduction: Inherited retinal diseases are the leading cause of sight impairment in people of working age in England and Wales, and the second commonest in childhood. Gene therapy offers the potential for benefit.

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Areas of agreement: Gene therapy can improve vision in *RPE65*-associated Leber Congenital Amaurosis (*RPE65*-LCA). Potential benefit depends on efficient gene transfer and is limited by the extent of retinal degeneration.

Areas of controversy: The magnitude of vision improvement from *RPE65*-LCA gene therapy is suboptimal, and its durability may be limited by progressive retinal degeneration.

Growing points: The safety and potential benefit of gene therapy for inherited and acquired retinal diseases is being explored in a rapidly expanding number of trials.

Areas timely for developing research: Developments in vector design and delivery will enable greater efficiency and safety of gene transfer. Optimisation of trial design will accelerate reliable assessment of outcomes.

<u>Introduction</u>

The retina is a highly specialised, multi-layered tissue that includes a layer of light-sensitive cone- and rod-photoreceptor cells, which initiate neuronal signalling in response to light stimulation by means of a highly sophisticated cascade of enzymatic reactions (phototransduction). The photoreceptor cells are supported by a monolayer of pigmented cells, the retinal pigment epithelium (RPE), which performs many key processes including the regeneration of visual pigment (the visual cycle) which is bleached following light exposure. Diseases of the retina, including age-related macular degeneration, inherited retinal diseases (IRDs), diabetic retinopathy, and vascular occlusion represent the commonest cause of severe sight impairment in the developed world. Inherited retinal diseases are the leading cause of blindness in people of working age in England and Wales, and the second commonest cause in children.[1] Defects in genes encoding proteins involved in the phototransduction cascade or the visual cycle account for a large proportion of IRDs.

Gene therapy offers an opportunity to improve outcomes of inherited monogenic disorders of the retina. In its simplest and commonest form, gene 'supplementation' therapy compensates for a genetic deficiency, resulting from loss-of-function mutations in the endogenous gene, by provision of the normal gene to the cells in which it is required.[2] The therapeutic gene, typically delivered using a viral vector, is utilised by the transcriptional machinery of the target cell to generate the normal gene product that is otherwise lacking. Alternative gene therapy techniques aim to

suppress the undesirable expression of a harmful protein product resulting from gain-of-function mutations, with or without simultaneous provision of the normal gene.[3] In addition, gene editing strategies to correct harmful mutations in endogenous genes, and anti-sense oligonucleotide mediated exon skipping to mitigate their impact, are also being investigated. The first gene therapy product approved by the European Medicines Agency was Glybera, for the treatment of lipoprotein lipase deficiency.[4]

Here we describe the key strategies of ocular gene therapy and focus on its application to disease of the retina, with emphasis on experimental therapies in clinical trials. Figure 1 is a schematic diagram of the location of genes in cells of the outer retina targeted in current gene therapy trials. Similar techniques have been used in clinical gene therapy trials targeting other single-gene diseases, including primary immune deficiencies, haemoglobinopathies, haemophilia B, neurological diseases, cancer immunotherapies.[4]
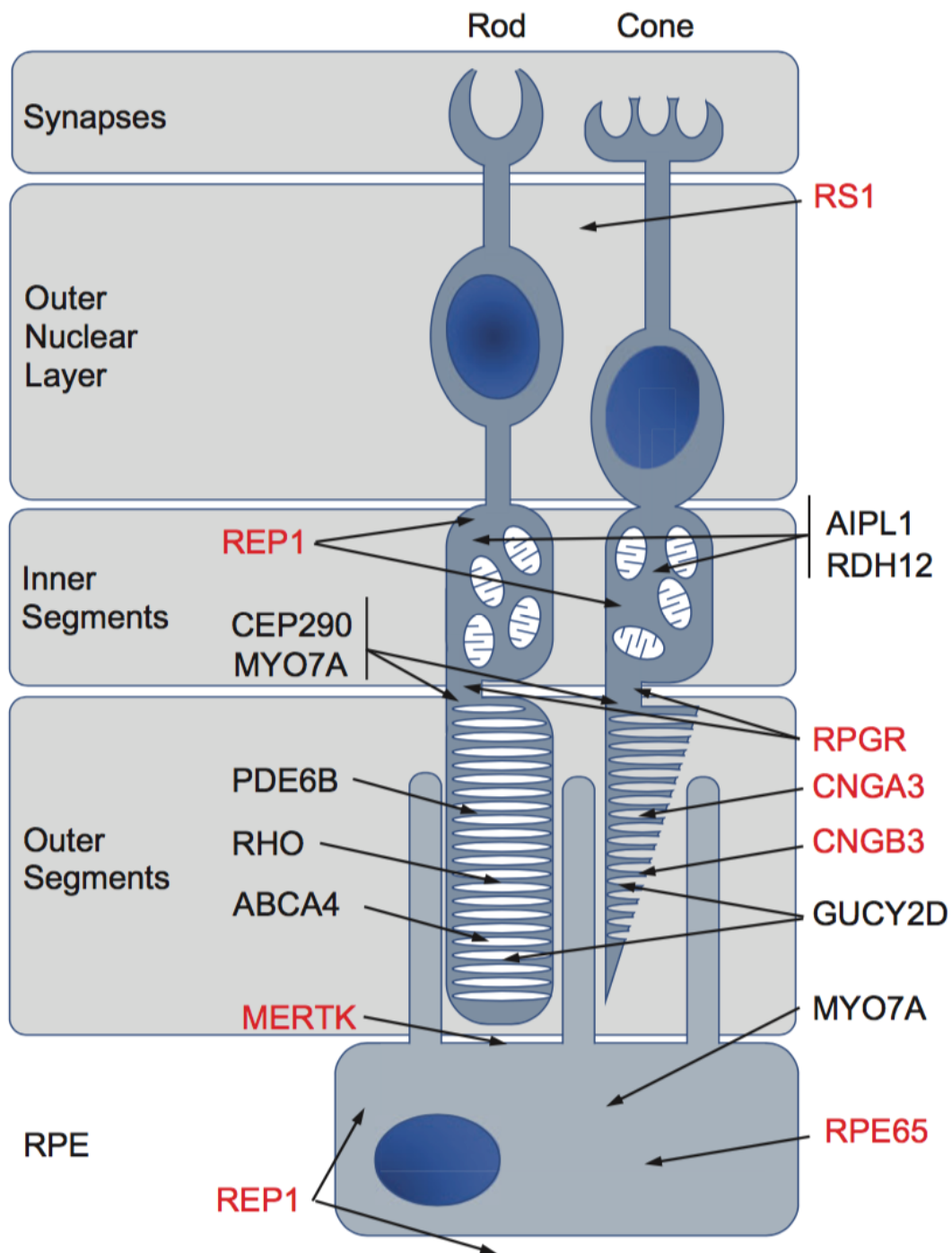
Figure 1: Schematic diagram showing the outer retina and the cellular location of poducts of the genes targeted by current gene therapy trials (red) and the genes explored for future trials (black).

Gene Therapy and the Eye

The retina has specific advantages as a target organ for gene therapy. The optical transparency of the ocular media provides accessibility for microsurgical delivery of vector suspension to the retina under direct visualisation, and for high-resolution imaging at a cellular level of definition for targeting of intervention and assessment of its impact. Vector suspension can be targeted to the retina with minimal systemic dissemination owing to the contained nature and compartmentalisation of the intraocular tissues. The intraocular environment provides the retina with a degree of immune privilege, which limits immune responses that could adversely affect retinal function and limit expression of the therapeutic gene. Since inherited retinal disease typically causes bilateral disease with significant symmetry, the untreated contralateral eye offers a valuable control for natural history, learning effects and intra-individual variability in performance.

For gene transfer to retinal cells, most clinical applications currently employ recombinant adeno-associated virus (AAV) or lentivirus vectors. AAV is a small, non-pathogenic single stranded DNA virus widely used for gene delivery in IRDs. AAV vectors can mediate efficient and sustained transduction of photoreceptor cells, retinal pigment epithelium, and ganglion cells. First generation AAV2 vectors are limited by relatively slow onset of expression and small capacity (4.7 kB)[5]. However, the isolation of alternative serotypes and the development of self-complementary vectors and novel variants, by rational design and/or directed evolution, have provided a broad range of alternatives with more rapid expression and cell tropisms.[6,7] Measures to address the limited capacity include dual AAV vector strategies in which a large gene delivered in component parts by AAV is

reconstituted by splicing.[8] Since lentiviral vectors have substantially greater capacity (approximately 8 kB) than AAV, they can naturally accommodate larger genes. Lentiviral vectors mediate efficient transduction that is typically limited to retinal pigment epithelial cells but one type of lentiviral vector, derived from the equine infectious anaemia virus, mediates variable transgene expression in photoreceptor cells.[9] Vector capacity is a fundamentally important issue given that the most common genes causing IRD are large, including *ABCA4* (Stargardt Disease) and *USH2A* (syndromic and non-syndromic Retinitis Pigmentosa).

Intraocular Administration

Since defects in genes involved in phototransduction or the visual cycle account for many IRDs, photoreceptors and retinal pigment epithelial cells are important target populations for gene therapy. Viral vectors deliver genes to these cells efficiently when the vector suspension is placed in direct contact with the cells in the outer retina. This is typically achieved by injecting the vector suspension between the retinal pigment epithelium and the overlying photoreceptor cell layer. Injection into this potential subretinal space is typically performed using a fine cannula that is advanced through the sclera anteriorly, across the vitreous cavity and through the inner retina (Figure 2a). Injection into this site generates a bleb of vector suspension that temporarily separates the neurosensory retina from the underlying retinal pigment epithelium, before it is absorbed over a period of hours or days. Injection of vector suspension into the vitreous cavity (Figure 2b) can result in gene delivery to cells of the inner retina, including ganglion cells. Although intravitreal vector is

technically simpler than subretinal injection, anatomical barriers prevent efficient gene delivery to the outer retina and this route of administration may be more immunogenic than subretinal injection.[10] Compromise of inner retinal integrity, in conditions such as X-linked Retinoschisis, may enable enhanced access of intravitreal vector suspensions to the inner retina.[11] Delivery of vector suspensions into the suprachoroidal potential space (between the sclera and choroid) may enable targeting of the choroid, for conditions such as age-related macular degeneration and idiopathic polypoidal choroidal vasculopathy.[12]
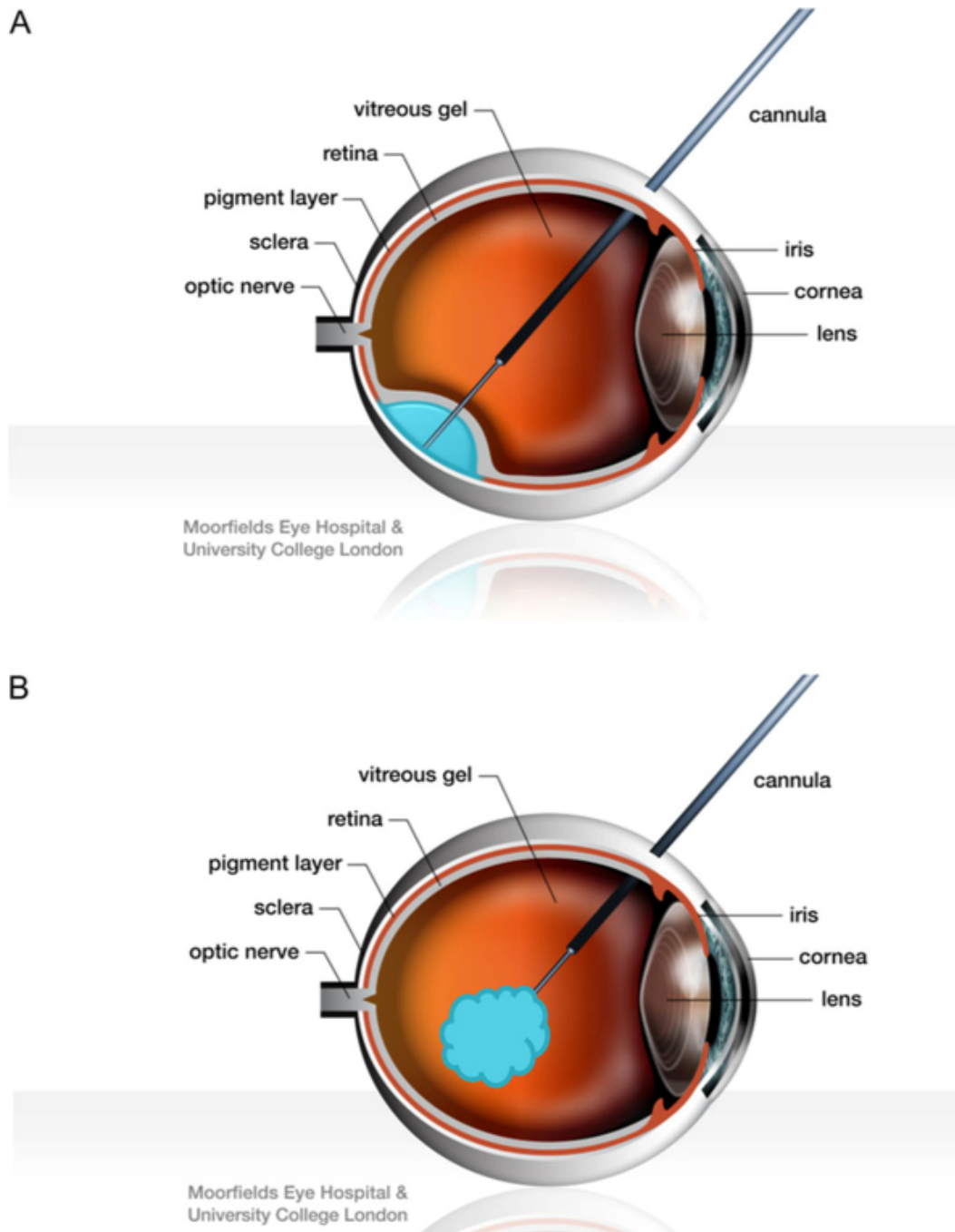
A

vitreous gel
retina
pigment layer
sclera
optic nerve

cannula

iris
cornea
lens

Moorfields Eye Hospital &
University College London

B

vitreous gel
retina
pigment layer
sclera
optic nerve

cannula

iris
cornea
lens

Moorfields Eye Hospital &
University College London

Figure 2: Schematic diagram identifying ocular structures and location of (A)

subretinal injection and (B) intravitreal injection.

Current Gene Therapy Clinical Trials

RPE65

Leber Congenital Amaurosis (LCA), first described by Theodore Leber in 1869, is a group of recessively inherited infantile-onset rod-cone dystrophies. The prevalence ranges from 1 in 33,000 to 1 in 81,000.[13] LCA accounts globally for 5% of IRDs and 20% of children attending specialist schools for students with sight impairment.[14] Mutation of one of several genes, including *RPE65*, causes impaired vision from birth/early infancy and typically progresses to severe sight impairment. Figure 3 demonstrates the appearance of the retina in *RPE65*-associated Leber congenital amaurosis. *RPE65* is expressed in the retinal pigment epithelium and encodes a 65-kD protein that is a key component of the visual cycle, a biochemical pathway that regenerates the visual pigment after exposure to light. [15,16] A lack of functional RPE65 results in deficiency of 11-*cis* retinal such that rod photoreceptor cells are unable to respond to light.[17] Cone photoreceptor cells have access to 11-*cis*–retinaldehyde chromophore through an alternative pathway that does not depend on retinal pigment epithelium–derived RPE65 thus allowing cone-mediated vision in children.[18] However, progressive degeneration of cone photoreceptor cells ultimately results in the loss of cone-mediated vision. Gene-replacement therapy can improve visual function in rodent models of *RPE65*-LCA, and in the Swedish Briard dog, which has a naturally occurring mutation in *RPE65*.[19] The treated eyes of dogs showed improved responses on electroretinography, pupillometry and flash-evoked cortical potentials in the dark-adapted state, with improvements sustained for as long as 10 years.[19]
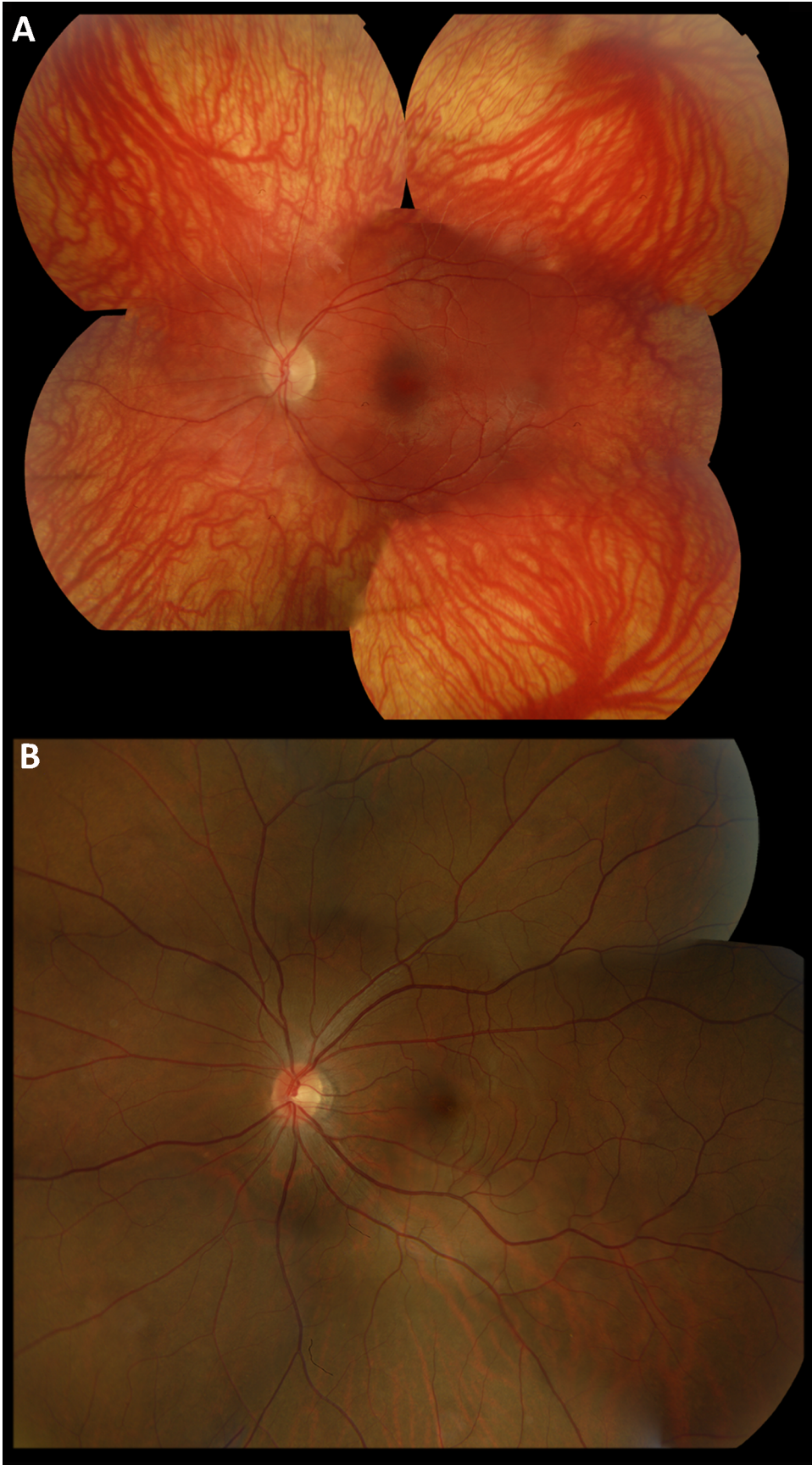
Figure 3: Colour fundus photographs of (A) a patient with RPE65-associated Leber congenital amaurosis and (B) an unaffected individual for comparison. (A) shows peripheral RPE atrophy with a tessellated appearance to the fundus owing to the choroidal vasculature, with central preservation of retinal structure.

The first trial of ocular gene therapy for humans with *RPE65*-LCA was reported in 2008[20]. Several phase I/II trials have provided proof of principle that subretinal injection of a recombinant AAV 2/2 vector containing the *RPE65* cDNA can improve retinal function and vision.[20-23] The findings of a subsequent open-label randomised controlled trial confirm benefit at 1 year to night vision, as indicated by improved performance in a test of vision-guided mobility in low luminance, and to visual fields.[24] In 2017 the US FDA approved voretingene neparvovec (Luxturna, Spark Therapeutics Inc) for the treatment of RPE65-associated LCA. Longer term findings indicate that, despite improved function of surviving retina, the durability of benefit can be limited by progressive retinal degeneration.[23,25-27] To investigate the hypothesis that greater provision of RPE65 will provide more durable, robust benefit, the impact of a more efficient optimised AAV 2/5 vector is being investigated.[28] Figure 4 illustrates one example of improved retinal sensitivity in RPE65-associated LCA following intervention gene therapy, as demonstrated by advanced hill of vision modelling.[29]
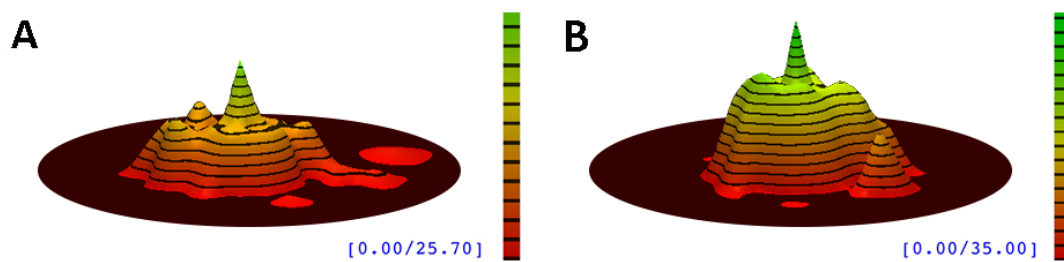
Figure 4: An oblique topographical view of the central hill of vision, produced by Visual Field Modelling and Analysis (VFMA, Office of Technology Transfer and Business Development [OHSU], Portland, Oregon, USA)[29] in a subject (A) prior to and (B) following gene therapy intervention (A) shows residual central visual field prior to intervention, in comparison to (B) which demonstrates increased retinal sensitivity and therefore a larger and taller hill of vision at one year post-intervention.

CNGA3, CNGB3

Achromatopsia (ACHM) is a recessively inherited disorder of cone photoreceptor function affecting approximately 1 in 30,000 people. The condition causes severe impairment of sight from birth with poor visual acuity, absent or markedly reduced colour vision, disabling photophobia and pendular nystagmus.[30] ACHM can be caused by mutations in any one of at least 6 genes including *CNGA3* and *CNGB3,* which encode the alpha and beta subunits respectively of the cone photoreceptor cyclic nucleotide gated channels, and account for the majority of people affected.[30] Structural preservation of individual cone photoreceptors can be determined in affected humans by adaptive optics scanning laser ophthalmoscopy (AO-SLO)[30], to evaluate their potential to benefit from gene therapy and determine the impact of intervention. AAV-mediated gene replacement therapy can improve cone function in

rodent models of both *CNGA3*-ACHM[31] and *CNGB3*-ACHM[32], and in canine models of

CNGB3-ACHM.[30] Early phase clinical trials of gene therapy for both *CNGA3*-ACHM

and *CNGB3*-ACHM will determine the extent to which this approach might benefit

visual acuity, colour discrimination, photophobia and nystagmus in affected humans.

(NCT02599922, NCT03001310, NCT02610582, NCT02935517).

RPGR

Retinitis Pigmentosa (RP) is a term used to describe the clinical phenotype of rod-

cone retinal degenerations, which can be caused by defects in a wide range of genes

that collectively affect 1 in 2-3,000 people. X-linked RP (XLRP) accounts for 15-25% of

RP and is particularly severe, with onset in childhood and progressively severe sight

impairment during early adulthood. Seventy to eighty percent of XLRP is caused by

sequence variants in the *RPGR* gene, which encodes the retinitis pigmentosa GTPase

regulator.[33] In both rodent and canine models of the condition, AAV-mediated gene

supplementation using truncated or codon-optimised constructs to improve

transgene stability have slowed retinal degeneration.[34,35] Phase I/II trials of AAV-

mediated gene therapy in affected humans are ongoing (NCT03116113,

NCT03252847).

CHM

Choroideraemia is an X-linked recessive disorder, characterised by night-blindness in

childhood, with gradually progressive constriction of peripheral vision leading to

impairment of central vision in later life. Choroideremia is caused by sequence

variants in the 1.9kb *CHM* gene that encodes Rab escort protein 1 (REP1), which is

required for intracellular vesicular transport.[36] In a phase I/II clinical trial, subretinal injection of AAV2 vector expressing REP1 is reported to be well tolerated and associated with improved function in some instances.[37,5]. Long-term follow up will be needed to determine whether gene therapy can protect against progressive constriction of visual fields owing to retinal degeneration. (NCT01461213, NCT02553135, NCT02671539, NCT02077361).

MERTK

Defects in the gene encoding MERTK, a receptor tyrosine kinase essential for removal of waste material from photoreceptors, result in accumulation of debris and progressive rod-cone retinal degeneration (retinitis pigmentosa).[38] [39] In a rodent model of the disease, gene replacement therapy by subretinal administration of AAV2 vectors encoding *Mertk* can improve the outcome.[40,41] In a phase I/II clinical trial, an AAV2- *MERTK* vector was well tolerated in affected humans with a suggestion of temporary benefit in some participants.[42]

RS1

X-Linked Retinoschisis (XLRS) causes impairment of sight in childhood, with variable progression in later adulthood. The prevalence is estimated to be 1 in 10,000 men. Associated features include strabismus, refractive error, and anisometropia. Gene defects in *RS1*, which encodes retinoschisin, impair adhesion and transmission between photoreceptor and bipolar cells, leading to schisis of the macula and retinal dysfunction. 50% of patients also have peripheral retinoschisis which presents a risk of associated retinal detachment and vitreous haemorrhage. Intravitreal delivery of

AAV2 or AAV8 vectors encoding RS1 improves the outcome in *Rs1*-deficient mice, and appears safe in rabbits.[11,43,44] Phase I/II dose-escalation clinical trials of intravitreal gene replacement of *RS1* using AAV2 and AAV8 vectors are on-going (NCT02317887, NCT02416622).

Candidate genes for future clinical trials

AIPL1

Aryl hydrocarbon receptor-interacting protein-like 1 (AIPL1) is a molecular chaperone of phosphodiesterase 6, which mediates rod photoreceptor specific phototransduction. Mutations in *AIPL1* cause a particularly severe, rapidly progressive form of LCA *(AIPL1*-LCA). Affected individuals present with severe sight impairment from birth and rapid retinal degeneration. Although the natural history is very poor, some preservation of retinal structure during infancy in humans[45] indicates a window of opportunity for intervention by gene replacement therapy, with the potential for benefit demonstrated experimentally in a rodent model.[46,47]

GUCY2D

Retinal guanylate cyclase-1 is essential in photoreceptor cells for timely recovery from photoexcitation. Mutations in the *GUCY2D* gene account for 10-20% of LCA and photoreceptor architecture is relatively well preserved.[48] Improved retinal function following gene replacement therapy using AAV5 and AAV2/8 and AAV8 based gene therapy in mouse models indicates that affected humans may benefit.[48,49]

CEP290

*CEP29*0 encodes a centrosomal protein involved in trafficking through the connecting cilia of photoreceptor cells. Mutations in *CEP290* account for 30% of LCA. The size of the full-length gene exceeds the capacity of AAV vectors for a gene replacement strategy. However, the most common disease-causing variant, the intronic variant c.2991+1655 A>G, creates a cryptic splice donor site and premature stop codon that may be addressed by alternative strategies such as anti-sense oligonucleotides or CRISPR/Cas9-mediated gene editing.[50]

ABCA4

Stargardt disease (STGD1) results from mutations in the photoreceptor-specific flippase ABCA4, leading to intracellular accumulation of a toxic retinoid, and degeneration of the outer retina. STGD1 is the most common inherited macular degeneration, with an incidence of 1 in 10,000[51], causing progressively severe impairment of sight from early childhood or adulthood. The full-length *ABCA4* gene (6.8kb) exceeds the carrying capacity of AAV vectors. Alternative strategies for gene replacement include the use of oversized AAV5 vectors[52], trans-splicing and hybrid AAV2 dual vector systems[8]. The use of a lentiviral vector based on Equine Infectious Anaemia Virus (EIAV) is reported to improve the outcome in a rodent model of the condition[53] and to be well-tolerated in non-human primates.[54] A phase I/II dose escalation clinical trial of EIAV-*ABCA4* vector is on-going (NCT01367444).

MYO7A

Usher Syndrome is a recessively inherited condition characterised by impairment of sensorineural hearing and progressive impairment of sight owing to rod-cone degeneration. It is clinically and genetically heterogeneous, and is associated with defects in as many as 10 genes.[55] Usher syndrome type 1B is caused by defects in the myosin VIIa (*MYO7A*) gene, resulting in abnormal accumulation of opsin in the cilia of photoreceptor cells. Like *ABCA4*, the large size of the *MYO7A* (8.1kb) gene[52] exceeds the carrying capacity of conventional AAV2/2 vectors. Alternative strategies include the use of dual vectors[8],[56] to deliver gene fragments that are reassembled by homologous recombination following transduction, oversized AAV5 vectors[52], and lentiviral vectors[57,58]. Subretinal injection of EIAV-*MYO7A* is well tolerated in non-human primates, and the potential for benefit to vision in humans is being explored in an on-going phase I/II clinical trial (NCT01505062).[58]

RHO

Many disease-causing sequence variants in *RHO*, which encodes the rod-photoreceptor pigment rhodopsin, have dominant negative effects in which the protein interferes with essential cell functions leading to variably severe rod-cone degeneration [59]. More than 150 such mutations in *RHO* have been identified, accounting for 20-30 % of autosomal dominant retinitis pigmentosa.[60] Strategies to suppress expression of the disease allele specifically are currently unfeasible owing to the substantial mutational heterogeneity. One alternative strategy is to suppress both the mutant and wild-type allele non-specifically, and simultaneously to provide a replacement gene that encodes the wild-type protein which has been modified to

resist suppression.[61] This approach can improve the outcome in a rodent model but has yet to be explored in affected humans.

Age-related macular degeneration (AMD)

Age related macular degeneration (AMD) is the leading cause of vision loss in individuals over the age of 60. AMD can be classified as neovascular (wet) or dry. Impairment of sight from neovascular AMD and proliferative diabetic retinopathy is a direct consequence of pathological neovascularisation which is driven strongly through the up-regulation of vascular endothelial growth factor (VEGF.) The use of therapeutic anti-VEGF antibodies has resulted in substantially improved outcomes for these conditions, but sustained benefit requires regularly repeated intraocular injections. Vector-mediated gene expression of angiostatic proteins offers the opportunity to achieve sustained intraocular delivery following a single injection. Subretinal injection of a rAAV 2/2 vector expressing the soluble VEGF receptor sFlt-1 appears to be well tolerated in humans with neovascular AMD, though a larger study will be needed to determine benefit (NCT0149805).[62,63] Intravitreal injection of an AAV2 vector expressing sFlt-1 in advanced neovascular AMD was followed by improved structure in a minority.[64] Intraocular expression of sFlt-1 was sustained but variable and possibly limited by antibody-mediated immune responses to AAV2, with clinical signs of inflammation evident in some instances (NCT01024998).

Subretinal delivery of Retinostat[TM,] a non-replicating EIAV vector containing genes encoding the angiostatic proteins Endostatin and Angiostatin, appears safe in

rodent[65] and non-human primate models [66]. In humans with neovascular AMD, subretinal injection of Retinostat™ results in sustained intraocular transgene expression, and appears well tolerated (NCT01301443.)[67]

Dry AMD is characterised by dysfunction and degeneration of retinal pigment epithelial cells and formation of deposits called drusen. Multiple theories have been proposed to explain the underlying pathogenies including a predominantly inflammatory aetiology, with an over active complement cascade resulting in the accumulation of a membrane attack complex (MAC) leading to cell damage and death having been implicated.[68] The protein CD59 is seen in normal human cells to block MAC.[69] A gene therapy product to increase expression of a soluble form of CD59 (sCD59) is currently being investigated (NCT03144999).

The Future

The benefits of gene therapy for LCA-*RPE65* have led to approval by the FD of the first gene therapy for ocular disease, and to a rapid expansion in clinical trials exploring the safety and potential benefit of gene therapy for other inherited and acquired retinal diseases. The results will help define for each condition the potential window of opportunity for effective intervention. Further developments in vector design and delivery will enable greater efficiency and safety of gene transfer. Rapid reliable assessment of outcomes will be accelerated by optimisation of clinical trial design.

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Table 1

Disease	Gene	Gene Function	Vector	Mode	Phase	Current Status	Clinical Trials ID	Sponsor	Location
LCA-2	RPE65	Retinoid cycle	AAV2/2	Subretinal	III	Ongoing	NCT00999609 NCT01208389	Spark Therapeutics	UK
LCA-2	RPE65	Retinoid cycle	AAV2/2	Subretinal	I	Ongoing	NCT00516477	Spark Therapeutics	USA
LCA-2	RPE65	Retinoid cycle	AAV2/5	Subretinal	I/II	Ongoing	NCT02781480 NCT02946879	MeiraGTx UK II Ltd	UK
LCA-2	RPE65	Retinoid cycle	AAV2	Subretinal	I	Unknown	NCT00821340	Hadassah Medical Organization	Israel
LCA-2	RPE65	Retinoid cycle	AAV2/2	Subretinal	I	Ongoing	NCT00481546	University of Pennsylvania and National Eye Institute	USA
LCA-2	RPE65	Retinoid cycle	AAV2	Subretinal	I/II	Ongoing	NCT00749957	Applied Genetic Technologies Corp	USA
LCA-2	RPE65	Retinoid cycle	AAV2/2	Subretinal	I/II	Completed	NCT00643747	University College London	UK
LCA-2	RPE65	Retinoid cycle	AAV2/4	Subretinal	I/II	Completed	NCT01496040	Nantes University Hospital	France
LCA-10	CEP290	Ciliary transport	N/A*	Intravitreal	I/II	Ongoing	NCT03140969	ProQR Therapeutics	USA, Belgium
Stargadt Macular Degeneration	ABCA4	Retinoid transfer	EIAV	Subretinal	I/II	Ongoing	NCT01367444	Sanofi/Oxford BioMedica	USA, France

Disease	Gene	Mechanism	Vector	Delivery	Phase	Status	NCT	Sponsor	Location
RP assoc. with Usher's Syndrome Type 1B	MYO7A	Intracellular transport	EIAV	Subretinal	I/II	Ongoing	NCT01505062	Sanofi/Oxford BioMedica	USA, France
Choroideraemia	REP1	Intracellular trafficking	AAV2	Subretinal	II	Ongoing	NCT02553135	University of Miami	USA
Choroideraemia	REP1	Intracellular trafficking	AAV2	Subretinal	II	Ongoing	NCT02671539	STZ Eyetrial	Germany
Choroideraemia	REP1	Intracellular trafficking	AAV2	Subretinal	I/II	Ongoing	NCT01461213	University of Oxford/ NightstaRx	UK
Choroideraemia	REP1	Intracellular trafficking	AAV2	Subretinal	I/II	Ongoing	NCT02077361	University of Alberta/ NightstaRx	Canada
Choroideraemia	REP1	Intracellular trafficking	AAV2	Subretinal	II	Ongoing	NCT02407678	University of Oxford/ NightstaRx	UK
Choroideraemia	CHM	Intracellular trafficking	AAV2	Subretinal	I/II	Ongoing	NCT02341807	Spark Therapeutics	USA
MERTK-RP	MERTK	Cellular signalling	AAV2	Subretinal	I	Ongoing	NCT01482195	King Khaled Eye Specialist Hospital	Saudi Arabia
X-Linked RP	RPGR	Intracellular transport	AAV8	Subretinal	I/II	Ongoing	NCT03116113	NightstaRx	UK
X-Linked RP	RPGR	Intracellular transport	AAV2/5	Subretinal	I/II	Ongoing	NCT03252847	MeiraGTx UK II Ltd	UK
Achromatopsia	CNGB3	Phototransduction cascade	AAV2	Subretinal	I/II	Ongoing	NCT02599922	Applied Genetic Technologies Corp	USA
Achromatopsia	CNGB3	Phototransduction	AAV2/8	Subretinal	I/II	Ongoing	NCT03001310	MeiraGTx UK II	UK

		cascade						Ltd	
Achromatopsia	CNGA3	Phototransduction cascade	AAV8	Subretinal	I/II	Ongoing	NCT02610582	STZ Eyetrial/ University Hospital Tuebingen	Germany
Achromatopsia	CNGA3	Phototransduction cascade	AAV2	Subretinal	I/II	Ongoing	NCT02935517	Applied Genetic Technologies Corp	USA, Israel
X-Linked Retinoschisis	RS1	Intercellular adhesion	AAV8	Intravitreal	I/II	Ongoing	NCT02317887	National Eye Institute	USA
X-Linked Retinoschisis	RS1	Intercellular adhesion	AAV2	Intravitreal	I/II	Ongoing	NCT02416622	Applied Genetic Technologies Corp	USA
Neovascular-AMD	sFLT01	Anti-angiogenesis	AAV2	Intravitreal	I	Ongoing	NCT01024998	Sanofi	USA
Neovascular-AMD	AntiVEGFfab	Anti-angiogenesis	AAV8	Subretinal	I	Ongoing	NCT03066258	Regenxbio	USA
Neovascular-AMD	sFLT01	Anti-angiogenesis	AAV2	Subretinal	I/II	Completed	NCT01494805	Lions Eye Institute	Australia
Neovascular-AMD	Endostatin/ Angiostatin	Anti-angiogenesis	EIAV	Subretinal	I	Completed	NCT01301443	Oxford BioMedica	USA
Dry-AMD	sCD59	MAC inhibitory protein	AAV2	Intravitreal	I	Ongoing	NCT03144999	Hemera Biosciences	USA
Retinitis Pigmentosa	ChR2	Light-gated ion channels	AAV2	Intravitreal	I/II	Ongoing	NCT02556736	Allergan	USA

Table 1: Clinical trials of retinal gene therapy (LCA: Leber Congenital Amaurosis, RP: Retinitis Pigmentosa.) *RNA antisense oligonucleotides are administered without a vector.