THE EVOLUTION OF GENE THERAPY TECHNOLOGIES

Researchers are hard at work looking for the best way to succeed with novel therapies.

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With the tremendous evolution of gene therapies in the field of retina, the hope and excitement for further development of treatments for patients who have no options are ever-present and palpable. The discussion of retinal gene therapies is extremely important as we continue to work on innovative approaches and develop further treatments for previously untreatable diseases.

Adeno-associated viral (AAV) vector therapy consists of proteins that encapsulate and protect a small, single-stranded DNA genome.[1] These vectors work by inserting themselves into a targeted cell to deliver genetic material, thereby causing translation of the new genetic material into working proteins.[2] AAV vectors have become progressively advanced in recent years and are increasingly popular due to their safety profile, lack of pathogenesis, and straightforward production process.[3]

As a result of the success surrounding the AAV vector therapy voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics), the research around AAV-based gene therapies for inherited retinal diseases (IRDs) and other retinal conditions has skyrocketed.

Clustered, regularly interspaced, short palindromic repeats (CRISPR) use targeted gene editing that allows for targeted revisal, removal, and replacement of DNA to another location in the genome sequence. There are two components of CRISPR: the nuclease, which is a protein that edits DNA, and the guide RNA, which leads the nuclease to the correct space in the genome to edit.[4]

Non-viral gene delivery is under investigation because of the concerns associated with gene therapies that use viral vectors, as these vectors may cause an immune reaction to the virus itself, leading to cytotoxic, inflammatory reactions in the body. Along with this, insertional mutagenesis is a concern for AAV-based gene therapies, which could potentially result in malignant modifications of cells within the body. Non-viral gene therapies have a higher biosafety profile compared with viral vectors, with decreased pathogenicity, lower production costs, and easier development.[5]

Optogenetics, an innovative and mutation-independent approach, uses a combination of AAV vectors and, in some scenarios, engineered goggles to detect changes in the intensity of light and project these light stimuli onto the retina, thereby activating retinal ganglion cells that are optogenetically transduced.[6]

RESEARCH CONCERNS

There is a substantial need to consider the risks versus benefits of gene therapies, especially in wet AMD patients, for whom effective and safe treatments are already the standard of care. Viral delivery of gene therapies poses the risk of causing an unwanted immune response.[7] AAV vectors may

AT A GLANCE

- The research around viral vector-based gene therapies for inherited retinal diseases and other retinal conditions has skyrocketed.
- Investigators must consider the risks versus benefits of gene therapies, especially in wet AMD patients, for whom effective and safe treatments are already the standard of care.
- Research organizations must be vigilant when developing and conducting clinical trials for gene therapies to ensure they find the appropriate patients, optimize endpoints, and prioritize safety.

also cause insertional mutations, which could potentially result in malignant transformation of cells.[5]

Intravitreal administration of a gene therapy may create a higher likelihood of an inflammatory response versus subretinal administration, as larger quantities of the viral vector may remain in higher doses and for a longer period post-administration.[8] The potential for an inflammatory response should be considered when determining the route of administration for future gene therapies to prioritize patient safety and outcome of the procedure.

Unfortunately, many gene therapy clinical trials have failed due to either lack of significant visual outcomes or safety concerns. Notwithstanding, the lack of excitement caused by some unsatisfactory results should not dissuade scientists and industry from considering the tremendous vision benefits that these innovative new therapies may have for patients in improving functional vision.

ONWARD AND UPWARD

With vast strides made in gene therapy development, there is remarkable excitement for the future of these innovative solutions for genetic disorders of the retina and beyond. Bearing this in mind, research organizations must be vigilant when developing and conducting clinical trials for gene therapies to ensure they find the appropriate patients for these studies, optimize endpoints, and prioritize the safety and wellbeing of participants. ■

1. Naso MF, Tomkowicz B, Perry WL, Strohl WR. Adeno-associated virus (AAV) as a vector for gene therapy. *BioDrugs*. 2017;31(4):317-334.
2. Gao J, Hussain RM, Weng CY. Voretigene neparvovec in retinal diseases: a review of the current clinical evidence. *Clin Ophthalmol*. 2020;14:3855-3869.
3. Colón-Thillet R, Jerome KR, Stone D. Optimization of AAV vectors to target persistent viral reservoirs. *Virology Journal*. 2021;18(1).
4. CRISPR gene editing. Editas Medicine. February 22, 2022. Accessed April 29, 2022. www.editasmedicine.com/crispr-gene-editing
5. Ramamoorth M, Narvekar A. Non viral vectors in gene therapy–an overview. *J Clin Diagnostic Res*. 2015;9(1):GE01–GE06.
6. Sahel J-A, Boulanger-Scemama E, Pagot C, et al. Partial recovery of visual function in a blind patient after optogenetic therapy. *Nature Medicine*. 2021;27(7):1223-1229.
7. Amato A, Arrigo A, Aragona E, et al. Gene therapy in inherited retinal diseases: An update on current state of the art. *Frontiers in Medicine*. 2021;8.
8. Ochakovski GA, Bartz-Schmidt KU, Fischer MD. Retinal gene therapy: surgical vector delivery in the translation to clinical trials. *Frontiers in Neuroscience*. 2017;11.

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