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Gene Therapy: Can be an Effective Solution for Patients Diagnosed with Retinal Diseases?

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Abstract

Background: Gene therapy for retinal diseases is a cutting-edge treatment that delivers functional genes to retinal cells, aiming to correct genetic mutations and restore vision.

Objective: This study aims to evaluate the effectiveness and potential of gene therapy as a treatment for retinal diseases (RDs), focusing on its ability to restore or improve retinal function, slow disease progression, and provide long-term therapeutic benefits for patients with retinal conditions.

Methods: We searched about retinal diseases regarding gene therapy for retinal diseases, gene therapy for inherited retinal disorders, Visual cycle, visual cycle enzymes, gene therapy mechanisms, adeno-associated viral vectors, gene replacement, RPE65, optogenetics, antisense oligonucleotides, CRISPR/CAS9-based therapy, Genome editing, BRILLIANCE trial, Voretigene neparvovec, Luxturna, gene therapy in RDs using PubMed, Google Scholar, Cochran, web of science, and scups.

Results: Gene therapy has tremendous potential for retinal conditions due to its ease of accessibility, immune-privileged status, and tight blood-retinal barriers, limiting systemic side effects of the drug. In recent years, advances in gene therapy in retinal conditions have increased significantly, with progress in cell-specific targeting and transduction efficiency of gene products using adeno-associated viral vectors (AAVs), suggesting that even greater success in future clinical trials is possible.

Conclusion: Gene therapy holds great promise as a potential solution for patients diagnosed with retinal diseases, offering hope for individuals who previously had limited treatment options. By addressing the root causes of these conditions at the genetic level, gene therapy has demonstrated the ability to restore or preserve vision in some cases. While still in the early stages of development and clinical testing, the advances made so far indicate a significant potential to revolutionize the treatment of retinal diseases. However, challenges such as safety, accessibility, and long-term efficacy must be carefully evaluated as research progresses. As our understanding and technology continue to evolve, gene therapy may ultimately provide a transformative pathway for patients suffering from retinal disorders.

Keywords: Visual Cycle; Voretigene Neparvovec; Diabetic Retinopathy; Gene Delivery Systems; Gene Therapy; Inherited Retinal Diseases; Retinal Detachment; Retinitis Pigmentosa

Abbreviations: CNV: Choroidal Neovascularization; AAV's: Adeno-Associated Viral Vectors; DR: Diabetic Retinopathy; RVO: Retinal Vein Occlusion; AMD: Age-Related Macular Degeneration; RP: Retinitis Pigmentosa; ROP: Retinopathy of Prematurity; NICU's: Neonatal Intensive Care Units; CMV: Cytomegalovirus; DNA: Deoxyribonucleic Acid; AAV: Adeno-Associated Virus; SCID: Severe Combined Immunodeficiency; RPE: Retinal Pigment Epithelium; RNA: Ribonucleic Acid; AON: Antisense Oligonucleotide Therapy; VN: Voretigene Neparvovec; LCA2: Leber Congenital Amaurosis Type 2; NHEJ: Non-Homologous End Joining; HDR: Homology Directed Repair; ZFN's: Zinc-Finger Nucleases; TALEN's: Transcription Activator-Like Effector Nucleases; ZFNs: Zinc-Finger Nucleases

Retinal Disease Overview

The retina serves as the principal mechanism for receiving, arranging, and transmitting visual stimuli to the brain via the optic nerve [1]. Retinal disorders are a major contributor to visual impairment and blindness globally, impacting millions of individuals. These encompass a range of ailments, such as age-related macular degeneration, diabetic retinopathy, retinal

vein occlusions, retinitis pigmentosa, glaucoma, choroidal neovascularization (CNV), Myopia, epiretinal membrane, retinoblastoma, and retinal detachment [2]. Aging populations, an increase in chronic conditions like diabetes, and lifestyle choices all have an impact on the prevalence of these diseases [3]. Early identification of these retinal conditions is essential for prompt and efficient treatment, as they tend to result in visual impairment and blindness if not addressed timely [4].

Prevalence of Retinal Disease

Retinal diseases are a major cause of vision impairment globally, with prevalence rates varying by condition, population, and risk factors such as age and systemic diseases [5]. Diabetic Retinopathy (DR) affects approximately 27% to 34% of diabetic patients worldwide, with a higher prevalence among individuals who have had diabetes for over 20 years [6]. The prevalence of early AMD is estimated at 8% to 12% in adults aged 50 and older, while late AMD (exudative form) occurs in 1.5% to 3% of individuals over 60 years. A study focusing on exudative AMD in eyes with central retinal vein occlusion found a prevalence of 5.4% in affected individuals [7]. In a study of patients undergoing laser photocoagulation, 4.18% had Retinal Vein Occlusion (RVO), while 95.82% had other retinal diseases. Among those with RVO, 54.65% were female and 45.35% were male [8]. The prevalence of high myopia has increased dramatically, affecting about 10% of the global population [9]. This condition raises the risk of retinal detachment and myopic maculopathy, which were found in 1% to 3% of myopic patients [10]. A study assessing hypertensive patients found that 40% had retinal microvascular changes due to hypertension, with a strong correlation to cardiovascular risk factors [11,12].

Causes of Retinal Diseases

Retinal diseases can arise from a range of causes, including metabolic disorders, vascular abnormalities, genetic mutations, degenerative changes, developmental issues, and inflammatory or infectious conditions. Each cause affects the retina in different ways, leading to vision impairment or blindness if not diagnosed and managed early [13].

Metabolic Causes

Diabetic Retinopathy (DR)

Diabetic retinopathy is caused by prolonged high blood sugar levels in individuals with diabetes mellitus (Type 1 and Type 2) [14]. Chronically elevated glucose damages the small blood vessels in the retina, making them leak fluid and blood. This results in swelling of the retina and, in severe cases, the growth of abnormal new blood vessels (neovascularization), which can cause scarring and retinal detachment [15].

Vascular Causes

Hypertensive Retinopathy (HR)

Hypertensive retinopathy occurs due to long-term high blood pressure (hypertension), which damages the delicate retinal blood vessels [16]. This condition leads to arteriosclerosis (thickened and narrowed arteries), hemorrhages, retinal swelling, and even optic nerve damage (papilledema) in severe cases. Uncontrolled hypertension, kidney disease, and cardiovascular conditions significantly increase the risk retinal diseases [17].

Degenerative Causes

Age-Related Macular Degeneration (AMD)

Age-related macular degeneration (AMD) is a leading cause of vision loss in older adults. It occurs due to aging and oxidative stress, which lead to the accumulation of drusen (protein deposits) in the macula—the central part of the retina responsible for sharp vision. Over time, these deposits damage retinal cells, leading to blurry or distorted central vision [18,19].

Retinal Detachment

Retinal detachment occurs when the retina separates from the underlying layer that supplies it with nutrients and oxygen [20]. This can be triggered by age-related degeneration, severe myopia (nearsightedness), or trauma [21]. A tear or hole in the retina allows fluid to accumulate, further pulling the retina away from the underlying tissues. Symptoms include sudden flashes of light, floaters, and a shadow or curtain over the vision. If untreated, retinal detachment can cause permanent blindness, making immediate medical intervention crucial [22].

Genetic Causes

Retinitis Pigmentosa (RP)

Retinitis pigmentosa is an inherited retinal disease caused by genetic mutations affecting photoreceptor cells (rods and cones) [23]. Mutations in genes like RHO, RPGR, and USH2A lead to progressive degeneration of rod and cone cells, causing night blindness and peripheral vision loss, eventually progressing to complete blindness. Since RP is genetic, there is currently no cure, but research in gene therapy and retinal implants is showing promise in slowing disease progression [24].

Developmental Causes

Retinopathy of Prematurity (ROP)

Retinopathy of prematurity (ROP) occurs in premature infants who are born before their retinal blood vessels have fully developed [25]. When exposed to high oxygen levels in neonatal intensive care units (NICUs), abnormal blood vessels grow in the

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retina, which can cause scarring and detachment. Infants born 32 weeks before gestation or weighing less than 1500 grams are at the highest risk [26].

Inflammatory and Infectious Causes

Uveitis and Retinitis

Inflammatory conditions such as uveitis and infectious retinitis can also lead to retinal damage [27]. Autoimmune diseases like Behçet's disease and sarcoidosis cause chronic inflammation, leading to swelling and scarring in the retina. Infections like toxoplasmosis and cytomegalovirus (CMV) can directly damage retinal tissue, especially in immunocompromised individuals [28].

Gene Therapy

Gene therapy involves the modification of defective deoxyribonucleic acid (DNA) in recipient cells or tissues to achieve a desired therapeutic effect. Compared to other organs, the eye has a greater potential for gene therapy due to its easy accessibility via injections and surgical interventions, immune-privileged status, presence of tight ocular barrier preventing exposure to other organs, and ready assessment of retinal structure and anatomy by non-invasive technique to determine response to treatment [29]. Also, retinal dystrophies are usually symmetrical and bilateral, allowing one eye to serve as a control in clinical trials. A major disadvantage is that advanced retinal dystrophies or degenerations are usually irreversible, and successful treatment depends on the presence of live neuronal cells at the time of initiating gene therapy [30].

History of Gene Therapy Development for RDs

Although the history of gene therapy goes back to the 1950s, retinal gene therapies have been studied only since the 1990s. In 1994, the first attempts to identify a vector for retinal gene delivery occurred, using adenovirus-based systems in mice [31,32] (Figure 1). In 1996, Bennett et al. went on to show successful gene therapy using an adenoviral vector in the rd1 mouse model of recessive retinal degeneration.30 Around that same time, other groups used HIV-based lentiviral or adeno-associated virus (AAV)-based vectors to demonstrate efficient photoreceptor and RPE transduction (Ali et al. 1996, Miyoshi et al. 1997) [33,34].

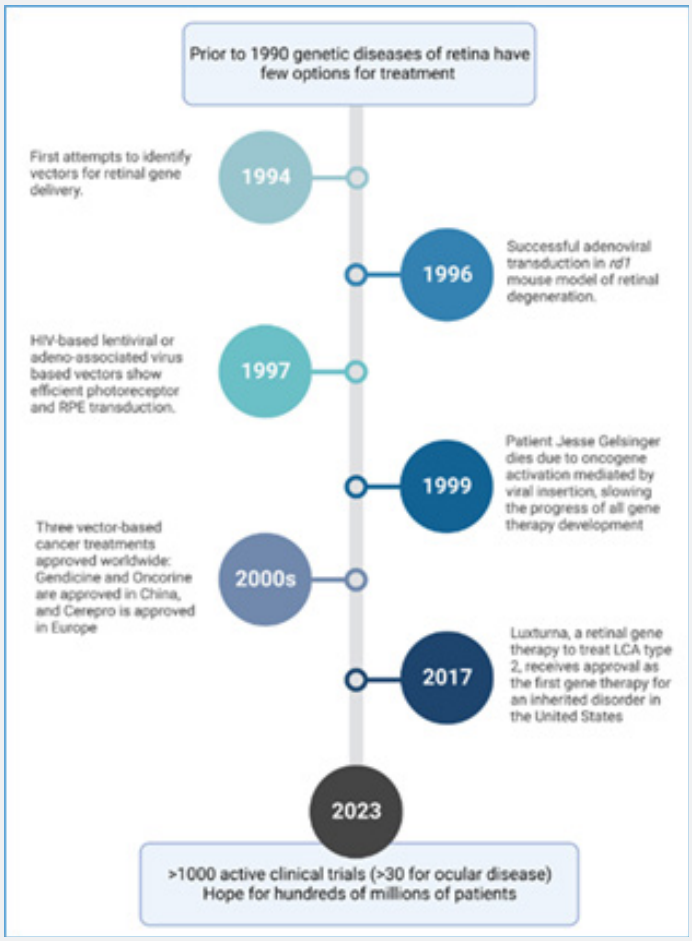

Figure 3: Macular OCT: thinning of the photoreceptor layer with macular edema in the right eye. Normal appearance in the left eye.

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Figure 1 History of the development of retinal gene therapy (created with BioRender.com), [35]. In 1999, gene therapy, in general, suffered a setback due to the tragic death of the gene therapy patient, Jesse Gelsinger, who was enrolled in a gene therapy trial to treat ornithine transcarbamoylase deficiency. Later, 5 of 20 patients with severe combined immunodeficiency (SCID)-X1, treated with retrovirus gene therapy, developed T-cell leukemia within 2 to 6 years following treatment [36,37]. These tragedies slowed gene therapy development as researchers, clinicians, and regulators grappled with the risks associated with this technology [38]. Despite the serious setbacks in these clinical trials, advancements continued, with the first gene therapy products Gendicine, Oncorine, and Cerepro being approved for clinical use [39,36], An overview of the history of retinal gene therapy is provided in Figure 1.

Gene Therapy Approaches for Retinal Diseases

Retinal gene therapy approaches vary based on the nature of the mutation (Figure 2) and maybe gene replacement/augmentation, silencing/editing the mutated gene, or supplying a gene that affects the upstream or downstream pathways from the defective gene to improve cellular function (as in modifier therapy). Retinal gene therapies include the use of diverse vectors and routes of administration (Figure 2).

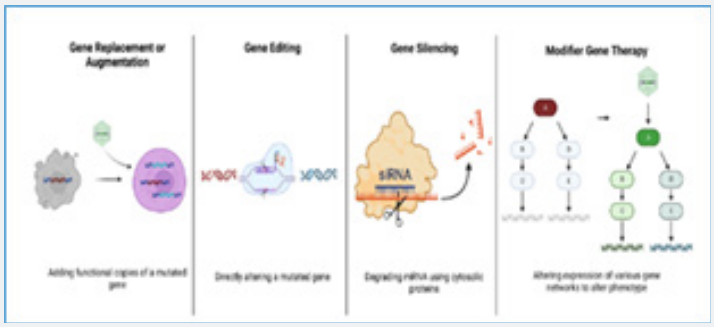

Figure 2: Gene therapy approaches. There are four major approaches to gene therapy (left to right). Gene replacement or augmentation is when a functional copy of a damaged, non-functional gene is added to augment the production of functional protein. In gene editing, mutations in a gene are corrected or expression of the mutated protein is reduced to alter a diseased state. Gene silencing uses the RNAi mechanism to eliminate the aberrant expression of the targeted pathogenic protein in acquired diseases. Modifier gene therapies provide a modifier gene that can affect pathways downstream or upstream from the damaged gene, allowing for the expression of multiple genes to be altered with a single treatment (created with BioRender.com) [35].

Figure 2 Gene therapy approaches. There are four major approaches to gene therapy (left to right). Gene replacement or augmentation is when a functional copy of a damaged, non-functional gene is added to augment the production of functional protein. In gene editing, mutations in a gene are corrected or expression of the mutated protein is reduced to alter a diseased state. Gene silencing uses the RNAi mechanism to eliminate the aberrant expression of the targeted pathogenic protein in acquired diseases. Modifier gene therapies provide a modifier gene that can affect pathways downstream or upstream from the damaged gene, allowing for the expression of multiple genes to be altered with a single treatment (created with BioRender.com) [38].

Visual Cycle

The visual cycle (Figure 3) is the process that takes place in the photoreceptors and the retinal pigment epithelium (RPE) involving several enzymatic reactions, which have been described subsequently. RPE65 is an example of a very important enzyme in this cascade, responsible for converting all-trans-retinyl ester to 11-cis-retinol (Figure 4). In cells with a defect RPE65, 11-cis-retinal levels are reduced and retinyleste accumulates in the RPE leading to recessive blinding disorders like Leber congenital amaurosis [40].

Mechanism of Gene Therapy

In recessive diseases with a loss of function, a gene complementation approach of introducing an extra copy of the normal gene is a popular strategy. Dominant disorders with a dominant-negative effect require a combined approach of mutant gene suppression with or without gene complementation. Newer, upcoming variants of gene therapy like optogenetics, utilizing antisense oligonucleotides, and genome editing systems like CRISPR, have been described subsequently [41].

Gene Delivery Systems

Both viral and nonviral vectors have been tried and evaluated for their efficacy for delivering desirable genes into target cells affected by retinal degeneration. However, viral vectors are the most popular and widely used in therapeutic applications [38]. Vectorology deals with the design, construction, and production of different viral vectors for gene delivery and expression into different cell types. Most of the current third-generation therapeutic vectors are replication-defecti and can infect the target cells only once to safely deliver the transgenes. They are incapable of replication in the host and require at least two or more helpers for amplification and expansion under controlled

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lab environments [30]. The types of vectors include viral and nonviral. Viral vectors studied so far include adenoviruses, retroviruses, lentiviruses, and adeno-associated viruses (AAVs). Among these vectors, AAVs are the most promising in gene therapeutics. They exhibit several desirable vector properties such as lack of pathogenicity, low immunogenicity, ability to transduce non-dividing cells, and maintenance of sustained levels of therapeutic gene expression. However, a major disadvantage of AAVs is their limited packaging capacity precluding their ability to carry genes larger than 5 kb. Various advances have been made to increase their transfer capacity beyond 5 kb through novel strategies [42]. Gene therapies can be delivered to the retina by ocular or systemic routes (Figure 5), although generally it is preferred to use a route that will bring the therapy as close to the target tissue as possible, such as subretinal injections for the outer retina targets and intravitreal injections for inner retina targets [43]. Systemic administration has the advantage of convenience, but the lack of specific targeting can lead to nonspecific effects in non-ocular tissues, reduced bioavailability in the target tissue, and an increase in the risk of immunogenicity as more of the body is exposed to the therapy [44].

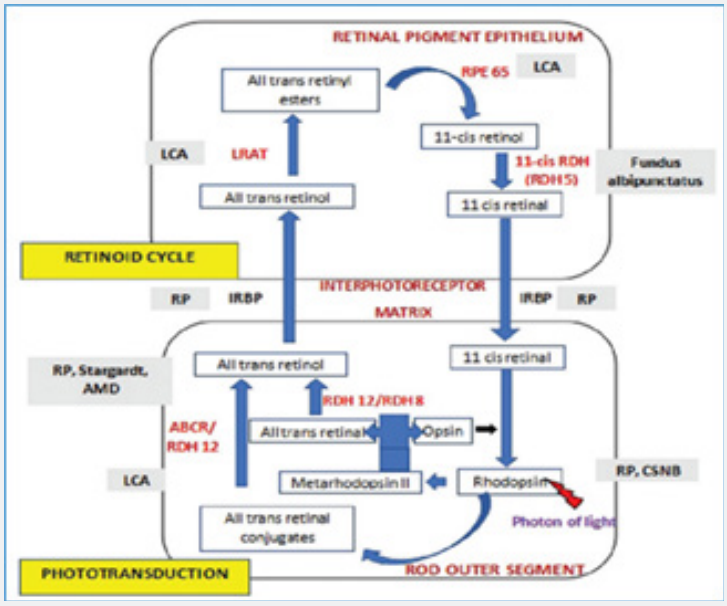

Figure 3: Schematic representation of Wald's visual cycle–Rod enzymes and diseases overview [30].

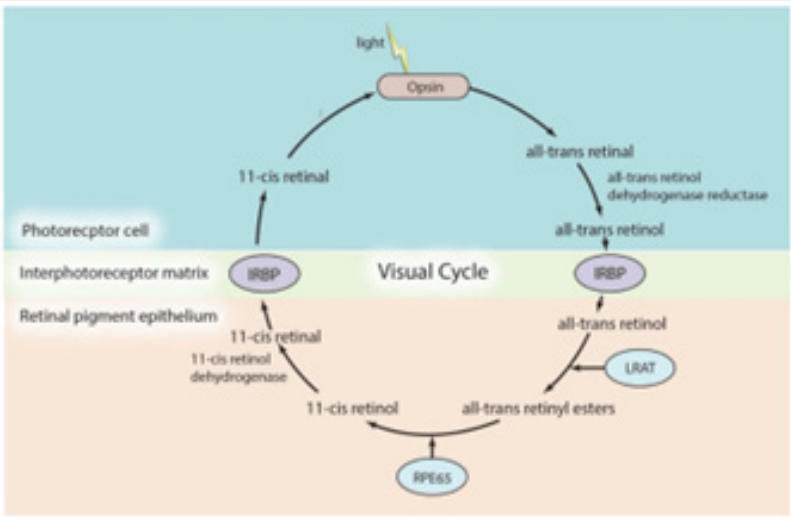

Figure 4: Visual Cycle.

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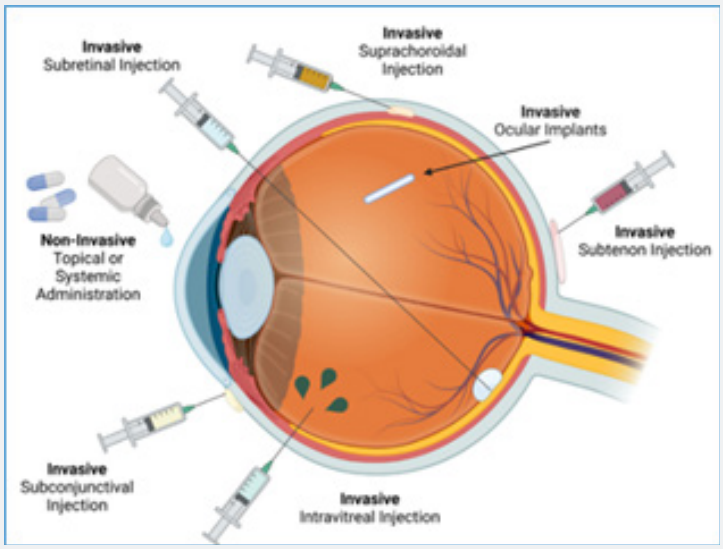

Figure 5: Ocular routes of administration may be invasive or non-invasive (created with BioRender.com) [43].

Mode of Administration of Vectors

Two distinct routes by which the vectors can be administered include injection into the subretinal space or intravitreal injection. The subretinal space is a potential space that gives the injected material direct access to the plasma membrane of the RPE and photoreceptors. However, the subretinal delivery requires specialized skills. It involves creating a transient iatrogenic neurosensory retinal detachment near the fovea which must be carefully controlled to prevent the development of retinal detachment or macular hole [45]. In contrast, delivery into the vitreous cavity via intravitreal injection has greater ease of administration, is less risky than a subretinal injection, and is preferred in conditions of the inner retina which is closer to the vitreous cavity. However, this method of delivery of AAV is less efficient than subretinal delivery for the treatment of outer retinal disease [46]. This may be due to the physical barrier required for the virus to traverse the retina, as well as the potential dilution of the vector in the vitreous cavity leading to a lower concentration in the outer retina. Most of the current vectors are injected into the subretinal space, exception X-linked juvenile retinoschisis, where the vector is preferred to be injected intravitreally to reduce the risk of retinal detachment and vitreous hemorrhage [30].

Other Variants of Gene Therapy

Optogenetics

This technology overcomes the limitation of the lack of photoreceptors in advanced diseases, which cannot be treated with conventional gene therapy. The inner retinal cells are targeted to convert them to light-sensitive cells in the absence of photoreceptors. Here, the AAV vector delivers light-sensitive opsins, such as rhodopsin and melanopsin, to bipolar or retinal ganglion cells which are still functional, thus overcoming the lack of availability of photoreceptors. Opsins in bipolar or ganglion cells get activated by photons, triggering nerve impulses downstream [47].

Antisense Oligonucleotide Therapy

This is another innovative field of therapeutics for retinal-inherited diseases. Antisense oligonucleotide therapy (AON) targets the aberrant splicing mechanisms, preventing the translation of disease-causing proteins. AONs are DNA or Ribonucleic acid (RNA) molecules that can be delivered as naked oligonucleotides or through viral vectors. There may be several potential advantages of AONs. Increased penetration after intravitreal injections due to their small size may offer an alternative to the complex procedure of subretinal delivery [46]. The limited stability of naked AONs may be associated with fewer side effects. While a single administration of AAV-mediated AON could give therapeutic benefits for a long time, naked AONs may need multiple intravitreal dosing over a lifetime. The efficacy of AAV-mediated and naked AON delivery for the treatment of CEP290-related disease has been studied. In LCA, the aberrant splice junction created by the mutation in the CEP290 gene was corrected, and restored protein levels [30].

Voretigene Neparvovec-Luxturna

Voretigene neparvovec (VN) is the first USFDA-approved gen replacement therapy. It was approved under the trade name Luxturna for the treatment of a more severe form of Leber congenital amaurosis type 2 (LCA2). Biallelic mutations in the RPE65 gene cause LCA2 and are responsible for the fraction of all

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LCAs. RPE65 is responsible for retinol isomerization and converts all-trans-retinyl to 11-cis-retinol in phototransduction. The 11-cis-retinol gets converted to 11-cis-retinal and is used in the regeneration of visual pigments in the photoreceptor cells [48]. The subretinal delivery of the RPE65 gene with AAV serotype 2 (AAV2) efficiently infects the RPE cells. The AAV2 vector delivers a normal copy of RPE65 into the cell as a free-floating DN outside of the chromosomes called an episome, which does not integrate with the host nuclear DNA. This free-floatin viral genome containing the transgene uses the host nuclear gene expression machinery to make the RPE65 mRNA, which then gets translated into a functional protein. This was found to improve the navigational abilities of treated patients [49].

CRISPR/CAS9-Based Therapy-Genome Editing

Gene editing is a process of introduction of an engineered nuclease leading to the generation of a double-strand break at a desired location on the genome, followed by an endogenous DNA repair process in the presence or absence of a gene correction donor DNA template. The repair process can be achieved by either of the following methods: Non-homologous end joining (NHEJ), or Homology directed repair (HDR) [50]. CRISPR-Cas9 system is an engineered endonuclease guided by a short RNA containing a 20-nucleotide long complementarity region that recognizes the target DNA site by complement base paring and precisely makes a nick or a cut in the genome. These cuts are then repaired using cellular DNA repair pathways such as NHEJ and HDR pathways [51]. During this induced DNA editing process, pathogenic gene mutations can be corrected inside a living cell. It is a simplified molecular tool that does not require complex engineered proteins to recognize and cleave specific DNA sequences as in the case of other gene-editing tools such as Zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs). Because of its simple construction, it has become the most popular genome-editing tool and gained utility in disease modeling, genetic screening, epigenome editing, cell labeling, and gene therapy applications [52].

AAV-Mediated Gene Therapy for Retinal Diseases

The eye is a promising target for AAV gene therapy, due to its status as an immune-privileged site, the small tissue volume in a closed environment, and the relatively low dosage required for patients. Retinal diseases include retinal detachment, retinal vascular disease, macular degeneration, and retinitis pigmentosa [53]. Given the complex structure of the retina, the non-regenerative nature of neurons, and the presence of the blood-retinal barrier, treatments of retinal diseases currently face significant challenges. Luxturna, the first approved rAAV to treat inherited retinal dystrophy due to Leber congenital amaurosis RPE65 deficiency [54], has demonstrated the ability to improve vision, the duration of transgene expression of the RPE65. However, such administration delivered by subretinal injection is injurious and requires significant technical demands on clinicians [55].

Gene Therapy Challenges

Some of the very traits that make the retina an ideal candidate for gene therapies (i.e., immune privilege) can also introduce additional challenges to gene delivery, such as identification of the disease-causing gene or mutation, ensuring targeted delivery of the product, appropriate route of administration, feasibility in the clinic, and immune responses to the product that may exacerbate already fragile tissue. Simply delivering the product to the desired tissue can be a physical challenge, both due to the isolated nature of the eyes and the delicate nature of diseased tissue. These challenges remain for all products and clinical trials, and several different approaches have been developed to address them.

The Future of Gene Therapy

- Over the past 25 years, retinal gene therapy has made significant progress, improving both safety and efficacy. However, challenges remain, particularly in reducing healthcare costs and improving patient outcomes. Future research is likely to focus on enhancing vector design, improving product safety, and addressing issues like the high cost of production and the need for genetic diagnoses. New strategies may allow treatments to address multiple mutations with a single product, improving accessibility and cost-effectiveness.

- Advances in vector design are expected to reduce immunogenicity, enhance target specificity, and increase transduction efficiency, with non-viral options and multi-vector approaches showing promise. As gene therapy expands, improvements in manufacturing methods, such as shifting to more efficient production systems, will help increase product quality and reduce costs.

- The approval of Luxturna, a retinal gene therapy, highlights the potential of this field to provide innovative solutions for complex diseases. Although challenges remain, ongoing research and focus on patient well-being will continue to drive advancements, offering hope for improved treatments and quality of life for patients with retinal diseases.

Conclusions

Gene therapy holds great promise as a potential solution for patients diagnosed with retinal diseases, offering hope for individuals who previously had limited treatment options. By addressing the root causes of these conditions at the genetic level, gene therapy has demonstrated the ability to restore or preserve vision in some cases. While still in the early stages of development and clinical testing, the advances made so far indicate a significant potential to revolutionize the treatment of retinal diseases. However, challenges such as safety, accessibility, and long-term efficacy must be carefully evaluated as research progresses.

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As our understanding and technology continue to evolve, gene therapy may ultimately provide a transformative pathway for patients suffering from retinal disorders. Consent for publication: all authors have read and revised well for the manuscript and agree to publish.

Availability of Data and Material: All data supporting the study are presented in the manuscript or available upon request.

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