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ILLUMINATING THE FUTURE: ADVANCES IN TARGETED GENE THERAPY AND OPTOGENETICS IN THE TREATMENT OF INHERITED RETINAL DISEASES

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ABSTRACT

Introduction: Inherited retinal diseases (IRDs) are a group of disorders that lead to progressive vision loss, for which no effective treatments have previously been available. Advances in molecular biology have enabled the development of gene therapies and innovative strategies such as optogenetics, offering hope for improvement or restoration of visual function.
Aim: The aim of this work is to present the current state of knowledge regarding gene therapies used in IRDs, with particular emphasis on their mechanisms of action, possibilities for personalization, integration with other methods, and the potential of optogenetics as an alternative in advanced stages of the disease.
Methods: A literature review was performed using PubMed, Google Scholar, Scopus, and Web of Science. Thirty-nine English publications relevant to inherited retinal diseases and gene therapies were selected. Studies covered mechanisms, efficacy, safety, and diagnostic advances. Irrelevant or methodologically weak papers were excluded.
Results: Therapies based on AAV vectors, CRISPR/Cas9 techniques, prime editing, and antisense oligonucleotides demonstrate effectiveness depending on the type of mutation and disease stage. Optogenetics enables the restoration of light sensitivity regardless of the mutation, even in the absence of photoreceptors. Combining gene therapy with other methods, such as stem cells or neuroprotection, enhances therapeutic potential.
Conclusions: Gene and optogenetic therapies are transforming the treatment approach for IRDs. Selecting strategies based on the molecular background and disease stage enables a personalized approach. Technical and regulatory challenges remain, but development trends indicate a real possibility of effective treatment for many forms of IRDs.

KEYWORDS

Retinal Diseases, Genetic Therapy, Photoreceptor Cells, Optogenetics, Adeno-Associated Virus

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1.1 Introduction

Inherited retinal diseases (IRDs) constitute a heterogeneous group of genetic disorders that lead to progressive deterioration of vision and, in some cases, complete blindness. They may manifest as early as childhood or adolescence and represent one of the leading causes of vision loss in this population. These conditions are caused by genetic mutations that affect the function of retinal cells, particularly photoreceptors and the retinal pigment epithelium (RPE). The close interdependence between photoreceptors and the RPE is of critical importance; degeneration of one of these structures often results in the degeneration of the other, emphasizing their mutual role in maintaining retinal integrity. Mutations can be inherited through mitochondrial DNA or follow Mendelian inheritance patterns, resulting in widespread retinal changes (e.g. retinitis pigmentosa or Usher syndrome) or being limited to the macula (e.g. Stargardt disease or Best disease) [1,2]. Mutations leading to dysfunction of various components of retinal cells result in a range of distinct disease entities with varying clinical courses and prevalence. Among the most common inherited retinal diseases are: retinitis pigmentosa, Stargardt disease, Leber's congenital amaurosis (LCA), and various forms of macular dystrophy (e.g., cone or cone-rod dystrophy). Despite the extensive genetic heterogeneity of IRDs, a retrospective study conducted at a reference center involving a cohort of 2,790 patients has improved our understanding of their molecular basis. The collected data provided key insights into the frequency of pathogenic mutations and the genes most commonly involved. It has been demonstrated that the most frequently mutated gene was *ABCA4*, followed by *USH2A, RPGR*, and less commonly occurring genes such as *CHM, MYO7A*, and *CRB1*. Autosomal recessive (AR) inheritance is by far the most prevalent pattern, while mitochondrial DNA variants accounted for 2.1% of cases [3]. Knowledge of the molecular background of IRDs forms the foundation for understanding their clinical course. These diseases are typically characterized by progressive retinal degeneration, which leads to gradually worsening visual impairment. The clinical

presentation of these conditions is highly variable and may include symptoms such as: impaired twilight and night vision (nyctalopia), loss of peripheral vision, increased light sensitivity (photophobia), color vision defects, and the most severe outcome: central vision loss, including complete blindness [1,4]. Due to the severe and irreversible nature of these changes, inherited retinal diseases have become the focus of intensive research aimed at developing effective diagnostic and therapeutic strategies. The diagnosis of IRDs has been revolutionized by the introduction of advanced imaging techniques such as fundus autofluorescence (FAF), optical coherence tomography (OCT/OCTA), fluorescence lifetime imaging ophthalmoscopy, and wide-field imaging. These methods allow for detailed assessment of retinal layers and structures, and even enable visualization of the retinal and choroidal microcirculation (through OCTA). Current diagnostic approaches make it possible to perform a comprehensive analysis of phenotypic heterogeneity and may suggest specific genetic mutations, thereby supporting accurate diagnosis and treatment planning [5,6]. Thanks to the dynamic development of diagnostic and therapeutic methods, patients have the opportunity for earlier disease detection and faster adjustment of treatment strategies aimed at preventing irreversible damage. Contemporary technological advances and the progress in gene therapy have made targeted gene treatments and optogenetics a promising direction in the treatment of inherited retinal diseases.

1.2 Aim of the Study

The aim of this review paper is to present the latest achievements and advancements in the field of targeted gene therapy and optogenetics as innovative treatment approaches for inherited retinal diseases. The paper seeks to discuss the mechanisms of action of these therapies, their efficacy, safety, and clinical potential, as well as to highlight the challenges and future development prospects that may contribute to improving the quality of life for patients affected by these conditions. Moreover, the review will focus on current clinical studies, technological innovations, and examples of the practical application of gene therapy and optogenetics in ophthalmic practice.

2. Materials and Methods

A literature review was conducted using electronic databases, including PubMed, Google Scholar, Scopus, and Web of Science. A total of 39 sources were analyzed, from which only publications in English were selected. The search was performed using the following keywords: “Retinal Diseases”, “Genetic Therapy”, “Photoreceptor Cells”, “Optogenetics”, “Adeno-Associated Virus”, “Retinal Pigment Epithelium”, “Retinitis Pigmentosa”, “Leber Congenital Amaurosis”, “Gene Editing”, “CRISPR/Cas9”, “Antisense Oligonucleotide Therapy”, both individually and in various combinations. Studies were included if they analyzed the mechanisms, clinical efficacy, safety, and potential of targeted gene therapy and optogenetics in the treatment of inherited retinal diseases, with particular attention to the use of AAV vectors, gene augmentation, gene editing (including CRISPR/Cas9), antisense oligonucleotide therapy, and advances in molecular diagnostics and retinal imaging. Publications not directly related to the review’s scope, lacking detailed methodological descriptions, or raising concerns about reliability were excluded.

3. Targeted Gene Therapy

The first attempts to use gene therapy in the treatment of retinal diseases date back to the 1990s. Until that time, therapeutic options were mainly limited to symptomatic treatment. Recent advances in targeted gene therapy and optogenetics have profoundly transformed the management of inherited retinal diseases. These developments offer expanded therapeutic options through various vectors and gene delivery methods. These cutting-edge strategies focus on restoring vision by correcting genetic defects or bypassing malfunctioning photoreceptors. The integration of these therapies into clinical practice appears promising, and ongoing clinical trials suggest their potential efficacy and safety [7].

3.1 Mechanisms of Targeted Gene Therapy in Hereditary Retinal Diseases

3.1.1 Gene Augmentation Therapy

Gene augmentation therapy entails introducing a functional version of a gene into cells to reinstate normal gene expression. The eye is an excellent organ for this type of intervention, in part due to its enclosed structure. Focusing on photoreceptor cells or the retinal pigment epithelium (RPE), subretinal injection facilitates direct delivery of vectors to the targeted cellular location, bypassing any epithelial or anatomical barriers [8]. This method proves especially beneficial for autosomal recessive and X-linked retinal disorders, in which the mutation leads to a loss of function of the gene product [9]. Vectors, which can be divided into

viral and non-viral types, are used to deliver therapeutic genes to the appropriate cells. Viral vectors, such as adeno-associated virus (AAV), are commonly employed in gene therapy because they can infect both actively dividing and non-dividing cells without integrating into the host genome [7]. Non-viral methods, such as the use of plasmids with minimal bacterial backbones and scaffold/matrix attachment region (S/MAR) sequences, although less common, can carry larger genes and maintain episomal expression, potentially offering a safer alternative due to a reduced risk of eliciting an immune response. While non-viral gene delivery methods have many advantages, the low transfection efficiency in the retina remains a significant limitation.To address this issue, various strategies have been developed, such as DNA integration with chemical carriers like nanoparticles and electroporation techniques, including iontophoresis and electrotransfection. Importantly, these methods have shown promising results in preclinical studies. Therefore, non-viral gene therapy may, in the future, prove to be not only safer but also a more effective alternative for treating inherited retinal diseases [8]. Although gene augmentation therapy shows promising results, it does have certain limitations when it comes to treating inherited retinal diseases (IRDs). A significant obstacle is the extensive genetic variability found in these disorders, which greatly complicates the application of standardized therapeutic approaches. Consequently, a comprehensive strategy is being increasingly suggested - one that integrates both gene-specific techniques and gene-agnostic methods. While gene therapy can produce remarkable outcomes for specific mutations, it fails to encompass the entire range of genetic irregularities. Thus, there is a rising interest in gene-agnostic therapies that provide more inclusive, mutation-independent treatment alternatives for different subtypes and stages of IRDs. Such methods encompass neuroprotective therapies, optogenetics, cell-based treatments, modulation of the retinal microenvironment, strategies for regulating gene expression, and cutting-edge retinal implants [10]. When analyzing gene therapies based on the gene augmentation strategy, it is impossible to overlook the breakthrough moment represented by the introduction of Luxturna (voretigene neparvovec) therapy. This is the first gene therapy approved by the FDA for the treatment of inherited retinal diseases, used specifically to treat Leber congenital amaurosis (LCA) caused by mutations in the RPE65 gene. Luxturna uses a viral vector to deliver a functional RPE65 gene to retinal cells. This gene therapy targets patients with low or absent RPE65 protein to restore vision. It is given as a single subretinal injection in each eye, approved for biallelic RPE65 mutation-related vision loss [7,11]. While Luxturna has set a new standard in the treatment of genetic retinal diseases, it also highlights the complexities involved in developing and implementing gene therapies. The therapy's success underscores the potential of gene-based treatments to transform the management of genetic disorders, yet it also calls attention to the need for continued innovation and collaboration across scientific, regulatory, and clinical domains. In this context, the field of inherited retinal diseases continues to evolve rapidly. Although no other gene therapies for IRDs have been approved to date beyond Luxturna, numerous candidates are currently undergoing clinical evaluation - many of them in advanced stages (Phase 2/3). The most notable examples of gene augmentation therapies currently in clinical development include: AAV8-RPGR (MeiraGTx/Janssen), AAV-RPGR (Biogen/Nightstar) or USH2A [12,13,14].

Table 1. Selected Gene Augmentation Therapies in Clinical Development for Inherited Retinal Diseases (IRDs)

Therapy	Target Gene	Disease	Mechanism	Clinical Status
Luxturna (voretigene neparvovec)	RPE65	LCA2 / RP with RPE65 mutations	AAV2 delivers functional RPE65 gene copy	Approved (FDA/EMA)
AAV8-RPGR (MeiraGTx/ Janssen)	RPGR	X-linked Retinitis Pigmentosa (XLRP)	AAV8 delivers functional RPGR gene	Phase 3
AAV-RPGR (Biogen/ Nightstar)	RPGR	XLRP	AAV delivers functional RPGR gene	Phase 2
USH2A (preclinical studies)	USH2A	Usher Syndrome Type 2A	AAV-mediated gene replacement	Preclinical

3.1.2 Gene Editing

Gene editing stands as one of the most thrilling frontiers in the treatment of inherited retinal disorders. This groundbreaking method offers renewed optimism to patients who previously had limited treatment alternatives. As scientific progress continues, gene editing has the potential to transform the possibilities of restoring vision and averting blindness. Gene editing in inherited retinal diseases (IRDs) involves the precise correction of disease-causing mutations directly within the DNA of affected cells. Instead of adding a new, healthy copy of a gene (as in gene augmentation) this approach targets the faulty sequence itself. By editing specific mutations within a gene, the underlying genetic error can be repaired at its source, potentially restoring normal gene function. This is typically achieved using molecular tools like CRISPR/Cas9, which act as programmable "scissors" to cut the DNA at the desired site, allowing the cell's natural repair mechanisms to correct the sequence [7]. This mechanism unfolds in several steps, which help explain how targeted correction is achieved. The CRISPR/Cas9 system operates primarily through two key components, with the single guide RNA (sgRNA) guiding the Cas9 protein, which possesses endonuclease activity, to execute precise DNA cleavage. The cell's natural repair mechanisms enable it to effectively reconnect the severed genes. Consequently, gene knock-in or knock-out can be accomplished through this method. Because of its accuracy, effectiveness, and low cost, CRISPR/Cas9 has been widely used for human disease treatment and has shown great potential in gene therapies for hereditary diseases [15]. In ophthalmology, this approach has already been applied to correct mutations in genes such as *RPGR* and *CEP290*, which are associated with inherited retinal diseases like Retinitis Pigmentosa and Leber congenital amaurosis. Moreover, its expanding application in conditions such as Alzheimer's disease, sickle cell anemia, and Duchenne muscular dystrophy (disorders that remain difficult to treat with existing therapies) further highlights the transformative potential of gene editing in modern medicine [7,15]. It is worth noting that the first CRISPR/Cas9-based gene editing therapy administered to patients with Leber congenital amaurosis type 10 (LCA10) began in 2019 with the initiation of the EDIT-101 clinical trial. This represented a landmark moment as the first in vivo application of CRISPR technology in humans. However, despite its innovative character, EDIT-101 is still considered an investigational therapy and has not yet received regulatory approval. Its future clinical use will depend on the outcomes of ongoing safety and efficacy evaluations [16]. While CRISPR/Cas9 presents a promising pathway for addressing IRDs, it is crucial to explore alternative viewpoints and challenges. The intricate nature of IRDs, characterized by genetic diversity and different inheritance models, demands a comprehensive strategy for treatment. Moreover, the long-term safety and effectiveness of CRISPR-based therapies are still being evaluated, underscoring the necessity for ongoing research and development. Alongside these initiatives, novel gene editing technologies have surfaced, providing improved accuracy and adaptability. Among these, base editing and prime editing are notable as advanced tools that expand upon the CRISPR framework. Base editing facilitates the direct transformation of one DNA base into another without causing double-strand breaks, whereas prime editing merges CRISPR technology with reverse transcription to enable precise insertions, deletions, or substitutions of DNA sequences. These cutting-edge methods are especially effective for rectifying point mutations and have already demonstrated promising outcomes in preclinical models of genetic retinal disorders [17].

3.1.3 RNA Modification and Antisense Oligonucleotide Therapy

Among the different targeted gene therapies, the modulation of RNA stands out as a promising approach for IRDs. Instead of modifying the DNA sequence, this strategy aims to adjust or manage gene expression at the RNA level. Antisense oligonucleotides (AONs) are short, synthetic strands of nucleic acids designed to bind to specific RNA sequences, thereby modulating gene expression or correcting splicing defects. Many IRDs are caused by mutations that disrupt pre-mRNA splicing of the affected genes. By binding to pre-mRNA, AONs can effectively correct splicing defects caused by intronic mutations that lead to pseudoexon insertion. Through restoring proper splicing and gene function, AON therapy offers a promising strategy for managing IRDs and mitigating the effects of these genetic disorders [18]. In Leber congenital amaurosis type 10 (LCA10), a prevalent mutation in the CEP290 gene causes abnormal splicing and the incorporation of a pseudoexon, leading to an inactive protein. The AON treatment: sepofarsen (QR-110) specifically targets this mutation by attaching to the faulty pre-mRNA and facilitating proper splicing. This process reinstates the synthesis of functional CEP290 protein, which may enhance retinal functionality and decelerate disease advancement [19]. Similarly, mutations in the *USH2A* gene frequently lead to improper splicing events that interfere with protein expression in Usher syndrome type 2 (USH2A). The experimental AON therapy QR-421a is intended to promote exon skipping, allowing for the exclusion of the mutated exon to create a shorter but functional variant

of the protein. This strategy seeks to protect photoreceptor cells and avert vision deterioration [20]. Antisense oligonucleotide (AON) strategies have also shown promise in addressing mutations in the *RPGR* gene, a common cause of X-linked retinitis pigmentosa (XLRP). This form of RP is among the most severe and early-onset subtypes, making it a critical target for innovative therapies. By correcting splicing defects or modulating RNA to restore proper protein expression, AONs offer a tailored approach to managing these mutations [21]. All RNA-targeting therapies in IRDs are still experimental and are in clinical trial phases, but they are not available as approved therapeutic options. Nevertheless, these approaches are not without limitations, including challenges posed by the genetic heterogeneity of IRDs, difficulties in achieving efficient and stable delivery of AONs, and the necessity for individualized therapeutic strategies.

3.1.4 Protective Gene Expression Therapy

Among the evolving strategies in targeted gene therapy for inherited retinal diseases, approaches based on the expression of protective genes are gaining increasing attention. Unlike gene augmentation or gene editing, which focus on correcting or replacing disease-causing mutations, this method aims to enhance cellular resilience by delivering genes that support photoreceptor survival and retinal homeostasis. By introducing genes with neuroprotective or anti-apoptotic properties, this strategy seeks to delay degeneration and preserve vision, regardless of the underlying genetic mutation. It offers a mutation-independent therapeutic avenue, particularly valuable for patients with advanced disease or unidentified genotypes. Protective gene therapy for inherited retinal diseases often involves delivering genes encoding neurotrophic, anti-apoptotic, or antioxidant factors. Ciliary neurotrophic factor (CNTF) has been explored as a therapeutic agent for retinitis pigmentosa (RP) due to its potential to support photoreceptor survival and delay degeneration. Clinical trials using encapsulated cell technology (ECT) to deliver CNTF have demonstrated safety and some structural preservation in patients with RP. This approach involves implanting cells that secrete CNTF directly into the eye, providing a continuous and localized delivery of the neurotrophic factor [22]. In addition to neurotrophic support, enhancing the retina's antioxidant defenses is another promising strategy. Nuclear factor erythroid 2–related factor 2 (Nrf2), a key regulator of antioxidant responses, has shown protective effects in preclinical models of various retinal dystrophies by reducing oxidative stress. Activators of Nrf2 have demonstrated efficacy across multiple retinal disease models, emphasizing their therapeutic potential. For example, Nrf2 knockout mice develop age-related retinal degeneration, underscoring the importance of this pathway in retinal health [23]. Other factors such as BDNF, GDNF, and XIAP remain under active investigation for their neuroprotective and anti-apoptotic potential. Despite promising preclinical results, therapies based on protective gene expression face several limitations. Additionally, it remains uncertain whether these approaches, which do not target the underlying genetic mutations, can do more than slow disease progression rather than offer a definitive cure.

3.2 Challenges of Gene Therapies in Inherited Retinal Diseases

Gene therapy stands out as one of the most promising pathways for tackling the root causes of inherited retinal diseases (IRDs). Nevertheless, as the discipline transitions from research models to clinical practice, it becomes increasingly evident that the journey towards widespread adoption is intricate and multifaceted. In this article, we examine the significant limitations of gene therapies for inherited retinal diseases, including immune reactions to viral vectors, the transient nature of gene expression, difficulties in accurate delivery, the size of the target genes, genetic diversity among patients, ethical implications, as well as regulatory and financial obstacles. A major concern is the immune response to viral vectors, particularly adeno-associated viruses (AAVs), which may trigger inflammation, reduce therapeutic gene expression, or cause adverse effects. Although the eye benefits from a degree of immune privilege, which helps reduce systemic immune reactions, local immune responses can still occur, potentially compromising treatment safety and efficacy. The long-term effects of gene therapies remain incompletely understood, especially regarding sustained expression and immune-related complications. Another critical issue is the uncertainty regarding the durability of therapeutic gene expression. In rapidly progressing retinal diseases, a single treatment may not provide lasting benefits, potentially necessitating repeated interventions. Advances in vector design and regulatory elements are being investigated to ensure longer-lasting expression. Delivery efficiency also remains a significant hurdle. Targeting specific retinal cells, especially photoreceptors and the retinal pigment epithelium, can be technically challenging. Inadequate or uneven gene delivery may result in suboptimal therapeutic outcomes. To improve precision, researchers are refining subretinal and intravitreal delivery methods, as well as engineering vectors with enhanced tropism. The size of therapeutic genes poses another limitation. AAV vectors have a restricted

cargo capacity, rendering them unsuitable for delivering large genes implicated in certain IRDs, such as USH2A. Alternative solutions include dual-vector systems, non-viral delivery methods, and nanoparticle-based platforms. Patient-related variability further complicates therapy design. IRDs are genetically heterogeneous, and different mutations in the same gene can lead to variable phenotypes. This reduces the applicability of standardized approaches and underscores the need for personalized or mutation-specific therapies. Additionally, ethical concerns around genome editing tools like CRISPR/Cas9 have tempered their rapid clinical adoption. Current efforts focus on somatic cell editing, while fears about unintended effects and germline modifications demand strict oversight. From a regulatory standpoint, gene therapies for rare diseases often face lengthy, costly approval processes. This delays patient access and drives high treatment costs, limiting availability in resource-poor settings. Programs for accelerated approval and cost-reduction strategies are being explored. Biologically, there is often a limited therapeutic window - gene therapy is generally more effective in early disease stages. Advanced degeneration may render treatments ineffective, emphasizing the need for early diagnosis and for developing therapies that retain efficacy in later stages. Finally, concerns about off-target effects in gene editing and variable patient response must be addressed. Unintended genomic changes pose risks, including cancer, while patient-specific factors like age or immune status can influence treatment outcomes. Improving precision technologies and adopting more personalized approaches are key to overcoming these obstacles [7, 24].

3.3 Future Directions of Gene Therapies in Inherited Retinal Diseases

Gene therapies for inherited retinal diseases (IRDs) are rapidly evolving, with several promising directions poised to significantly improve treatment efficacy and broaden the range of available interventions. One of the most important advances is the development of modern gene editing techniques, such as prime editing, which enables precise mutation correction without causing double-stranded DNA breaks. This technology offers greater safety and flexibility, although its clinical application and effective delivery to target cells remain challenging [25]. In tandem, significant efforts are being made to enhance the systems for delivering genetic material, with an increasing focus on using non-viral vectors like nanoparticles, liposomes, and electroporation techniques. Non-viral approaches serve as a compelling alternative to traditional viral vectors because they offer a superior safety profile - minimizing the chances of insertional mutagenesis and serious immune responses that may arise from therapies utilizing viral vectors. Furthermore, these methods are typically more straightforward and economical to scale up, as they do not depend on intricate biological systems for replication. Thanks to these advantages, non-viral systems have the potential not only to improve therapy safety but also to increase the accessibility of gene therapies [26]. However, challenges remain in ensuring high efficiency and durable gene expression, as well as effective and selective penetration across the retinal barrier to the appropriate target cells. Tailored therapies designed to align with an individual's unique genetic makeup also hold significant potential. While this method may enhance efficacy and minimize side effects, it entails substantial costs and intricate regulatory challenges. Combination strategies that integrate gene therapy with pharmacological treatment, surgical interventions, or optogenetics are gaining increasing attention, as they can provide synergistic effects - especially in patients with advanced disease stages or where monotherapy is insufficient. Another innovative method involves the integration of gene therapy with stem cell therapy, presenting the possibility not only to rectify mutations but also to restore damaged retinal cells. Nevertheless, this method poses difficulties concerning the regulation of cell differentiation and ensuring immunological safety. In addition to these advances in therapeutic techniques, broader systemic developments will also shape the future of gene therapy for IRDs. One key direction involves extending gene therapy applications to complex polygenic and multifactorial diseases, such as age-related macular degeneration (AMD). This expansion has the potential to benefit a much wider patient population but also requires deeper insight into the underlying disease mechanisms. Furthermore, the incorporation of sophisticated diagnostic technologies such as high-resolution retinal imaging and the identification of molecular biomarkers will be crucial for early detection and improved patient stratification, which in turn can enhance therapeutic outcomes. Equally important is the implementation of robust long-term monitoring systems to evaluate the durability and safety of treatments over time. Such frameworks are critical to building and maintaining trust in gene therapies among both clinicians and patients. Lastly, harmonizing international regulatory and ethical standards will be necessary to streamline approval processes and ensure the safe and equitable global application of gene therapy innovations [7, 27, 28, 29].

4. Optogenetics

The idea of optogenetics was introduced in the early 1980s, based on the premise that light manipulation could specifically target and regulate individual neurons. Due to the accurate and swift modulation of neural signals, optogenetics has gained extensive use in neurobiological studies and is increasingly recognized for its therapeutic potential, particularly in the field of ophthalmology. Employing this technique enables the restoration of visual capabilities through the light-based stimulation of retinal cells, thereby creating new avenues for addressing degenerative eye diseases [30]. Combining optogenetics with other advanced methods, such as gene therapy, pharmacotherapy, or neuroprosthetic systems, may yield synergistic effects. The use of advanced optical devices and artificial intelligence for precise control of light stimulation further enhances the chances of improving visual quality and patients' quality of life.

4.1 Mechanism of Optogenetic Therapy

Optogenetics in ophthalmology involves restoring light sensitivity in the degenerated retina by introducing light-sensitive proteins called opsins into cells. These proteins enable modulation of retinal neuron activity in response to specific wavelengths of light. In contrast to traditional phototransduction that takes place in rods and cones via endogenous rhodopsin and intricate signaling pathways (which involve transducin and phosphodiesterase), the optogenetic method circumvents the damaged photoreceptors and harnesses the remaining retinal cells - typically ganglion cells or bipolar cells - as novel effector cells that can react to light. Opsins can be divided into two categories: microbial opsins (type I) and animal opsins (type II). In optogenetic therapy, microbial opsins (type I) are primarily used, which are delivered into target cells using adeno-associated virus (AAV) vectors. Among them, the best-known is Channelrhodopsin-2 (ChR2) - a cation channel activated by blue light which, when expressed in ganglion cells, allows the influx of Na^+, Ca^{2+}, and H^+ ions into the cell, causing its depolarization and the generation of an electrical signal. This signal is then transmitted to higher visual centers, ultimately enabling partial restoration of visual function. Due to the limited penetration of blue light in biological tissues and its potential phototoxicity, opsins sensitive to longer wavelengths (red-shifted opsins, e.g., ChrimsonR, ReaChR) are being developed. These enable more efficient neuronal stimulation at lower light intensities and greater penetration depths, making them preferable for clinical applications, particularly in deep retinal layers. However, their use requires careful optimization of stimulation parameters to avoid spectral interference with blue-light-activated opsins. Another group of opsins used in optogenetics includes light-driven ion pumps such as halorhodopsin (HR) and archaerhodopsin (Arch). These function by transporting anions (Cl^-) or protons (H^+) in a light-dependent manner, leading to hyperpolarization of the cell membrane and suppression of neuronal activity. Although they are not directly employed to restore photosensitivity, their ability to inhibit pathological retinal neuron activity makes them valuable as supportive therapies, particularly in cases involving neuronal hyperexcitability. The most technologically advanced optogenetic strategies involve enzymatic/kinase opsins (e.g., Rh-GC, Rh-PDE, HKR), which, instead of directly affecting membrane potential, modulate secondary intracellular signaling pathways in response to light. This enables more selective and precise control of retinal cell activity, although these approaches remain in the experimental research phase. A key component of effective optogenetic therapy is also the choice of an appropriate light source. Since opsin activation depends on light intensity and wavelength, patients often use specially designed optogenetic goggles after treatment. These devices convert visual scenes from the environment into light stimuli with optimized parameters, allowing selective activation of target retinal cells [30,31].

Table 2. Comparison of Microbial Opsins Used in Retinal Optogenetics

Opsin Type	Mechanism of Action	Peak Wavelength (λmax)	Target Retinal Cells
Channelrhodopsin-2 (ChR2)	Light-gated cation channel	~440 nm (blue light)	Retinal ganglion cells (RGCs)
ChrimsonR / ReaChR	Red-light activated cation channel	~590–650 nm (red light)	RGCs or bipolar cells
Halorhodopsin (HR)	Light-driven chloride pump	~570 nm (yellow light)	Hyperactive or modulated cells
Archaerhodopsin (Arch)	Light-driven proton pump	~530–560 nm (green light)	RGCs (experimental)
Rh-GC / Rh-PDE / HKR	Light-activated enzymatic signaling opsins	Variable (depends on type)	Inner retinal neurons

4.2 Application of Optogenetics in the Treatment of Inherited Retinal Diseases

In contrast to traditional gene therapy, which is restricted to the initial phases of a disease and necessitates intact photoreceptor architecture, optogenetics presents a different approach focused on reestablishing photosensitivity by incorporating external opsins into the surviving retinal neurons. The most common targets are retinal ganglion cells or bipolar cells, which often remain structurally intact even in advanced stages of degeneration. Importantly, the efficacy of optogenetic therapy does not depend on the specific genetic mutation underlying the disease, which significantly broadens its clinical applicability [32]. This approach is particularly relevant in conditions such as retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), and Stargardt disease. These disorders are characterized by progressive loss of photoreceptors, while the inner retinal architecture is relatively preserved. This anatomical preservation enables targeting of intermediate neurons involved in visual signal transmission. Increasing attention is being paid to bipolar cells, which play a key role in the complex processing of visual information. Their stimulation may allow for restoration of higher-quality visual perception compared to direct targeting of ganglion cells [33]. One of the most advanced clinical applications of optogenetics in the treatment of retinitis pigmentosa (RP) is the GS030 therapy developed by GenSight Biologics. This approach uses a modified AAV2.7m8 vector to deliver the gene encoding the channelrhodopsin ChRimsonR into retinal ganglion cells. Simultaneously, patients are provided with specially designed optogenetic goggles that convert environmental images into red light (wavelength 590–600 nm), enabling effective opsin activation. In the Phase I/II clinical trial (NCT03326336), partial restoration of visual perception and improvement in spatial orientation were observed in some patients, confirming a functional therapeutic effect. These results suggest that combining optogenetic gene expression with assistive visual technology may enable partial vision recovery even in advanced stages of the disease [32]. A similar strategy is being developed by Bionic Sight, which is working on the BS01 therapy. In this case, opsins are also expressed in retinal ganglion cells. An innovative element of this approach is the use of artificial intelligence systems that analyze neuronal activity in real time and convert it into visual signals that mimic natural retinal encoding. Preliminary findings suggest that BS01 may successfully reconstruct functional vision even in individuals with profound blindness [32, 34]. Preclinical studies, conducted primarily in mouse models, suggest that optogenetic approaches may have applications not only in the treatment of retinitis pigmentosa (RP). They are increasingly being considered in the context of other inherited retinal diseases, such as Leber congenital amaurosis (LCA) and geographic atrophy in age-related macular degeneration (AMD). These strategies are particularly valuable in advanced stages of disease, when photoreceptors have already degenerated. In such cases, optogenetics offers a potential alternative [35, 36]. Ongoing research aims to enhance visual resolution, improve the temporal dynamics of perception, and develop more physiologically relevant image encoding systems, which may significantly broaden the clinical indications for this technology in the future.

4.3 Challenges and Limitations in the Application of Optogenetic Therapies

The selection of appropriate retinal cells for opsin expression is a key element in the effectiveness of optogenetic therapy. So far, retinal ganglion cells have been the primary target; however, ON-type bipolar cells appear to be a more attractive target due to their significant role in processing visual signals. Unfortunately, structural and functional changes in the inner retinal layers during disease progression significantly complicate the possibility of precisely and effectively targeting these cells. Additionally, limitations related to AAV vector tropism affect the efficiency of gene delivery, and promoter specificity can restrict opsin expression to selected cell types only. Structural and functional remodeling of the retina poses a serious challenge, as these structural and functional alterations may weaken the effectiveness of optogenetic interventions [37]. The design and implantation of optogenetic devices, such as optrodes, require addressing several significant technical challenges. One of the main issues is enzymatic degradation and glial encapsulation, which can lead to the loss of device functionality over time. These biological responses greatly hinder the long-term ability to record neural signals and to precisely illuminate opsin-expressing tissues. Moreover, the implantation of foreign materials into brain tissue triggers an inflammatory reaction, the severity of which correlates with the size and stiffness of the implant. Therefore, current engineering efforts focus not only on miniaturizing optrodes and increasing their flexibility but also on reducing immune responses by lowering the elastic modulus of the materials. Ensuring long-term functional stability, precise positioning, and effective integration of the implants with neural tissue remains critical [38]. An additional challenge lies in the development of closed-loop optogenetic systems, which integrate actuators and sensors to enable real-time neuromodulation. Implementing such systems requires ensuring spectral orthogonality and developing

advanced decision-making algorithms, which considerably complicates both the design and control of the therapy. Optogenetic therapies require further evaluation of their long-term safety and efficacy, particularly concerning the use of viral vectors and chronic implants. It remains crucial to determine whether prolonged light stimulation may cause tissue damage or trigger immune responses. Taken together, these factors hinder achieving full success in vision restoration through optogenetic approaches [39].

5. Differences in Therapeutic Mechanisms Depending on the Inherited Retinal Disease

The therapeutic mechanisms for these diseases vary significantly depending on the specific genetic mutations and the pathophysiological mechanisms involved. Recent advancements in molecular biology and genomics have led to the development of various therapeutic strategies, each targeting different aspects of these diseases. In diseases caused by recessive loss-of-function mutations, such as dystrophies associated with mutations in the *RPE65* gene, the production of functional protein is impaired. This leads to disruption of the visual cycle and degeneration of photoreceptors. In such cases, gene supplementation using adeno-associated viral (AAV) vectors has proven effective. A notable example is the clinically approved gene therapy Luxturna, which enables expression of functional *RPE65* protein in retinal pigment epithelium (RPE) cells, thereby contributing to the improvement of visual function [11]. In diseases with a dominant inheritance pattern, such as certain forms of retinitis pigmentosa caused by mutations in the *RHO* gene (which encodes rhodopsin – a key protein in retinal rod photoreceptors), conventional gene supplementation therapy may prove ineffective. Moreover, it can even worsen the patient's condition, as the mutant allele often produces proteins with toxic or dominant-negative effects on cellular function. In such cases, more promising approaches involve silencing the expression of the mutated gene, for example through RNA interference techniques. Alternative strategies include modern genome editing tools such as CRISPR/Cas9, as well as precise DNA correction methods like base editing and prime editing, which allow for mutation repair without introducing double-strand breaks [16,17]. In cases where a mutation disrupts pre-mRNA splicing, such as in *CEP290* (Leber congenital amaurosis type 10) or *USH2A* (Usher syndrome), therapies based on antisense oligonucleotides (AONs) are employed to modulate RNA splicing and enable the production of functional protein. The mechanism of action of AONs involves the “correction” of splicing defects by blocking aberrant splice sites or activating alternative exons, which can restore a normal cellular phenotype [18,20]. In advanced stages of degenerative diseases, where photoreceptors are completely lost, standard gene therapies become ineffective due to the absence of target cells for repair. In such cases, gene-agnostic strategies are employed. These include optogenetic therapies, which involve introducing light-sensitive proteins (opsins) into preserved inner retinal neurons, such as ganglion or bipolar cells [10]. Alternatives also include cell-based therapies, which rely on the transplantation of photoreceptor cells or pluripotent progenitor cells, as well as retinal neuroprostheses, which restore vision by directly stimulating the optic nerve through electrical impulses [1]. The variable clinical course and genetic heterogeneity of inherited retinal diseases (IRDs) necessitate a personalized treatment approach. For instance, patients presenting with early-onset and severe phenotypes, such as Leber congenital amaurosis (LCA), may require rapid therapeutic intervention. In contrast, milder forms of cone-rod dystrophies can be managed with long-term strategies, including modified vectors or therapies aimed at delaying degeneration. Detailed genotyping, phenotyping, and retinal imaging (e.g., OCT, autofluorescence) are essential for selecting the most appropriate therapeutic approach for each patient [1,4]. In light of advances in molecular biology and genetic engineering, precisely matching the therapeutic strategy to the specific characteristics of the disease not only enhances treatment efficacy but also minimizes the risk of adverse effects. This approach forms the foundation of modern personalized medicine in ophthalmology.

6. Discussion

The rapid advancement of gene and cell therapies aimed at inherited retinal diseases (IRDs) signifies a significant transformation in the treatment options for previously untreatable forms of blindness. These innovations embody more than mere technological advancement, they denote a fundamental shift in our approach to intricate neurodegenerative disorders affecting the retina. This review emphasizes that the effectiveness of these interventions is fundamentally contingent upon choosing a therapeutic approach that is closely aligned with the molecular defect at the core of the disease, its pathophysiological backdrop, and the clinical phase at which treatment begins. For example, while gene supplementation may be effective in early-stage recessive conditions, more advanced or dominantly inherited diseases often require genome editing or gene-silencing approaches. This level of personalization ensures not only greater therapeutic efficacy but also minimizes the risk of off-target effects, immune responses, or other iatrogenic complications. Ultimately,

tailoring treatments to the unique genetic and phenotypic profile of each patient enhances both safety and long-term visual outcomes [3,4]. In early-stage inherited retinal diseases caused by monogenic, recessive mutations - such as Leber congenital amaurosis associated with *RPE65* mutations - gene augmentation therapy using adeno-associated virus (AAV) vectors has shown sustained therapeutic benefit. A notable example is Luxturna, the first FDA-approved gene therapy for a retinal disorder, which delivers a functional copy of the *RPE65* gene to retinal pigment epithelial cells [11]. The success of this approach, however, critically depends on the presence of viable target cells, including functional photoreceptors and an intact retinal pigment epithelium. As the disease progresses and these structures degenerate, the therapeutic window narrows significantly. Consequently, gene augmentation becomes less feasible in advanced stages of degeneration, where substantial loss of retinal architecture limits transduction efficacy and potential visual improvement [7]. In contrast to recessive conditions, dominant-negative mutations such as those found in rhodopsin-associated retinitis pigmentosa necessitate fundamentally different therapeutic strategies. Instead of adding a functional gene copy, treatment must target the pathogenic allele directly. Allele-specific gene silencing or gene-editing technologies have emerged as promising approaches in this context. Tools such as CRISPR/Cas9, base editing, and prime editing enable precise modification of the disease-causing sequence within the genome. These interventions mark a significant shift in the therapeutic paradigm. Rather than compensating for genetic defects, they aim to correct or neutralize them at their source. This molecular precision opens the door to more durable, potentially curative outcomes that go beyond temporary symptom management [15,17,25]. For splicing-defective variants, such as those in *CEP290* or *USH2A*, antisense oligonucleotide (AON) therapy has emerged as a promising transcript-level intervention. Agents such as sepofarsen and QR-421a have shown encouraging molecular responses and measurable gains in visual function during early-phase clinical trials [19, 20]. However, AON-based strategies require repeated intravitreal delivery, are often transient in effect, and can elicit innate immune responses [8,18]. Gene-agnostic approaches offer critical alternatives when classical gene therapies are no longer viable. These include protective gene expression (e.g., CNTF, Nrf2) and optogenetic therapies, which aim to restore light sensitivity by targeting surviving retinal interneurons. Clinical trials with GS030 (GenSight) and BS01 (Bionic Sight) have demonstrated partial restoration of visual perception in patients with profound blindness, despite the absence of functional photoreceptors. While current visual acuity remains low, these therapies represent a groundbreaking option for patients previously excluded from intervention [10,22,23,32,33]. Nevertheless, significant limitations remain. Immune reactions to viral vectors, AAV packaging constraints, variability in transgene expression, and progressive retinal remodeling can all reduce therapeutic durability [24]. Optogenetic and implant-based approaches face technical hurdles including spatial targeting, opsin activation dynamics, and long-term biocompatibility. The development of flexible, miniaturized devices and closed-loop systems is ongoing but faces considerable engineering and biological complexity [37,38,39]. In light of these challenges, combined therapeutic strategies that integrate gene augmentation with neuroprotective interventions, optogenetic approaches, or stem cell-based treatments may offer superior outcomes. This is particularly relevant in complex cases or in the advanced stages of inherited retinal diseases. In addition, early and precise diagnosis remains a cornerstone of effective therapy planning. Comprehensive genotyping, detailed clinical phenotyping, and high-resolution retinal imaging - including optical coherence tomography, fundus autofluorescence, and angiography - are essential tools for guiding individualized treatment decisions [5,6,30]. As therapeutic modalities mature, ensuring equitable access, long-term follow-up, and post-marketing safety surveillance will be essential. The future of IRD treatment lies not only in molecular innovation but also in establishing a robust infrastructure for personalized, stage-specific care guided by precise genetic diagnosis.

7. Conclusions

Modern therapeutic strategies go beyond classical molecular approaches by focusing on common pathophysiological features of diseases. This enables treatment of patients with diverse genetic backgrounds. Crucial tools include gene replacement therapies using AAV vectors, targeted gene expression modulation via CRISPR/Cas9, base and prime editing techniques, RNA splicing modification with antisense oligonucleotides, and advanced optogenetic technologies. These approaches not only halt neurodegeneration progression but also functionally restore retinal responses to light stimuli in cases where traditional therapies are no longer effective. Therapies that act independently of mutation type are especially important, as they allow treatment of a broad patient population, including those with unidentified genetic profiles or carrying very rare pathogenic variants. Thanks to advances in molecular diagnostics, retinal structural imaging, and improved understanding of the pathophysiology of individual disorders, it is increasingly possible to tailor therapeutic

strategies precisely to the phenotype and disease stage of each patient. These therapies, previously developed mainly in preclinical research, are now increasingly advancing through clinical trial phases and show potential for practical clinical application. This represents a breakthrough in treating diseases such as retinitis pigmentosa, Leber congenital amaurosis, and cone-rod dystrophies, which were considered untreatable for decades. Despite these significant advances, therapy for inherited retinal diseases still faces major limitations. These include difficulties in achieving stable and safe long-term expression of therapeutic genes, immunogenicity issues related to viral vectors, complexity of structural changes occurring in advanced disease stages, and incomplete knowledge regarding long-term effects of the applied interventions. Additionally, implementation of optogenetics and other advanced technologies requires further engineering refinements and development of compatible supportive devices to enable their effective use in patients' daily lives.

Disclosure

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REFERENCES

1. Sahel JA, Marazova K, Audo I. Clinical characteristics and current therapies for inherited retinal degenerations. Cold Spring Harb Perspect Med. 2014 Oct;5(2):a017111. https://doi.org/10.1101/cshperspect.a017111
2. Francis PJ. Genetics of retinal disease. eLS. 2010. https://doi.org/10.1002/9780470015902.A0023109
3. Karali M, Testa F, Di Iorio G, et al. Genetic epidemiology of inherited retinal diseases in a large patient cohort followed at a single center in Italy. Sci Rep. 2022;12(1):20815. https://doi.org/10.1038/s41598-022-24636-1
4. Georgiou M, Robson A, Fujinami K, et al. Phenotyping and genotyping inherited retinal diseases: Molecular genetics, clinical and imaging features, and therapeutics of macular dystrophies, cone and cone-rod dystrophies, rod-cone dystrophies, Leber congenital amaurosis, and cone dysfunction syndromes. Prog Retin Eye Res. 2024;100:101244. https://doi.org/10.1016/j.preteyeres.2024.101244
5. Ong SS, Patel TP, Singh MS. Optical coherence tomography angiography imaging in inherited retinal diseases. J Clin Med. 2019 Dec;8(12):2078. https://doi.org/10.3390/jcm8122078
6. Birtel J, Gliem M, Harmening WM, Holz FG. Ophthalmic phenotyping: Imaging. In: Retinal Gene Therapy. 2022:53–62. https://doi.org/10.1016/B978-0-12-813944-8.00038-X
7. Jain R, Daigavane S. Advances and challenges in gene therapy for inherited retinal dystrophies: A comprehensive review. Cureus. 2024 Sep;16(9):e69895. https://doi.org/10.7759/cureus.69895
8. Toualbi L, Toms M, Moosajee M. The landscape of non-viral gene augmentation strategies for inherited retinal diseases. Int J Mol Sci. 2021;22(5):2318. https://doi.org/10.3390/ijms22052318
9. Gopinath C, Sarkar S, Ghosh A. Gene therapy for retinal diseases. In: Gene Therapy - Principles and Challenges. 2021:435–454. https://doi.org/10.1007/978-981-15-9184-6_30
10. John M, Quinn J, Hu M, Cehajic-Kapetanovic J, Xue K. Gene-agnostic therapeutic approaches for inherited retinal degenerations. Front Mol Neurosci. 2023;15:1068185. https://doi.org/10.3389/fnmol.2022.1068185
11. Kang C, Scott LJ. Voretigene neparvovec: A review in RPE65 mutation-associated inherited retinal dystrophy. Mol Diagn Ther. 2020;24(4):487–495. https://doi.org/10.1007/s40291-020-00475-6
12. Cehajic-Kapetanovic J, Xue K, Martinez-Fernandez de la Camara C, 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(3):354–359. https://doi.org/10.1038/s41591-020-0763-1

13. Sladen P, Naeem A, Adefila-Ideozu T, et al. AAV-RPGR gene therapy rescues opsin mislocalisation in a human retinal organoid model of RPGR-associated X-linked retinitis pigmentosa. Int J Mol Sci. 2024;25(3):1839. https://doi.org/10.3390/ijms25031839
14. Toms M, Dubis AM, de Vrieze E, et al. Clinical and preclinical therapeutic outcome metrics for USH2A-related disease. Hum Mol Genet. 2020;29(11):1882–1899. https://doi.org/10.1093/hmg/ddaa004
15. Liu S. CRISPR/Cas9 mechanism and applications progression. Trans Mater Biotechnol Life Sci. 2024;3:312–317. https://doi.org/10.62051/b7416e56
16. Reyon D, Ta T, Tabbaa DG, et al. Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10. Nat Med. 2019;25(2):229–233. https://doi.org/10.1038/s41591-018-0327-9
17. Yee T, Wert KJ. Base and prime editing in the retina—From preclinical research toward human clinical trials. Int J Mol Sci. 2022;23(20):12375. https://doi.org/10.3390/ijms232012375
18. Garanto A, Collin RWJ. Design and in vitro use of antisense oligonucleotides to correct pre-mRNA splicing defects in inherited retinal dystrophies. Methods Mol Biol. 2018;1715:61–78. https://doi.org/10.1007/978-1-4939-7522-8_5
19. Russell SR, Drack AV, Cideciyan AV, et al. Intravitreal sepofarsen for Leber congenital amaurosis type 10 (LCA10). SSRN. 2020. https://doi.org/10.2139/ssrn.3745122
20. Audo I, Birch DG, Meunier I, et al. QR-421a RNA therapy in retinitis pigmentosa due to mutations in USH2A: Stellar trial Phase 1b/2 interim results. Acta Ophthalmol. 2022;100:267. https://doi.org/10.1111/j.1755-3768.2022.205
21. Casarosa S, Covello G, Haas D. Exon skipping through chimeric antisense U1 snRNAs to correct retinitis pigmentosa GTPase-regulator (RPGR) splice defect. Nucleic Acid Ther. 2022;32(4):333–349. https://doi.org/10.1089/nat.2021.0053
22. Sieving PA, Caruso RC, Tao W, et al. Ciliary neurotrophic factor (CNTF) for human retinal degeneration: Phase I trial of CNTF delivered by encapsulated cell intraocular implants. Proc Natl Acad Sci U S A. 2006;103(10):3896–3901. https://doi.org/10.1073/pnas.0600236103
23. Nakagami Y. Nrf2 is an attractive therapeutic target for retinal diseases. Oxid Med Cell Longev. 2016;2016:7469326. https://doi.org/10.1155/2016/7469326
24. Dotiwala F, Upadhyay AK. Gene therapy for retinal degenerative diseases: Progress, challenges, and future directions. Invest Ophthalmol Vis Sci. 2023;64(7):39. https://doi.org/10.1167/iovs.64.7.39
25. Hansen S, McClements ME, Corydon TJ, MacLaren RE. Future perspectives of prime editing for the treatment of inherited retinal diseases. Cells. 2023;12(3):440. https://doi.org/10.3390/cells12030440
26. Fenner BJ, Tan TE, Barathi A, et al. Gene-based therapeutics for inherited retinal diseases. Front Genet. 2022;12:794805. https://doi.org/10.3389/fgene.2021.794805
27. Chira S, Jackson CS, Oprea I, et al. Progresses towards safe and efficient gene therapy vectors. Oncotarget. 2015;6:30675–30703. https://doi.org/10.18632/oncotarget.5169
28. John MC, Quinn J, Hu ML, Cehajic-Kapetanovic J, Xue K. Gene-agnostic therapeutic approaches for inherited retinal degenerations. Front Mol Neurosci. 2022;15:1068185. https://doi.org/10.3389/fnmol.2022.1068185
29. Kichula EA, Proud CM, Farrar MA, et al. Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. Muscle Nerve. 2021;64:413–427. https://doi.org/10.1002/mus.27363
30. Kulbay M, Tuli N, Akdag A, Kahn Ali S, Qian CX. Optogenetics and targeted gene therapy for retinal diseases: Unravelling the fundamentals, applications, and future perspectives. J Clin Med. 2024;13(14):4224. https://doi.org/10.3390/jcm13144224
31. Terakita A. The opsins. Genome Biol. 2005;6:213. https://doi.org/10.1186/gb-2005-6-3-213
32. Yan B, Viswanathan S, Brodie SE, et al. A clinically viable approach to restoring visual function using optogenetic gene therapy. Mol Ther Methods Clin Dev. 2023;29:406–417. https://doi.org/10.1016/j.omtm.2023.05.005
33. Rodgers J, Hughes S, Ebrahimi AS, et al. Enhanced restoration of visual function by bipolar cell-targeted optogenetic therapy compared to retinal ganglion cell targeting. Mol Ther. 2025;33(1):123-135. https://doi.org/10.1016/j.ymthe.2025.01.030
34. GenSight Biologics. Dose-escalation study to evaluate the safety and tolerability of GS030 in subjects with retinitis pigmentosa. ClinicalTrials.gov. 2017. http://clinicaltrials.gov/ct2/show/NCT03326336. (Access: 09.07.2025)
35. Dibas A, Batabyal S, Kim S, et al. Efficacy of intravitreal multi-characteristic opsin (MCO-010) optogenetic gene therapy in a mouse model of Leber congenital amaurosis. J Ocul Pharmacol Ther. 2024;40(10):702–708. https://doi.org/10.1089/jop.2024.0084
36. Borchert GA, Shamsnajafabadi H, Ng BWJ, et al. Age-related macular degeneration: Suitability of optogenetic therapy for geographic atrophy. Front Neurosci. 2024;18:1415575. https://doi.org/10.3389/fnins.2024.1415575
37. Stefanov A, Flannery JG. A systematic review of optogenetic vision restoration: History, challenges, and new inventions from bench to bedside. Cold Spring Harb Perspect Med. 2022;13(6):a041304. https://doi.org/10.1101/cshperspect.a041304
38. Vandekerckhove B, Missinne J, Vonck K, et al. Technological challenges in the development of optogenetic closed-loop therapy approaches in epilepsy and related network disorders of the brain. Micromachines. 2020;12(1):38. https://doi.org/10.3390/mi12010038
39. Shen Y, Campbell RE, Côté D, Paquet ME. Challenges for therapeutic applications of opsin-based optogenetic tools in humans. Front Neural Circuits. 2020;14:41. https://doi.org/10.3389/fncir.2020.00041