Review of Contemporary Philosophy
ISSN: 1841-5261, e-ISSN: 2471-089X
Vol 22 (1), 2023
Pp 5975 - 5987

The Potential of Gene Therapy as A Ground Breaking Approach to Treating Inherited Retinal Diseases and Other Genetic Eye Conditions: Review

[1]-Dina IdarousMisky,[2]-Fahad Bader Alharbi,[3]- Samar Mohammad Alghamdi,[4]-Maha Khalofah Alghamdi,[5]-Hassan Mohammed Alshehri

[1.] Ksa, Ministry Of Health, Hera General Hospital Makkah
[2.] Ksa, Ministry Of Health, Ohud General Hospital
[3.] Ksa, Ministry Of Health, Ohud General Hospital
[4.] Ksa, Ministry Of Health, Ohud General Hospital
[5.] Ksa, Ministry Of Health, Ohud Hospital

Abstract

Background: Inherited retinal degenerations (IRDs) represent a diverse group of genetic disorders that often lead to significant visual impairment and were historically considered untreatable. Recent advancements in molecular biology have spurred the development of gene therapies, notably the FDA-approved voretigene neparvovec-rzyl, which targets RPE65-associated Leber congenital amaurosis (LCA).

Methods: This review examines various therapeutic strategies currently in clinical trials for IRDs, including gene augmentation, gene editing, optogenetics, neuroprotection, and stem cell therapies. The efficacy of these methods is assessed through a comprehensive analysis of ongoing interventional clinical trials and preclinical investigations.

Results: Over 60 active clinical trials are exploring gene therapies for different IRDs, with promising results indicating potential improvements in visual function. Notably, gene augmentation therapies using adeno-associated viruses (AAVs) have shown efficacy in restoring vision in patients with specific genetic mutations. Emerging techniques such as RNA interference and CRISPR/Cas9 gene editing are also being evaluated for their ability to address a wider range of genetic mutations associated with retinal diseases.

Conclusion: The field of gene therapy in ophthalmology is rapidly evolving, offering new hope for patients with inherited retinal diseases. Ongoing research and clinical trials are critical for establishing the safety and long-term efficacy of these innovative therapies. The future of ophthalmologic treatments is likely to see a shift towards personalized medicine that targets the underlying genetic causes of visual impairment.

Keywords: Gene therapy, inherited retinal disease, RPE65, visual impairment, CRISPR.

Received: 07 October 2023 **Revised**: 22 November 2023 **Accepted**: 06 December 2023

1. Introduction

Inherited retinal degenerations (IRDs) are a genetically and clinically diverse category of illnesses often marked by significant visual impairment. Historically deemed untreatable, current progress in molecular biology has resulted in the first FDA-approved gene therapy for retinal dystrophy, voretigene neparvovec-rzyl (LUXTURNA), targeting RPE65-associated Leber congenital amaurosis (LCA). Presently, several medicines for various illnesses are under assessment in more than 60 active interventional clinical trials and preclinical investigations. Numerous medicines under research aim to address inherited retinal diseases (IRDs) linked to particular genotypes; nevertheless, the field is progressively concentrating on universal therapy techniques applicable to a wide array of retinal dystrophies and degenerations. This study will examine several tactics used in clinical research for the treatment of inherited retinal diseases

(IRDs), emphasizing neuroprotection, gene augmentation, gene editing, optogenetics, and stem or precursor cell treatments.

Researchers in vision science have led advancements in gene therapy and regenerative medicine. This is not coincidental, since the eye provides several benefits for the research and advancement of these technologies. These ocular investigations provide structural benefits due to the eye's compartmentalized architecture, enabling precise targeted delivery of cell and molecular treatments, including viral vectors, to the target tissue under direct view [1]. The eye is regarded as an immune-privileged organ, which may mitigate the inflammatory response linked to gene therapy administration [2-4]. Although antibodies against viral vectors have been observed after treating one eye [5], the treatment of the contralateral eye has demonstrated safety and efficacy [6]. Nonetheless, monitoring the eye for inflammation after viral-mediated gene therapy is a crucial issue. The contralateral eye may function as the untreated control in clinical studies to assess the effectiveness of the medication under evaluation, which is essential due to the variability in disease development among patients with retinal dystrophies [3]. Furthermore, there exists an extensive array of non-invasive techniques to assess the visual system using objective functional metrics (electroretinography, ERG), structural metrics (retinal imaging), and psychophysical evaluations (visual fields, microperimetry) to monitor alterations post-therapy. Advanced multimodal imaging methods including optical coherence tomography (OCT), fundus autofluorescence, and color fundus photography. Nonetheless, significant advancements in therapeutic therapy would have been unattainable without diverse experimental animal models for hereditary retinal degenerations, which have accelerated our comprehension of the pathobiology of vision loss. These models have facilitated the development of novel experimental therapeutics and proof-of-concept studies that demonstrated their therapeutic efficacy in decelerating retinal degeneration and perhaps restoring eyesight.

2. Genomics of Hereditary Retinal Disorders

Progress in molecular genetics during the last three decades has enabled the identification of mutations in over 300 distinct genes responsible for hereditary retinal degenerations [7,8]. Although some reported mutations are few, recent research estimated that almost 2.7 billion individuals globally, or over one-third of the human population, are healthy carriers of a mutation in a gene linked to an autosomal recessive inherited retinal disease (IRD) [7]. This may represent the greatest prevalence among all Mendelian disorders in humans. Most hereditary retinal dystrophies are monogenic illnesses that adhere to standard Mendelian inheritance patterns, including autosomal dominant, autosomal recessive, and X-linked transmission. Primarily thanks to advancements in next-generation sequencing (NGS) technology, clinical genetic testing is becoming more accessible and cost-effective, enabling many individuals diagnosed with clinical retinal dystrophy to get a molecular diagnosis [8-10].

Current estimations indicate that 90% of individuals with an inherited retinal disease (IRD) possess a mutation in one of the identified causal genes [11]. To reduce expenses and enhance accessibility to genetic testing, retinal dystrophy gene panels and clinical syndrome-specific gene panels (e.g., for macular dystrophies) have been developed and are used at academic medical facilities and clinical labs. These methodologies enable the identification of the causal mutation in roughly 70% of cases, with variable contingent upon the clinical condition or population examined [12,13]. For patients whose underlying mutation remains unidentified via these approaches, whole exome and whole genome sequencing may be conducted, and it is anticipated that this will become more commonplace as the cost and accessibility of genetic sequencing increase. The domain of ocular genetics is enhanced by genetic sequencing data-sharing networks via worldwide databases like ClinVar and the Leiden Open Variation Database [14,15]. By using enhanced patient sequencing and genetic analysis, we will find more genes implicated in retinal dystrophies and discern complicated variations that influence both coding and noncoding regulatory areas responsible for these conditions.

Due to the enhanced accessibility and precision of genetic sequencing technology, several IRD experts have proposed sequencing all patients and substituting traditional clinical diagnostic nomenclature for syndromes with a molecular-based classification for these diseases [16]. This proposal recognizes the

genetic diversity of clinical inherited retinal disease syndromes, such as retinitis pigmentosa (RP), which is attributable to mutations in more than 75 genes, and Leber Congenital Amaurosis (LCA), resulting from mutations in over 24 genes. It underscores the significance of identifying these mutations. This is particularly pertinent in an age when an increasing number of gene treatments are under development.

A further benefit of accessible genetic testing is its contribution to estimating the incidence of certain causal gene mutations and particular alleles, so enhancing our ability to allocate resources for the development of future medicines. Although allele frequency varies among populations, collectively, mutations in the ABCA4 gene (Stargardt disease), EYS (linked to non-syndromic RP, cone-rod dystrophy, and LCA), USH2A (associated with Usher syndrome type 2 and non-syndromic RP), CEP290 (related to LCA type 10), and MYO7A (connected to Usher syndrome type 1) constitute over one third of all instances of inherited retinal diseases (IRDs) [7,18-20]. These genes have emerged as leading prospects for the development of novel gene treatments. Nonetheless, the treatment of common variations in each of these genes presents distinct molecular problems.

3. Neuroprotection

The shared characteristic of retinal dystrophies is the premature degeneration of photoreceptor cells [21-26]. The retina contains light-responsive cells, namely high-sensitivity rods and cones, which are triggered by strong light of various hues based on the photopigments they express. Cones are densely located in the macula, while rods are distributed over the macula and peripheral retina [27-33]. Photoreceptors are terminally differentiated neurons that do not recover after degeneration or damage in adult animals [34-38]. Autosomal recessive dystrophies mostly result from mutations in genes expressed by photoreceptors and retinal pigmented epithelium (RPE) cells, which are essential for the proper development, function, and survival of photoreceptor cells [8,38,39]. Considering the extensive array of mutations associated with inherited retinal diseases (IRDs) and the widespread occurrence of acquired retinal degenerations, including age-related macular degeneration (AMD) and diabetic retinopathy, there is a strong impetus to devise treatment strategies independent of the molecular mechanisms of the underlying conditions.

4. Gene Replacement Therapies: Initial Achievements and Prospective Obstacles

Progress in molecular biology and a comprehensive knowledge of the pathogenesis of retinal illness facilitated the creation of the first FDA-approved gene therapy for biallelic RPE65-associated Leber congenital amaurosis (LCA), voretigene neparvovec-rzyl (LUXTURNA). RPE65 is an isomerase essential for the visual pigment cycle, functioning inside retinal pigment epithelium (RPE) cells. Prior to the development of gene treatments for retinal diseases, researchers created animal models in many species, including rats and Briard dogs, which facilitated the comprehension of the physiological function of the RPE65 enzyme in vision and pathology. Subsequently, these models served as the foundation for the creation and validation of experimental gene treatments aimed at restoring the function of mutant RPE65 [39-41]. Although tiny animal models were advantageous in laboratory settings for investigating the cell biology of illness, owing to their genetic manipulability and abbreviated life spans, bigger animal models were essential for the preclinical advancement of surgical techniques pertinent to vector administration in humans. Concurrent natural history investigations of disease development in RPE65-associated retinal dystrophy revealed that these patients had a slower anatomical progression regarding photoreceptor cell loss compared to other types of LCA [42-44]. This notable structure-function separation creates an environment conducive for enough cells to act as a substrate for gene substitution. Three distinct clinical investigations used various vectors derived from adeno-associated virus (AAV)-2 to provide a functional copy of the RPE65 coding sequence to participants [45-47].

A crucial insight gained from the successful RPE65 gene therapy research is the need for creativity in assessing enhancements in visual function among a low-vision patient group [16]. Outcome measurements must extend beyond central visual acuity to include both physiologically significant responses and those pertinent to the limits patients encounter in their everyday activities. Metrics used in the RPE65 trials included pupillometry [99], full-field sensitivity testing [100], microperimetry [101], dark-adapted sensitivity [102], and visual mobility testing [6,48-52]. The multi-luminance mobility test

(MLMT), developed and validated for these research, effectively evaluates the functional difficulties patients encounter with low-luminance vision [53]. MLMT was a significant endpoint for assessing treatment response in the Phase 3 effectiveness study of voretigene neparvovec-rzyl [54]. Variants of this test are now used in more interventional studies for inherited retinal diseases (IRDs).

The efficacy of voretigene neparvovec-rzyl has initiated an exploration to discover more retinal dystrophies amenable to gene augmentation, namely the use of a viral vector to provide a functional copy of the defective gene. This procedure is applicable for treating loss-of-function mutations, and several ongoing Phase 1/2 clinical studies are using this method for certain inherited retinal diseases (IRDs) [16,55]. Adeno-associated viruses (AAVs) have been the preferred gene delivery vector for inherited retinal disease (IRD) therapies for the last three decades. The AAV2 and AAV8 vectors have proven effective in delivering genetic material to photoreceptor cells in the outer retina. Vectors are designed to provide a standard copy of the target gene to photoreceptors or retinal pigment epithelium (RPE) cells, often administered surgically by subretinal injection or, in some instances, via intravitreal injection [55]. In 1998, an AAV vector was initially shown as effective in treating a preclinical model of inherited retinal degeneration (IRD) by restoring visual function in the retinal degeneration slow (rds) mouse by the restoration of a wild-type copy of the PRPH2 gene [56].

Additional clinical studies investigating the use of AAV vectors for the treatment of various IRD targets are included in Table 1. The quantity of simultaneous funded investigations spanning many inherited retinal diseases indicates the potential of gene therapy methods for treatment. Several, but not all, of these first studies are demonstrating encouraging outcomes and progressing to more advanced phases [57]. Ongoing research include Phase 1/2 trials for CNGA3- and CNGB3-associated achromatopsia (Sponsors: AGTC; MeiraGTx; STZ eyetrial). The findings from a Phase 1 trial assessing the delivery of CNGA3 via an AAV8 vector (NCT02610582, Sponsor: STZ Eyetrial) were published in 2020, indicating the therapy's safety and enhancements in contrast sensitivity (mean 0.33 log) and visual acuity (mean 2.9 letters) among nine participants. Active Phase 1/2 studies are now in progress for RS1-mediated X-linked retinoschisis, sponsored by AGTC and the National Eye Institute (NEI). The NEI's Phase 1 experiments using an AAV8 vector for RS1 delivery (NCT02317887; Sponsor: NIH/NEI) did not exhibit a significant improvement in visual acuity, retinal sensitivity, or electroretinography (ERG) outcomes. Adverse effects related to the medication included intraocular inflammation in four of the nine subjects [58].

Phase 1/2 studies (Sponsors: AGTC; MeiraGTx; 4D Molecular Therapeutics) and Phase 2/3 trials (Sponsor: Biogen/NightstaRx Therapeutics) are now in progress for RPGR-associated X-linked retinitis pigmentosa (XLRP). The outcomes of the Phase 1/2 trial employing an AAV8 vector to administer a codon-optimized variant of RPGR (NCT03116113, Sponsor: Biogen/NightstaRx) were published in 2020, revealing the therapy's safety, with the exception of mild subretinal inflammation (at the injection site) observed in patients receiving elevated doses of the therapy (up to 5 × 10^12 genomic particles (gp)/mL), which responded to oral steroids [59]. The research revealed enhanced retinal sensitivity and restoration of visual field loss in seven of the 18 patients (doses ranging from 5 × 10^11 to 5 × 10^12 gp/mL), sustained during the 6-month follow-up period [59]. In May 2021, it was revealed that the following Biogen-sponsored Phase 2/3 trial did not achieve its main goals of a ≥7 dB improvement from baseline in ≥5 of the 16 central loci in the 10-2 grid evaluated by microperimetry at 12 months post-treatment. Nonetheless, favorable developments were seen in several secondary clinical goals. The MeiraGTx-sponsored Phase 1/2 study for RPGR-associated XLRP demonstrated that the AAV5-RPGR product met safety endpoints and exhibited significant enhancements in secondary functional endpoints at three months, with sustained or improved effects observed at the six-month follow-up for low and intermediate doses. The data were evaluated using static perimetry and microperimetry, revealing substantial differences in mean retinal sensitivity and central visual field progression between treated and untreated eyes. MeiraGTx is advancing to a funded Phase 3 trial for this vector.

Additional significant RP studies are a Phase 1/2 study for PDE6B-associated autosomal recessive (ar) RP (Sponsor: Horama S.A.), a Phase 1/2 trial for RLBP1-associated arRP (Sponsor: Novartis), and a Phase 1/2 trial for MERTK-associated arRP (Sponsor: King Khaled Eye Hospital). The Phase 1 study findings using an

AAV2 vector for MERTK delivery (NCT01482195, Sponsor: King Khaled Eye Specialist Hospital) indicated the safety of subretinal vector administration throughout a two-year follow-up period. The authors found enhanced visual acuity in the treated eye in three of the six eyes that underwent the treatment; however, the improvements diminished within two years in two of the treated eyes [60]. The outcomes of a Phase 1 trial employing an AAV5 vector for GUCY2D delivery in patients with LCA1 (NCT03920007; Sponsor: Atsena Therapeutics) are accessible, revealing safety in the treatment of one eye in three patients over a nine-month follow-up, along with indications of visual enhancement [62]. Two patients exhibited enhancement in rod photoreceptor functionality as assessed by full-field stimulus testing; one patient showed enhanced pupillary responses, while another patient had a gain of 0.3 logMAR in best-corrected visual acuity [62]. Currently, Phase 1 and Phase 2 studies are in progress for choroideremia associated with CHM, sponsored by 4D Molecular Therapeutics, Spark Therapeutics, STZ Eyetrial, the University of Oxford, Bascom Palmer/U of Miami, the University of Alberta, and Biogen/Nightstar Therapeutics. Biogen recently disclosed the preliminary findings of their Phase 3 gene therapy trial for choroideremia (STAR study, NCT03496012) with timrepigeneemparvovec (BIIB111/AAV2-REP1). The trial failed to achieve its main goal of the proportion of individuals exhibiting an improvement above 15 letters from baseline Best-Corrected Visual Acuity (BCVA) as measured by the Early Treatment of Diabetic Retinopathy (ETDRS) chart at the 12-month follow-up. The trial did not indicate effectiveness on secondary endpoints; nevertheless, more long-term analysis is expected.

significant drawback of the AAV vector in IRD gene therapy is its limited size, restricting the delivered coding sequence to roughly 4.7 kilobases (kb) [63]. This has hindered its prompt use in treating prevalent retinopathies attributed to genes with extended coding sequences, such as the ABCA4 gene (6.8-kb), the predominant cause of hereditary macular dystrophy. Consequently, alternative viral vectors like lentiviruses, capable of delivering coding sequences up to 8 kb in length, have been engineered with the expectation that they would enable the transfer of bigger genetic payloads and ensure stable integration into the genomes of transduced cells. Nonetheless, lentiviruses possess inherent limitations, such as their suboptimal efficacy in transfecting photoreceptor cells and the potential danger of tumorigenicity due to the random integration of their coding sequences into the cellular genome. A lentiviral approach administering a wild-type variant of ABCA4 for Stargardt disease and MYO7A for Usher syndrome type 1B was evaluated in Phase 1/2 clinical trials; however, these studies were terminated by the sponsor (ABCA4, NCT01736592, NCT01367444; MYO7A, NCT01505062 Sanofi) [64]. Subsequent research on these methodologies has not yet been disclosed.

Alternative methods being investigated for the delivery of big genes to the retina include split-gene strategies, whereby the coding sequence of a substantial gene is divided and then encapsulated into distinct vectors for delivery. Numerous laboratories have successfully employed this split vector methodology in preclinical models, initially for the delivery of the erythropoietin genomic locus [65], and subsequently for retinal disease genes associated with variants in the MYO7A gene (Usher syndrome, type 1B) and the ABCA4 gene (Stargardt disease) [66]. This method depends on the recombination of the two vectors inside co-infected cells to produce the complete coding sequence of the gene. The efficacy of this method in clinical investigations has yet to be determined.

CEP290 is a substantial gene (8-kb) that has garnered considerable interest for gene therapy strategies. Mutations in CEP290 are the predominant contributors of LCA, representing about 25% of clinical instances. The clinical condition exhibits characteristics of structure-function dissociation, similar to RPE65-associated illness, making it a compelling candidate for gene augmentation treatment. This encompasses the extended maintenance of the outer retinal architecture in the fovea and central macula, the region of the retina accountable for optimal vision acuity. Researchers are exploring methods using a partial gene product, termed the “miniCEP290” fragment, which has shown the ability to restore function in a mouse model of CEP290-LCA and is sufficiently tiny for delivery via an AAV vector [67]. A further significant clinical experiment is under underway, using gene-editing technology to restore a wild-type copy of CEP290 in a patient's photoreceptor cells for the first time in humans. These technologies will be elaborated upon further in this study.

The safety of AAV vectors in the ocular region is corroborated by the lack of significant adverse effects in follow-up studies, which currently exceed 10 years for patients treated with RPE65. Functional tests to identify neutralizing antibodies were conducted throughout these studies, revealing that a subgroup of patients produced antibodies against the AAV2 capsid [5,44,45]. Notably, these reactions were less compared to those seen in people administered systemically injected AAVs, perhaps attributable, in part, to the reduced quantities of virus necessary in the ocular region [68,69]. Comparable investigations used an enzyme-linked immunosorbent spot test (ELISPOT) to demonstrate that antibodies were not produced against RPE65, with two exceptions deemed artifactual [70]. Comparable outcomes were seen in the NEI-sponsored X-linked retinoschisis experiment, where ocular inflammation was identified as the primary adverse event post-treatment, and the patients' sera exhibited positive findings for neutralizing antibodies against the AAV8 capsid, but not against the RS1 protein [59]. Significantly, the AAV delivery in this experiment was administered intravitreally. Antibodies targeting AAV2 were also identified in the Phase 1 study for MERTK-associated arRP [61]. The quantifiable humoral response to AAV capsids has prompted concerns over the timing of therapy for the contralateral eye, with animal studies indicating that neutralizing antibodies produced after treatment of the first eye may diminish the effectiveness of treatment in the contralateral eye [71].

The level of antibody presence may depend on the ocular compartment into which the AAV is administered. Neutralizing antibodies have been seen after intravitreal injection in animal models and human trials, however the sub-retinal compartment seems to function as an immune-privileged location [72,73]. The eye exhibits immunological modulation capabilities via processes such anterior chamber-associated immune deviation (ACAID), which depend on the stimulation of Tregs, anti-inflammatory M2 macrophages, and the production of cytokines that foster immune tolerance [71]. A mechanism analogous to ACAID has been proposed to explain the immunological tolerance seen in the subretinal area after AAV treatment [74]. Localized inflammation was seen in individuals with subretinal injections of large doses of the AAV8-coRPGR construct (5 × 10^12 gp/mL); nevertheless, the inflammation responded to oral drugs [50].

Ultimately, while the use of AAV vectors in ocular treatments has resulted in little detrimental effects, its utilization for systemic genetic illnesses has presented more difficulties. The administration of elevated systemic dosages was associated with liver failure, sepsis, and the fatalities of two people in an Audentes Therapeutics Phase 2 gene therapy trial for X-linked myotubular myopathy [75]. It is noteworthy that none of the patients given a reduced dosage of the medication had liver-related side effects. Other significant instances of high-dose systemic trials of AAV therapies (minimum 2 × 10^14 vector genomes (vg)/kg) with documented toxicities primarily associated with immune responses encompass AveXis'sZolgensma (onasemnogeneabeparvovec) for spinal muscular atrophy, alongside Solid Biosciences' SGT-001 and Pfizer's PF-06939926 for Duchenne muscular dystrophy [76].

5. RNA-Modification Therapies for Hereditary Retinal Degenerations

The aforementioned gene augmentation procedures are effective for retinal degenerations produced by loss-of-function mutations or dominant haploinsufficiency, but they are unsuitable for addressing dominant mutations arising from gain-of-function or dominant-negative alleles. A crucial technique to regulate the expression of these harmful alleles involves the degradation of messenger RNA (mRNA) prior to its translation into protein. Among them, RNA interference (RNAi) has the most comprehensive history of research as a possible treatment for inherited retinal diseases (IRDs). RNA interference (RNAi) functions via the post-transcriptional silencing of messenger RNA (mRNA). The technologies include ribozymes, short-interfering RNA (siRNA), short-hairpin RNA (shRNA), and antisense oligonucleotides (AONs) [77]. Ribozymes are naturally occurring RNAs inside the RNase-P complex that catalyze the conversion of precursor tRNA into its active form. Ribozymes can be artificially designed to cleave specific mRNAs, thereby inhibiting their translation into proteins; however, their limited in vivo catalytic activity has constrained their use in treating inherited retinal diseases (IRDs). Nevertheless, ongoing improvements in kinetic activity are being pursued to facilitate clinical applications. siRNA and shRNA are double-stranded RNAs that, upon expression in a cell, are converted into single-strand antisense guides,

which are integrated into the RNA-induced silencing complex (RISC) to destroy corresponding mRNA [78]. siRNA may be enclosed in lipid delivery systems, whereas shRNA is packed in viral vectors. shRNA may be administered concurrently with a wild-type coding sequence for the target gene, wherein the codon usage has been altered to confer resistance to the RNAi approach, thereby facilitating "knockdown-and-replace" strategies for autosomal dominant diseases, such as dominant RHO-associated retinitis pigmentosa [79]. This resulted in the creation of a dual AAV vector treatment, RhoNova (Roche), although there has been no update on its clinical progression as of this publication. A single AAV2/5 vector that expresses both the shRNA and a normal copy of the RHO gene has been generated and is now undergoing a Phase 1/2 clinical study with IVERIC bio.

Additional innovative RNA-based therapeutics use antisense oligonucleotides (AONs or ASOs), which are synthetic single-stranded RNA or DNA that hybridize with complementary mRNA transcripts. AONs can alter gene expression through various mechanisms, including the inhibition of translation, the cleavage and degradation of mRNA transcripts, or the modification of pre-mRNA splicing, resulting in the inclusion or exclusion of splice sites in frameshift alleles that would typically cause premature termination or transcript degradation [80]. Nucleic acid fragments may be administered to retinal cells by intravitreal injection, eliminating the need for viral or lipid vectors, so making them appealing for the treatment of inherited retinal diseases (IRDs). AONs may be administered with less invasiveness; but they will probably need repeated injections throughout the individual's lifespan.

Presently, Phase 2/3 studies funded by ProQR Therapeutics (NCT03913143, ILLUMINATE, and NCT04855045, BRIGHTEN) are evaluating the effectiveness of an AONs-based medication, sepofarsen, for treating the predominant mutation in the most often implicated gene for LCA, CEP290 [81]. This allele is defined by a point mutation that creates a cryptic splice donor site, resulting in the insertion of an early stop codon. The findings of the Phase 1/2 study (NCT03140969) were released in 2019, indicating that data from ten of the eleven patients who underwent this therapy demonstrated a clinically significant enhancement in visual acuity, with treated eyes exhibiting a measurement of 0.54 log10 MAR (26 letters) superior to untreated eyes three months post-initial dose [82]. Treated eyes exhibited superior performance in full-field stimulus testing (FST) for blue light, in comparison to untreated eyes [82]. CEP290 is a transition zone protein that regulates the proper transport of proteins from the inner segments to the outer segments, and the surviving cone photoreceptors in affected individuals are often anatomically aberrant [83].

Sepofarsen treatment seems to enhance imaging indicators of normal photoreceptor architecture at the junction of the inner and outer segments in two individuals [82]. At three months, ten of the eleven participants got a second injection. The eleventh patient in the experiment declined several injections to prevent early cataracts, and a recent case report documented improvements in visual acuity, FST light sensitivity, mobility assessment, and pupil constriction latency in the treated eye after a single injection. The peak advantage was seen around two months, although he exhibited prolonged benefit for a minimum of fifteen months [83]. The authors noted a temporary rise in OCT reflectivity around the photoreceptor ciliary transition zone between the third and fifth month, which corresponded with the patient's enhancement in visual function. This observation may indicate an imaging correlation between structural and functional improvements resulting from the therapy [83]. ProQR Therapeutics announced the conclusion of recruitment for their Phase 2/3 study (Illuminate) and expects to provide top-line findings in the first half of 2022.

6. Conclusions

Advancements in molecular biology, stem cell biology, and visual science have further enhanced our resources for addressing vision impairment caused by retinal dystrophies. A multitude of these novel methodologies are now being evaluation in clinical trials and are anticipated to provide efficacious medicines that may either avert more vision deterioration or rehabilitate eyesight in an increasing cohort of sufferers. Motivated by the efficacy of gene augmentation procedures, several currently investigated treatments promise to address the whole range of causal mutations associated with inherited retinal

diseases (IRDs). The first gene-editing experiment using CRISPR-Cas9 for the treatment of CEP290 illness is now under progress, and we will shortly ascertain the safety and effectiveness of this promising method in people. Advancements in the efficacy and safety of gene-editing techniques are anticipated to broaden the range of treatable illnesses and alleviate apprehensions about off-target genetic impacts. Additional promising prospects include the efficacy of neuroprotection, optogenetics, or regenerative cell-based treatments that are potentially mutation-agnostic. Certain methodologies may have the potential to restore vision in people with advanced illness or other acquired retinal degenerations. The efficacy of any of these methods would significantly influence the future of ophthalmology and medicine.

References

1. Bainbridge, J.W.B.; Tan, M.H.; Ali, R.R. Gene therapy progress and prospects: The eye. Gene Ther. 2006, 13, 1191–1197.
2. Bennett, J. Immune response following intraocular delivery of recombinant viral vectors. Gene Ther. 2003, 10, 977–982.
3. Gupta, P.R.; Huckfeldt, R.M. Gene therapy for inherited retinal degenerations: Initial successes and future challenges. J. Neural Eng. 2017, 14, 051002.
4. Bucher, K.; Rodríguez-Bocanegra, E.; Dauletbekov, D.; Fischer, M.D. Immune responses to retinal gene therapy using adeno-associated viral vectors—Implications for treatment success and safety. Prog. Retin. Eye Res. 2021, 83, 100915.
5. Bainbridge, J.W.B.; Mehat, M.S.; Sundaram, V.; Robbie, S.J.; Barker, S.E.; Ripamonti, C.; Georgiadis, A.; Mowat, F.M.; Beattie, S.G.; Gardner, P.J.; et al. Long-Term Effect of Gene Therapy on Leber's Congenital Amaurosis. N. Engl. J. Med. 2015, 372, 1887–1897.
6. Bennett, J.; Wellman, J.; Marshall, K.A.; McCague, S.; Ashtari, M.; DiStefano-Pappas, J.; Elci, O.U.; Chung, D.C.; Sun, J.; Wright, J.F.; et al. Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: A follow-on phase 1 trial. Lancet 2016, 388, 661–672.
7. Hanany, M.; Rivolta, C.; Sharon, D. Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases. Proc. Natl. Acad. Sci. USA 2020, 117, 2710.
8. RetNet. The Retinal Information Network. Available online: https://sph.uth.edu/retnet/sum-dis.htm.
9. Punetha, J.; Hoffman, E.P. Short read (next-generation) sequencing: A tutorial with cardiomyopathy diagnostics as an exemplar. Circulation. Cardiovasc. Genet. 2013, 6, 427–434.
10. Singh, S. The hundred-dollar genome: A health care cart before The genomic horse. CMAJ 2018, 190, E514.
11. Berger, W.; Kloeckener-Gruissem, B.; Neidhardt, J. The molecular basis of human retinal and vitreoretinal diseases. Prog. Retin. Eye Res. 2010, 29, 335–375.
12. Glöckle, N.; Kohl, S.; Mohr, J.; Scheurenbrand, T.; Sprecher, A.; Weisschuh, N.; Bernd, A.; Rudolph, G.; Schubach, M.; Poloschek, C.; et al. Panel-based next generation sequencing as a reliable and efficient technique to detect mutations in unselected patients with retinal dystrophies. Eur. J. Hum. Genet. 2014, 22, 99–104.
13. Stone, E.M.; Andorf, J.L.; Whitmore, S.S.; DeLuca, A.P.; Giacalone, J.C.; Streb, L.M.; Braun, T.A.; Mullins, R.F.; Scheetz, T.E.; Sheffield, V.C.; et al. Clinically Focused Molecular Investigation of 1000 Consecutive Families with Inherited Retinal Disease. Ophthalmology 2017, 124, 1314–1331.
14. Landrum, M.J.; Lee, J.M.; Benson, M.; Brown, G.R.; Chao, C.; Chitipiralla, S.; Gu, B.; Hart, J.; Hoffman, D.; Jang, W.; et al. ClinVar: Improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018, 46, D1062–D1067.
15. Fokkema, I.F.; Taschner, P.E.; Schaafsma, G.C.; Celli, J.; Laros, J.F.; den Dunnen, J.T. LOVD v.2.0: The next generation in gene variant databases. Hum. Mutat. 2011, 32, 557–563.
16. Ballios, B.G.; Pierce, E.A.; Huckfeldt, R.M. Gene editing technology: Towards precision medicine in inherited retinal diseases. Semin. Ophthalmol. 2021, 36, 176–184.
17. Kumaran, N.; Pennesi, M.E.; Yang, P.; Trzupek, K.M.; Schlechter, C.; Moore, A.T.; Weleber, R.G.; Michaelides, M. Leber Congenital Amaurosis/Early-Onset Severe Retinal Dystrophy Overview. In

GeneReviews®; Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Mirzaa, G., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.
18. Motta, F.L.; Martin, R.P.; Filippelli-Silva, R.; Salles, M.V.; Sallum, J.M.F. Relative frequency of inherited retinal dystrophies in Brazil. Sci. Rep. 2018, 8, 15939.
19. Pontikos, N.; Arno, G.; Jurkute, N.; Schiff, E.; Ba-Abbad, R.; Malka, S.; Gimenez, A.; Georgiou, M.; Wright, G.; Armengol, M.; et al. Genetic Basis of Inherited Retinal Disease in a Molecularly Characterized Cohort of More Than 3000 Families from the United Kingdom. Ophthalmology 2020, 127, 1384–1394.
20. Yang, L.; Fujinami, K.; Ueno, S.; Kuniyoshi, K.; Hayashi, T.; Kondo, M.; Mizota, A.; Naoi, N.; Shinoda, K.; Kameya, S.; et al. Genetic Spectrum of EYS-associated Retinal Disease in a Large Japanese Cohort: Identification of Disease-associated Variants with Relatively High Allele Frequency. Sci. Rep. 2020, 10, 5497.
21. Pang, J.-J.; Alexander, J.; Lei, B.; Deng, W.; Zhang, K.; Li, Q.; Chang, B.; Hauswirth, W.W. Achromatopsia as a potential candidate for gene therapy. Adv. Exp. Med. Biol. 2010, 664, 639–646.
22. Molday, R.S.; Kellner, U.; Weber, B.H. X-linked juvenile retinoschisis: Clinical diagnosis, genetic analysis, and molecular mechanisms. Prog. Retin. Eye Res. 2012, 31, 195–212.
23. Pelletier, V.; Jambou, M.; Delphin, N.; Zinovieva, E.; Stum, M.; Gigarel, N.; Dollfus, H.; Hamel, C.; Toutain, A.; Dufier, J.L.; et al. Comprehensive survey of mutations in RP2 and RPGR in patients affected with distinct retinal dystrophies: Genotype-phenotype correlations and impact on genetic counseling. Hum. Mutat. 2007, 28, 81–91.
24. Mehmood, R.; Ramzan, M.; Ali, A.; Riaz, A.; Zulfiqar, F.; Riazuddin, S. Identification of Genes Causing Autosomal Recessive Retinitis Pigmentosa. In Gene Therapy; Niewöhner, J., Tannert, C., Eds.; Elsevier Science B.V.: Amsterdam, The Netherlands, 2006; pp. 3–15.
25. Morimura, H.; Berson, E.L.; Dryja, T.P. Recessive mutations in the RLBP1 gene encoding cellular retinaldehyde-binding protein in a form of retinitis punctata albescens. Investig. Ophthalmol. Vis. Sci. 1999, 40, 1000–1004.
26. Audo, I.; Mohand-Said, S.; Boulanger-Scemama, E.; Zanlonghi, X.; Condroyer, C.; Démontant, V.; Boyard, F.; Antonio, A.; Méjécase, C.; El Shamieh, S.; et al. MERTK mutation update in inherited retinal diseases. Hum. Mutat. 2018, 39, 887–913.
27. Dimopoulos, I.S.; Chan, S.; MacLaren, R.E.; MacDonald, I.M. Pathogenic mechanisms and the prospect of gene therapy for choroideremia. Expert Opin. Orphan. Drugs 2015, 3, 787–798.
28. Chao, D.L.; Burr, A.; Pennesi, M. RPE65-Related Leber Congenital Amaurosis/Early-Onset Severe Retinal Dystrophy. In GeneReviews®; Adam, M.P., Ardinger, H.H., Pagon, R.A., Wallace, S.E., Bean, L.J.H., Mirzaa, G., Amemiya, A., Eds.; University of Washington: Seattle, WA, USA, 1993.
29. Wang, X.; Yu, C.; Tzekov, R.T.; Zhu, Y.; Li, W. The effect of human gene therapy for RPE65-associated Leber's congenital amaurosis on visual function: A systematic review and meta-analysis. Orphanet J. Rare Dis. 2020, 15, 49.
30. Bouzia, Z.; Georgiou, M.; Hull, S.; Robson, A.G.; Fujinami, K.; Rotsos, T.; Pontikos, N.; Arno, G.; Webster, A.R.; Hardcastle, A.J.; et al. GUCY2D-Associated Leber Congenital Amaurosis: A Retrospective Natural History Study in Preparation for Trials of Novel Therapies. Am. J. Ophthalmol. 2020, 210, 59–70.
31. Cremers, F.P.M.; Lee, W.; Collin, R.W.J.; Allikmets, R. Clinical spectrum, genetic complexity and therapeutic approaches for retinal disease caused by ABCA4 mutations. Prog. Retin. Eye Res. 2020, 79, 100861.
32. French, L.S.; Mellough, C.B.; Chen, F.K.; Carvalho, L.S. A Review of Gene, Drug and Cell-Based Therapies for Usher Syndrome. Front. Cell. Neurosci. 2020, 14, 183.
33. Aller, E.; Larrieu, L.; Jaijo, T.; Baux, D.; Espinós, C.; González-Candelas, F.; Nájera, C.; Palau, F.; Claustres, M.; Roux, A.F.; et al. The USH2A c.2299delG mutation: Dating its common origin in a Southern European population. Eur. J. Hum. Genet. 2010, 18, 788–793.
34. Yan, D.; Ouyang, X.; Patterson, D.M.; Du, L.L.; Jacobson, S.G.; Liu, X.Z. Mutation analysis in the long isoform of USH2A in American patients with Usher Syndrome type II. J. Hum. Genet. 2009, 54, 732–738.

35. Huang, L.; Mao, Y.; Yang, J.; Li, Y.; Li, Y.; Yang, Z. Mutation screening of the USH2A gene in retinitis pigmentosa and USHER patients in a Han Chinese population. Eye 2018, 32, 1608–1614.
36. Sullivan, L.S.; Bowne, S.J.; Birch, D.G.; Hughbanks-Wheaton, D.; Heckenlively, J.R.; Lewis, R.A.; Garcia, C.A.; Ruiz, R.S.; Blanton, S.H.; Northrup, H.; et al. Prevalence of disease-causing mutations in families with autosomal dominant retinitis pigmentosa: A screen of known genes in 200 families. Investig. Ophthalmol. Vis. Sci. 2006, 47, 3052–3064.
37. Sheck, L.; Davies, W.I.L.; Moradi, P.; Robson, A.G.; Kumaran, N.; Liasis, A.C.; Webster, A.R.; Moore, A.T.; Michaelides, M. Leber Congenital Amaurosis Associated with Mutations in CEP290, Clinical Phenotype, and Natural History in Preparation for Trials of Novel Therapies. Ophthalmology 2018, 125, 894–903.
38. MacLaren, R.E.; Bennett, J.; Schwartz, S.D. Gene Therapy and Stem Cell Transplantation in Retinal Disease: The New Frontier. Ophthalmology 2016, 123, S98–S106.
39. Acland, G.M.; Aguirre, G.D.; Ray, J.; Zhang, Q.; Aleman, T.S.; Cideciyan, A.V.; Pearce-Kelling, S.E.; Anand, V.; Zeng, Y.; Maguire, A.M.; et al. Gene therapy restores vision in a canine model of childhood blindness. Nat. Genet. 2001, 28, 92–95.
40. Acland, G.M.; Aguirre, G.D.; Bennett, J.; Aleman, T.S.; Cideciyan, A.V.; Bennicelli, J.; Dejneka, N.S.; Pearce-Kelling, S.E.; Maguire, A.M.; Palczewski, K.; et al. Long-term restoration of rod and cone vision by single dose rAAV-mediated gene transfer to the retina in a canine model of childhood blindness. Mol. Ther. J. Am. Soc. Gene Ther. 2005, 12, 1072–1082.
41. Jacobson, S.G.; Boye, S.L.; Aleman, T.S.; Conlon, T.J.; Zeiss, C.J.; Roman, A.J.; Cideciyan, A.V.; Schwartz, S.B.; Komaromy, A.M.; Doobrajh, M.; et al. Safety in nonhuman primates of ocular AAV2-RPE65, a candidate treatment for blindness in Leber congenital amaurosis. Hum. Gene Ther. 2006, 17, 845–858.
42. Paunescu, K.; Wabbels, B.; Preising, M.N.; Lorenz, B. Longitudinal and cross-sectional study of patients with early-onset severe retinal dystrophy associated with RPE65 mutations. Graefe's Arch. Clin. Exp. Ophthalmol. 2005, 243, 417–426.
43. Jacobson, S.G.; Aleman, T.S.; Cideciyan, A.V.; Sumaroka, A.; Schwartz, S.B.; Windsor, E.A.; Traboulsi, E.I.; Heon, E.; Pittler, S.J.; Milam, A.H.; et al. Identifying photoreceptors in blind eyes caused by RPE65 mutations: Prerequisite for human gene therapy success. Proc. Natl. Acad. Sci. USA 2005, 102, 6177–6182.
44. Jacobson, S.G.; Aleman, T.S.; Cideciyan, A.V.; Roman, A.J.; Sumaroka, A.; Windsor, E.A.; Schwartz, S.B.; Heon, E.; Stone, E.M. Defining the residual vision in leber congenital amaurosis caused by RPE65 mutations. Investig. Ophthalmol. Vis. Sci. 2009, 50, 2368–2375.
45. Maguire, A.M.; Simonelli, F.; Pierce, E.A.; Pugh, E.N., Jr.; Mingozzi, F.; Bennicelli, J.; Banfi, S.; Marshall, K.A.; Testa, F.; Surace, E.M.; et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. N. Engl. J. Med. 2008, 358, 2240–2248.
46. Hauswirth, W.W.; Aleman, T.S.; Kaushal, S.; Cideciyan, A.V.; Schwartz, S.B.; Wang, L.; Conlon, T.J.; Boye, S.L.; Flotte, T.R.; Byrne, B.J.; et al. Treatment of leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: Short-term results of a phase I trial. Hum. Gene Ther. 2008, 19, 979–990.
47. Bainbridge, J.W.; Smith, A.J.; Barker, S.S.; Robbie, S.; Henderson, R.; Balaggan, K.; Viswanathan, A.; Holder, G.E.; Stockman, A.; Tyler, N.; et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N. Engl. J. Med. 2008, 358, 2231–2239.
48. Melillo, P.; Pecchia, L.; Testa, F.; Rossi, S.; Bennett, J.; Simonelli, F. Pupillometric analysis for assessment of gene therapy in Leber Congenital Amaurosis patients. Biomed. Eng. Online 2012, 11, 40.
49. Bennett, J.; Ashtari, M.; Wellman, J.; Marshall, K.A.; Cyckowski, L.L.; Chung, D.C.; McCague, S.; Pierce, E.A.; Chen, Y.; Bennicelli, J.L.; et al. AAV2 gene therapy readministration in three adults with congenital blindness. Sci. Transl. Med. 2012, 4, 120ra115.
50. Cideciyan, A.V.; Hauswirth, W.W.; Aleman, T.S.; Kaushal, S.; Schwartz, S.B.; Boye, S.L.; Windsor, E.A.; Conlon, T.J.; Sumaroka, A.; Roman, A.J.; et al. Vision 1 year after gene therapy for Leber's congenital amaurosis. N. Engl. J. Med. 2009, 361, 725–727.

51. Ripamonti, C.; Henning, G.B.; Robbie, S.J.; Sundaram, V.; van den Born, L.I.; Casteels, I.; de Ravel, T.J.; Moore, A.T.; Smith, A.J.; Bainbridge, J.W.; et al. Spectral sensitivity measurements reveal partial success in restoring missing rod function with gene therapy. J. Vis. 2015, 15, 20.
52. Jacobson, S.G.; Cideciyan, A.V.; Ratnakaram, R.; Heon, E.; Schwartz, S.B.; Roman, A.J.; Peden, M.C.; Aleman, T.S.; Boye, S.L.; Sumaroka, A.; et al. Gene therapy for leber congenital amaurosis caused by RPE65 mutations: Safety and efficacy in 15 children and adults followed up to 3 years. Arch. Ophthalmol. 2012, 130, 9–24.
53. Chung, D.C.; McCague, S.; Yu, Z.F.; Thill, S.; DiStefano-Pappas, J.; Bennett, J.; Cross, D.; Marshall, K.; Wellman, J.; High, K.A. Novel mobility test to assess functional vision in patients with inherited retinal dystrophies. Clin. Exp. Ophthalmol. 2018, 46, 247–259.
54. Russell, S.; Bennett, J.; Wellman, J.A.; Chung, D.C.; Yu, Z.F.; Tillman, A.; Wittes, J.; Pappas, J.; Elci, O.; McCague, S.; et al. Efficacy and safety of voretigeneneparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: A randomised, controlled, open-label, phase 3 trial. Lancet 2017, 390, 849–860.
55. Sengillo, J.D.; Justus, S.; Cabral, T.; Tsang, S.H. Correction of Monogenic and Common Retinal Disorders with Gene Therapy. Genes 2017, 8, 53. Ali, R.R.; Reichel, M.B.; De Alwis, M.; Kanuga, N.; Kinnon, C.; Levinsky, R.J.; Hunt, D.M.; Bhattacharya, S.S.; Thrasher, A.J. Adeno-associated virus gene transfer to mouse retina. Hum. Gene Ther. 1998, 9, 81–86.
56. Fischer, M.D.; Michalakis, S.; Wilhelm, B.; Zobor, D.; Muehlfriedel, R.; Kohl, S.; Weisschuh, N.; Ochakovski, G.A.; Klein, R.; Schoen, C.; et al. Safety and Vision Outcomes of Subretinal Gene Therapy Targeting Cone Photoreceptors in Achromatopsia: A Nonrandomized Controlled Trial. JAMA Ophthalmol. 2020, 138, 643–651.
57. Cukras, C.; Wiley, H.E.; Jeffrey, B.G.; Sen, H.N.; Turriff, A.; Zeng, Y.; Vijayasarathy, C.; Marangoni, D.; Ziccardi, L.; Kjellstrom, S.; et al. Retinal AAV8-RS1 Gene Therapy for X-Linked Retinoschisis: Initial Findings from a Phase I/IIa Trial by Intravitreal Delivery. Mol. Ther. J. Am. Soc. Gene Ther. 2018, 26, 2282–2294.
58. Cehajic-Kapetanovic, J.; Xue, K.; Martinez-Fernandez de la Camara, C.; Nanda, A.; Davies, A.; Wood, L.J.; Salvetti, A.P.; Fischer, M.D.; Aylward, J.W.; Barnard, A.R.; et al. Initial results from a first-in-human gene therapy trial on X-linked retinitis pigmentosa caused by mutations in RPGR. Nat. Med. 2020, 26, 354–359.
59. Ghazi, N.G.; Abboud, E.B.; Nowilaty, S.R.; Alkuraya, H.; Alhommadi, A.; Cai, H.; Hou, R.; Deng, W.T.; Boye, S.L.; Almaghamsi, A.; et al. Treatment of retinitis pigmentosa due to MERTK mutations by ocular subretinal injection of adeno-associated virus gene vector: Results of a phase I trial. Hum. Genet. 2016, 135, 327–343.
60. Jacobson, S.G.; Cideciyan, A.V.; Ho, A.C.; Peshenko, I.V.; Garafalo, A.V.; Roman, A.J.; Sumaroka, A.; Wu, V.; Krishnan, A.K.; Sheplock, R.; et al. Safety and improved efficacy signals following gene therapy in childhood blindness caused by GUCY2D mutations. iScience 2021, 24, 102409.
61. Hirsch, M.L.; Wolf, S.J.; Samulski, R.J. Delivering Transgenic DNA Exceeding the Carrying Capacity of AAV Vectors. Methods Mol. Biol. 2016, 1382, 21–39.
62. Parker, M.A.; Choi, D.; Erker, L.R.; Pennesi, M.E.; Yang, P.; Chegarnov, E.N.; Steinkamp, P.N.; Schlechter, C.L.; Dhaenens, C.M.; Mohand-Said, S.; et al. Test-Retest Variability of Functional and Structural Parameters in Patients with Stargardt Disease Participating in the SAR422459 Gene Therapy Trial. Transl. Vis. Sci. Technol. 2016, 5, 10.
63. Yan, Z.; Zhang, Y.; Duan, D.; Engelhardt, J.F. Trans-splicing vectors expand the utility of adeno-associated virus for gene therapy. Proc. Natl. Acad. Sci. USA 2000, 97, 6716–6721.
64. Dyka, F.M.; Boye, S.L.; Chiodo, V.A.; Hauswirth, W.W.; Boye, S.E. Dual adeno-associated virus vectors result in efficient in vitro and in vivo expression of an oversized gene, MYO7A. Hum. Gene Ther. Methods 2014, 25, 166–177.
65. Trapani, I.; Colella, P.; Sommella, A.; Iodice, C.; Cesi, G.; de Simone, S.; Marrocco, E.; Rossi, S.; Giunti, M.; Palfi, A.; et al. Effective delivery of large genes to the retina by dual AAV vectors. EMBO Mol. Med. 2014, 6, 194–211.

66. Zhang, W.; Li, L.; Su, Q.; Gao, G.; Khanna, H. Gene Therapy Using a miniCEP290 Fragment Delays Photoreceptor Degeneration in a Mouse Model of Leber Congenital Amaurosis. Hum. Gene Ther. 2018, 29, 42–50.
67. Ledford, H. CRISPR treatment inserted directly into the body for first time. Nature 2020, 579, 185.
68. Maeder, M.L.; Stefanidakis, M.; Wilson, C.J.; Baral, R.; Barrera, L.A.; Bounoutas, G.S.; Bumcrot, D.; Chao, H.; Ciulla, D.M.; DaSilva, J.A.; et al. Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10. Nat. Med. 2019, 25, 229–233.
69. Willett, K.; Bennett, J. Immunology of AAV-Mediated Gene Transfer in the Eye. Front. Immunol. 2013, 4, 261.
70. Verdera, H.C.; Kuranda, K.; Mingozzi, F. AAV Vector Immunogenicity in Humans: A Long Journey to Successful Gene Transfer. Mol. Ther. J. Am. Soc. Gene Ther. 2020, 28, 723–746.
71. Maguire, A.M.; High, K.A.; Auricchio, A.; Wright, J.F.; Pierce, E.A.; Testa, F.; Mingozzi, F.; Bennicelli, J.L.; Ying, G.S.; Rossi, S.; et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: A phase 1 dose-escalation trial. Lancet 2009, 374, 1597–1605.
72. Li, Q.; Miller, R.; Han, P.Y.; Pang, J.; Dinculescu, A.; Chiodo, V.; Hauswirth, W.W. Intraocular route of AAV2 vector administration defines humoral immune response and therapeutic potential. Mol. Vis. 2008, 14, 1760–1769.
73. Dalkara, D.; Byrne, L.C.; Klimczak, R.R.; Visel, M.; Yin, L.; Merigan, W.H.; Flannery, J.G.; Schaffer, D.V. In vivo-directed evolution of a new adeno-associated virus for therapeutic outer retinal gene delivery from the vitreous. Sci. Transl. Med. 2013, 5, 189ra176.
74. Anand, V.; Duffy, B.; Yang, Z.; Dejneka, N.S.; Maguire, A.M.; Bennett, J. A deviant immune response to viral proteins and transgene product is generated on subretinal administration of adenovirus and adeno-associated virus. Mol. Ther. J. Am. Soc. Gene Ther. 2002, 5, 125–132.
75. Wilson, J.M.; Flotte, T.R. Moving Forward After Two Deaths in a Gene Therapy Trial of Myotubular Myopathy. Hum. Gene Ther. 2020, 31, 695–696.
76. Agarwal, S. High-dose AAV gene therapy deaths. Nat. Biotechnol. 2020, 38, 910.
77. Sullivan, J.M.; Myers, J.; Trujillo, A.; Butler, M.C.; Fayazi, Z.; Punnoose, J.A.; Halvorsen, K.A. Facilitated Hammerhead Ribozymes- A New Therapeutic Modality for Inherited Retinal Degenerations. Investig. Ophthalmol. Vis. Sci. 2019, 60, 3412.
78. Guzman-Aranguez, A.; Loma, P.; Pintor, J. Small-interfering RNAs (siRNAs) as a promising tool for ocular therapy. Br. J. Pharmacol. 2013, 170, 730–747.
79. Millington-Ward, S.; Chadderton, N.; O'Reilly, M.; Palfi, A.; Goldmann, T.; Kilty, C.; Humphries, M.; Wolfrum, U.; Bennett, J.; Humphries, P.; et al. Suppression and replacement gene therapy for autosomal dominant disease in a murine model of dominant retinitis pigmentosa. Mol. Ther. J. Am. Soc. Gene Ther. 2011, 19, 642–649.
80. O'Reilly, M.; Palfi, A.; Chadderton, N.; Millington-Ward, S.; Ader, M.; Cronin, T.; Tuohy, T.; Auricchio, A.; Hildinger, M.; Tivnan, A.; et al. RNA interference-mediated suppression and replacement of human rhodopsin in vivo. Am. J. Hum. Genet. 2007, 81, 127–135.
81. Cideciyan, A.V.; Sudharsan, R.; Dufour, V.L.; Massengill, M.T.; Iwabe, S.; Swider, M.; Lisi, B.; Sumaroka, A.; Marinho, L.F.; Appelbaum, T.; et al. Mutation-independent rhodopsin gene therapy by knockdown and replacement with a single AAV vector. Proc. Natl. Acad. Sci. USA 2018, 115, E8547–E8556.
82. Evers, M.M.; Toonen, L.J.; van Roon-Mom, W.M. Antisense oligonucleotides in therapy for neurodegenerative disorders. Adv. Drug Deliv. Rev. 2015, 87, 90–103.
83. Cideciyan, A.V.; Jacobson, S.G.; Ho, A.C.; Garafalo, A.V.; Roman, A.J.; Sumaroka, A.; Krishnan, A.K.; Swider, M.; Schwartz, M.R.; Girach, A. Durable vision improvement after a single treatment with antisense oligonucleotide sepofarsen: A case report. Nat. Med. 2021, 27, 785–789.

الإمكانيات الواعدة للعلاج الجيني كنهج ثوري لعلاج أمراض الشبكية الوراثية وغيرها من الحالات الوراثية في العين: مراجعة

الملخص

الخلفية:تمثل أمراض تنكس الشبكية الوراثية (IRDs) مجموعة متنوعة من الاضطرابات الجينية التي غالبًا ما تؤدي إلى ضعف بصري كبير، وكانت تُعتبر سابقًا غير قابلة للعلاج. ومع ذلك، أدت التطورات الحديثة في علم الأحياء الجزيئي إلى تطوير علاجات جينية، أبرزها العقار voretigene neparvovec-rzylالمعتمد من إدارة الغذاء والدواء(FDA) ، والذي يستهدف حالة ضمور ليبر الخلقي المرتبط بـ.RPE65

الطرق: تستعرض هذه المراجعة استراتيجيات علاجية مختلفة قيد التجارب السريرية حاليًا لعلاج أمراض الشبكية الوراثية، بما في ذلك تعزيز الجينات، وتحرير الجينات، وعلم البصريات الوراثي (optogenetics) ، والحماية العصبية، والعلاجات بالخلايا الجذعية. تم تقييم فعالية هذه الأساليب من خلال تحليل شامل للتجارب السريرية التدخلية الجارية والدراسات قبل السريرية.

النتائج: هناك أكثر من 60 تجربة سريرية نشطة تستكشف العلاجات الجينية لمجموعة متنوعة من أمراض الشبكية الوراثية، حيث أظهرت نتائج واعدة بتحسين الوظيفة البصرية. وقد أثبتت العلاجات الجينية باستخدام الفيروسات المرتبطة بالغدة (AAVs) فعاليتها في استعادة البصر لدى المرضى الذين يعانون من طفرات جينية محددة. كما يتم تقييم تقنيات ناشئة مثل تداخل الحمض النووي الريبي (RNA interference) وتحرير الجينات باستخدام CRISPR/Cas9 لقدرتها على معالجة نطاق أوسع من الطفرات الجينية المرتبطة بأمراض الشبكية.

الخلاصة: يتطور مجال العلاج الجيني في طب العيون بسرعة، مما يوفر أملًا جديدًا للمرضى الذين يعانون من أمراض الشبكية الوراثية. الأبحاث والتجارب السريرية الجارية ضرورية لتحديد سلامة وفعالية هذه العلاجات المبتكرة على المدى الطويل. من المرجح أن يشهد مستقبل علاجات طب العيون تحولًا نحو الطب الشخصي الذي يستهدف الأسباب الجينية الأساسية لضعف البصر.

الكلمات المفتاحية: العلاج الجيني، أمراض الشبكية الوراثية، RPE65، ضعف البصر، .CRISPR