Journal of Chemical Health Risks

www.jchr.org

JCHR (2023) 13(3s), 68-72 | ISSN:2251-6727

Exploring Gene Therapy for Inherited Retinal Diseases: Preclinical Findings

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KEYWORDS
gene therapy, inherited retinal diseases, preclinical findings, animal models, delivery systems.

ABSTRACT:
Inherited retinal diseases (IRDs) are a heterogeneous group of genetic disorders characterized by progressive vision loss, posing a significant challenge for traditional treatments. Gene therapy offers a promising avenue for addressing the underlying genetic defects and potentially restoring vision. This paper provides a structured review of preclinical findings in the field of gene therapy for IRDs, focusing on five key aspects: (1) Introduction, (2) Mechanisms of Gene Therapy, (3) Animal Models and In Vivo Studies, (4) Delivery Systems, and (5) Safety and Ethical Considerations. In The "Mechanisms of Gene Therapy" section explores the various approaches, such as gene replacement, editing, and augmentation, that hold potential for treating IRDs. The "Animal Models and In Vivo Studies" section highlights the significance of preclinical research using animal models, emphasizing the relevance of mouse and non-human primate studies. In the "Delivery Systems" section, both viral and non-viral vectors are examined, and their importance in precision targeting is underscored. Finally, in the "Safety and Ethical Considerations" section, safety concerns and ethical dilemmas related to gene therapy are discussed, including the need for rigorous preclinical safety assessments and ethical frameworks.
Gene therapy for IRDs shows considerable promise, but the journey from preclinical research to clinical application necessitates rigorous investigation, ethical deliberation, and equitable access. This structured review sheds light on the multifaceted landscape of gene therapy for IRDs, emphasizing the critical role of preclinical findings in paving the way for potential treatments.

INTRODUCTION

Genetic conditions known as inherited retinal diseases (IRDs) impact the retina and result in progressive visual loss. They place a heavy strain on those who are impacted and their families. The degenerative processes associated with these disorders have only partially been stopped or reversed by conventional therapy. Gene therapy has gained traction as a viable treatment for IRDs in recent years. An overview of IRDs, their genetic origin, and the need for alternate treatments are given in this section. Mutations in several genes that are crucial for the retina's proper structure and function are the usual cause of inherited retinal disorders. Numerous clinical symptoms, including retinitis pigmentosa, Leber congenital amaurosis, and Stargardt syndrome, can result from these mutations. Creating efficient treatments has proven to be a substantial difficulty due to the complexity and genetic variety of IRDs [1-5].

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By directly focusing on the genetic abnormalities that cause the disorders, gene therapy shows potential for treating IRDs. Gene therapy tries to improve or restore retinal function by introducing functional copies of the mutant genes or by altering the existing genes. This contrasts with conventional therapies, which mainly target symptom management and delaying the onset of disease.

GENE THERAPY MECHANISMS

In order to restore or improve retinal function, genes may be added, altered, or modulated as part of gene therapy for IRDs. The mechanics behind gene therapy are examined in this section, including techniques for gene replacement, gene editing, and gene augmentation. We examine these methods' molecular and cellular components and talk about how they can be used to treat various IRDs. A promising treatment option for those with recessive IRDs brought on by mutations in a single gene is gene replacement therapy. This method involves inserting a functioning copy of the mutant gene into the afflicted retinal cells. The creation of Luxturna, a gene therapy for RPE65-associated retinal degeneration, is a noteworthy achievement in this field [4-6].

CRISPR-Cas9 and other gene editing technologies allow for precise change of the genome. These techniques can fix particular genetic mutations that cause IRDs. Gene editing has enormous potential, but it also sparks worries about unintended consequences and long-term security. In order to increase the synthesis of useful proteins, gene augmentation treatment involves adding extra copies of a healthy gene. This approach is especially pertinent for IRDs that are dominantly inherited and in which the generation of toxic or dysfunctional proteins is caused by mutations[1-6].

The precise genetic mutation, the disease's mode of inheritance, and the stage of disease progression all influence the choice of the gene therapy strategy. Each strategy has its own set of difficulties, such as making sure that the therapeutic genes are delivered precisely to the retinal cells.

IN VIVO RESEARCH AND ANIMAL MODELS

Preclinical studies are crucial for determining the safety and effectiveness of gene therapy for IRDs. Mice and non-human primates have been used as animal models to replicate human disease states and assess the efficacy of treatment approaches. In this section, we examine significant in vivo and animal research that has shed light on the viability and potential drawbacks of gene therapy. The long-term consequences of gene therapy, the possibility of immunological reactions, and the improvement of delivery techniques have all been investigated using animal models. For instance, researchers have been able to assess the effects of gene therapy on retinal structure and function using animal models with mutations that mimic human IRDs. To move gene therapy from the lab to the clinic, in vivo research in non-human primates is crucial. Because non-human primates are more genetically and physiologically similar to humans, it is possible to predict treatment outcomes and potential safety issues in clinical trials more precisely. These research have been crucial in advancing medicinal strategies [5-10].

Furthermore, research on animals has improved our knowledge of the best timing, dosage, and delivery strategies for gene therapy. To optimize the therapeutic effect, they have demonstrated the significance of precision targeting to particular retinal layers and cells.

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DELIVERY SYSTEMS

The efficacy of gene therapy depends on the efficient and precise delivery of therapeutic genes to the retina. The suitability of many viral and non-viral vectors for the transport of genes has been investigated. The benefits and drawbacks of various distribution methods are covered in this section along with how they relate to the treatment of IRD. We also highlight current vector development breakthroughs and their effects on clinical translation. It has been extensively researched whether viral vectors, such as adeno-associated viruses (AAV) and lentiviruses, can effectively deliver therapeutic genes to retinal cells. AAVs are especially valued for their long-lasting gene expression and low immunogenicity. Recent developments in AAV vector engineering have enhanced the precision of treatment by enabling better targeting of particular retinal cell types [8-11].

Alternative delivery methods that may lessen some of the drawbacks of viral vectors include non-viral vectors like nanoparticles and liposomes. These non-viral methods are typically safer and have a greater genetic payload, which opens the door to therapeutic options for various genetic abnormalities. As different IRDs affect distinct retinal cell populations, ensuring that the delivery system can penetrate the multiple layers of the retina and target particular cell types is an essential component of its development. To improve the accuracy and efficacy of gene therapy and minimize potential side effects, researchers are reworking delivery techniques [11-15].

CONSIDERATIONS FOR SAFETY AND ETHICS

There are difficulties with gene therapy, such as safety worries and moral issues. It is crucial to guarantee the long-term safety of gene therapy procedures. Concerns about availability to these medicines and ethical issues around genome editing must also be addressed. This section examines these issues while highlighting the significance of thorough preclinical safety evaluations and ethical guidelines. The first priority in gene therapy is safety. Immune reactions to viral vectors, unintended side effects from gene editing, and unforeseen long-term repercussions are some of the potential hazards. Before beginning human trials, preclinical research in animal models and in vivo investigations are crucial in identifying and resolving these safety concerns[4,5,9,11,16].

Equally significant are ethical considerations. There are worries about unexpected genetic modifications and the possibility of designer babies as a result of the usage of gene editing technologies like CRISPR-Cas9. It is crucial to guarantee ethical gene therapy use and equal access for all people with IRDs. To address these issues, the creation of ethical standards, legal frameworks, and open informed consent procedures is crucial. To avoid health inequities, it is also crucial to make sure gene therapy is affordable and accessible. In order to traverse these ethical challenges and guarantee that gene therapy benefits individuals who need it, collaborations between researchers, doctors, regulatory authorities, and patient advocacy organizations are required [15-17].

In conclusion, gene therapy has enormous promise as a potential treatment option for inherited retinal disorders. Preclinical research offers insightful information on gene therapy mechanisms, delivery methods, and safety considerations. However, the transfer from preclinical research to clinical application necessitates in-depth investigation, ethical consideration, and a dedication to making sure that patients with IRDs can benefit from gene therapy.

REFERENCES

1. Amato A, Arrigo A, Aragona E, Manitto MP, Saladino A, Bandello F, Battaglia Parodi M. Gene therapy in inherited retinal diseases: an update on current state of the art. Frontiers in Medicine. 2021 Oct 15;8:750586.
2. Fuller-Carter PI, Basiri H, Harvey AR, Carvalho LS. Focused update on AAV-based gene therapy clinical trials for inherited retinal degeneration. BioDrugs. 2020 Dec;34:763-81.
3. Patil PR, Shivsharan KJ, Salve VK, Shaikh SS. IMPROVEMENTS IN OPTHALMIC DRUG DELIVERY SYSTEM: A REVIEW.
4. Nuzbrokh Y, Ragi SD, Tsang SH. Gene therapy for inherited retinal diseases.Ann Transl Med. 2021 Aug;9(15):1278. doi: 10.21037/atm-20-4726. PMID: 34532415;PMCID: PMC8421966.
5. Battu R, Ratra D, Gopal L. Newer therapeutic options for inherited retinaldiseases: Gene and cell replacement therapy. Indian J Ophthalmol. 2022Jul;70(7):2316-2325. doi: 10.4103/ijo.IJO_82_22. PMID: 35791112; PMCID:PMC9426045.
6. Hu ML, Edwards TL, O'Hare F, Hickey DG, Wang JH, Liu Z, Ayton LN. Genetherapy for inherited retinal diseases: progress and possibilities. Clin ExpOptom. 2021 May;104(4):444-454. doi: 10.1080/08164622.2021.1880863. Epub 2021Mar 2. PMID: 33689657.
7. Moore NA, Morral N, Ciulla TA, Bracha P. Gene therapy for inherited retinaland optic nerve degenerations. Expert Opin Biol Ther. 2018 Jan;18(1):37-49. doi:10.1080/14712598.2018.1389886. Epub 2017 Oct 23. PMID: 29057663.
8. Hussain RM, Tran KD, Maguire AM, Berrocal AM. Subretinal Injection ofVoretigene Neparvovec-rzyl in a Patient With RPE65-Associated Leber's CongenitalAmaurosis. Ophthalmic Surg Lasers Imaging Retina. 2019 Oct 1;50(10):661-663.doi: 10.3928/23258160-20191009-01. PMID: 31671202.
9. Ciulla TA, Hussain RM, Berrocal AM, Nagiel A. Voretigene neparvovec-rzyl fortreatment of RPE65-mediated inherited retinal diseases: a model forocular gene therapy development. Expert Opin Biol Ther. 2020 Jun;20(6):565-578.doi: 10.1080/14712598.2020.1740676. Epub 2020 Mar 25. PMID: 32149547.
10. Padhy SK, Takkar B, Narayanan R, Venkatesh P, Jalali S. Voretigene Neparvovecand Gene Therapy for Leber's Congenital Amaurosis: Review of Evidence to Date.Appl Clin Genet. 2020 Nov 25;13:179-208. doi: 10.2147/TACG.S230720. PMID:33268999; PMCID: PMC7701157.
11. Michalakis S, Gerhardt M, Rudolph G, Priglinger S, Priglinger C. Gene Therapyfor Inherited Retinal Disorders: Update on Clinical Trials. Klin MonblAugenheilkd. 2021 Mar;238(3):272-281. English. doi: 10.1055/a-1384-0818. Epub2021 Mar 30. PMID: 33784790.
12. Chiu W, Lin TY, Chang YC, Isahwan-Ahmad Mulyadi Lai H, Lin SC, Ma C,Yarmishyn AA, Lin SC, Chang KJ, Chou YB, Hsu CC, Lin TC, Chen SJ, Chien Y, YangYP, Hwang DK. An Update on Gene Therapy for Inherited Retinal Dystrophy:Experience in Leber Congenital Amaurosis Clinical Trials. Int J Mol Sci. 2021Apr 26;22(9):4534. doi: 10.3390/ijms22094534. PMID: 33926102; PMCID: PMC8123696.
13. Sallum JMF, Kaur VP, Shaikh J, Banhazi J, Spera C, Aouadj C, Viriato D,Fischer MD. Epidemiology of

Mutations in the 65-kDa Retinal Pigment Epithelium(RPE65) Gene-Mediated Inherited Retinal Dystrophies: A Systematic LiteratureReview. Adv Ther. 2022 Mar;39(3):1179-1198. doi: 10.1007/s12325-021-02036-7.Epub 2022 Jan 30. PMID: 35098484; PMCID: PMC8918161.

14. Gregori NZ, Davis JL. Surgical Observations From the First 120 Cases ofSubretinal Gene Therapy for Inherited Retinal Diseases. Retina. 2023 Sep1;43(9):1608-1611. doi: 10.1097/IAE.0000000000003085. PMID: 33394965
15. Miraldi Utz V, Coussa RG, Antaki F, Traboulsi EI. Gene therapy forRPE65-related retinal disease. Ophthalmic Genet. 2018 Dec;39(6):671-677. doi:10.1080/13816810.2018.1533027. Epub 2018 Oct 18. PMID: 30335549.
16. Aoun M, Passerini I, Chiurazzi P, Karali M, De Rienzo I, Sartor G, Murro V,Filimonova N, Seri M, Banfi S. Inherited Retinal Diseases Due to RPE65Variants: From Genetic Diagnostic Management to Therapy. Int J Mol Sci. 2021 Jul5;22(13):7207. doi: 10.3390/ijms22137207. PMID: 34281261; PMCID: PMC8268668.
17. Chien JY, Huang SP. Gene therapy in hereditary retinal dystrophy. Tzu ChiMed J. 2022 Aug 23;34(4):367-372. doi: 10.4103/tcmj.tcmj_78_22. PMID: 36578644;PMCID: PMC9791861.