WHY GENE THERAPY IS PERFECT FOR TREATING OCULAR DISEASES

In this article, Yongdong Zhou, MD, PhD, Head of Ophthalmology Team, Senior Director, at WuXi AppTec, discusses the applications, advantages and challenges of gene therapy in the ophthalmic sector.

Gene therapy is not a new treatment, having been used to alter abnormal or mutated genes and produce valuable proteins since the 1970s. However, apart from a brief resurgence in the 1990s, gene therapy has largely lain dormant for decades. Today, it is once again a subject of investigation, as there has been a renaissance in gene therapy in the 21st century, in large part an international team of researchers having sequenced and mapped every gene as part of the Human Genome Project.

The Human Genome Project has essentially created a genetic blueprint for human beings. For the first time, researchers can identify diseases based on a specific gene's presence or absence within a patient's genetic make-up. As such knowledge grew, so too did researchers' understanding of the mechanisms of genetic diseases and the technology needed to combat conditions once thought to be untreatable.

Gene therapy began to gain steam in 2008 and, by the first half of 2021, the number of active cell and gene therapy developers worldwide had reached 1,195. The number of clinical trials sponsored by private companies, governments and academic institutions passed 2,600 over the same period. Of those trials, 243 have reached Phase III.[1]

The treatment of ocular diseases has benefited tremendously from the resurgence of gene therapy. Two ocular characteristics make gene therapy advantageous and, in some cases, the only option for some genetic diseases, cancers and viral infections. That said, drug developers and laboratory partners must understand the challenges that have already been encountered – and those that lay ahead – for novel genetic therapies.

WHAT MAKES THE EYE A GOOD CANDIDATE FOR GENE THERAPY?

Two characteristics of the human eye make it well suited for successful gene therapy. Whether a condition calls for gene replacement, editing, suppression or growth, researchers must engineer vectors to deliver the suitable genetic material to the right place in the ocular microenvironment. Vectors can be DNA molecules, bacteria or viruses and are engineered to integrate into chromosomes (i.e. retroviruses) or cell nuclei (i.e. plasmid DNA). Ocular disease patients can receive vectors through topical eye drops, oral medication or injections. Regardless of which method researchers use, the end goal is to deliver a new gene that can help create a functioning protein and improve vision.

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Immunologic Privilege

Alongside the central nervous system, the placenta and foetus, and the testicles, the human eye enjoys immunologic privilege. Tissue grafts or foreign antigens placed into sites with immunologic privilege can survive and thrive without the immune system attacking them or shutting down the host organ. This immunity occurs because those sites are insulated from direct contact with systemic circulation and thus are protected from strong immune reactions to foreign antigens like disease or viral vectors. Researchers believe immunologic privilege is an evolutionary protective measure developed to protect specific sites from inflammation and potential organ failure. In the case of the eye, inflammation could cause vision impairment, and rejection of the vector could lead to complete vision loss.

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Researchers first viewed ocular immunologic privilege as an experimental phenomenon explained by the eye's unique anatomical features. Experts do not fully understand the complexities of immunologic privilege but they do know that the ocular microenvironment regulates antigens within the eye via anti-inflammatory proteins and neuropeptides.[2] The anterior chamber, subretinal space and vitreous cavity all enjoy immunologic privilege and are thus good candidates for ocular gene therapy. It is also important to note that immunologic privilege helps to avoid severe inflammatory reactions to foreign antigens but it does not prevent such reactions altogether. Researchers and drug developers should be prepared for some level of immunologic response when conducting gene therapy but the duration and severity should be less than is experienced in other sites.

A Multitude of Options

The Human Genome Project sequenced and mapped around 30,000 genes in the human DNA. 55 of those genes have been isolated in the human eye, and 118 retinal disease loci have been mapped.[3] Many of the mutations in the isolated genes are responsible for damaging the structure and function of the retinal pigment epithelium (RPE) and photoreceptors. RPE cell and photoreceptor damage cause a host of degenerative diseases, including age-related macular degeneration (blurred or lost vision in older patients), retinitis pigmentosa (loss of night vision, side vision and finally central vision) and Stargardt's disease (an inherited disease that causes vision loss in children and young adults). The accessibility of ocular tissue and the number of associated diseases, combined with the various emerging delivery methods, provide researchers with many therapeutic strategies.

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OCULAR GENE THERAPY APPROACHES

The most common ocular gene therapies include gene replacement, suppression or enhancement. The mechanism of the disease (i.e. the defects in molecular or cellular processes) determines the approach that will be most successful in treating the condition.

If a single mutation causes a disease, gene replacement is often the best treatment. Not only is gene replacement the most common form of gene therapy but scientists Jean Bennett and Katherine A High used the procedure with patients possessing a mutation in the RPE65 gene to reverse Leber congenital amaurosis, an inherited form of vision loss that can lead to blindness. The therapy delivers an undamaged copy of the RPE65 gene to retinal cells and then provides instructions for producing the protein needed to restore vision. Bennett and High's research led to the US FDA's first ever gene therapy approval.[4]

But if a disease-causing mutation has a dominant molecular function or triggers an over-expression, researchers can use small interfering RNAs to suppress it. Finally, genes with multiple mutations and other risk factors (i.e. neurodegenerative diseases like glaucoma or age-related macular degeneration) can be enhanced by using adeno-associated virus (AAV) vectors to introduce various protective factors. AAV vectors are attractive candidates because they do not contribute to known diseases and the immune responses they provoke are insignificant.

Whether a target disease is acquired or inherited in nature, the procedures to treat it using gene therapy, whilst varying in complexity, are similar in their fundamentals. Of the more than 350 inherited ocular diseases, those with single mutations – e.g. choroideremia (progressive vision loss in males) and the subtypes achromatopsia (colour blindness), retinitis pigmentosa and Leber's congenital amaurosis – are the best candidates for success. Replacing the deficient gene with a fully functioning copy often results in a cure once thought unachievable.

Acquired ocular diseases have entirely different mechanisms and often require more complex treatments. The molecular and cellular processes that trigger these diseases can vary from genetic to environmental. Gene enhancement or suppression allows researchers to modify or manipulate gene function using a series of viral and non-viral vectors in multiple loci. For acquired ocular diseases, the treatment strategy is similar to that for inherited diseases with multiple mutations and other risk factors, such as age-related macular degeneration. The treatment may not target a specific disease-causing gene but it can indirectly target a gene introducing a protective factor or an antagonist to a problem-causing factor. Gene therapy could be an alternative to the conventional pharmaceutical approaches, especially those requiring long-term medication or supplemental trophic factors.

CHALLENGES & MISCONCEPTIONS WITH OCULAR GENE THERAPY

Gene therapy is a therapeutic reality that has the potential for groundbreaking results; however, it is far from an exact science. This is especially true when treating a site as delicate as the ocular microenvironment. Researchers must consider three factors when deciding the viability of gene therapy for their ocular patients.

Which are the Best Candidates?

There are two primary considerations when answering this question. First, researchers have a greater likelihood of success if they catch the disease early, which might mean treating young children using invasive and potentially risky procedures for inherited ocular diseases. Second, for clinical trial considerations, it is advantageous to treat the patient group with the most severe symptoms, such as patients whose vision is 20/200 or less and who are therefore legally blind. Slight vision improvements are easier to recognise in this patient group and ineffective treatments will not further decrease their vision.

What is the Best Delivery Method?

Choosing a suitable vector and administration route is critical to maximising safety and efficacy in ocular gene therapy. Researchers have largely abandoned adenoviruses and lentiviruses due to their strong immunogenicity and propensity to cause tumours, despite their effectiveness and ability to carry large genes. Very low immunogenicity and pathogenicity make AAVs the most common viral vectors used but they can only carry smaller genes.[5] Researchers can engineer non-viral vectors to carry larger genes safely but they lack the effectiveness and durability of their viral counterparts.

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The administration route is another challenge. Eye drops, intravitreal injections (i.e. an injection of medicine into the vitreous humour near the retina) and other pharmaceutical solutions can treat some conditions successfully. However, for genetic diseases, subretinal injections are the most effective method for delivering AAVs to the target cells and ultimately achieving success. It is a complex procedure that requires surgical intervention, which adds risk – the more invasive the procedure, the greater the immunogenicity and potential for adverse effects, such as retinal detachment and vitreous haemorrhage. Risk mitigation strategies exist for subretinal injections but their effectiveness depends on several factors, including proper patient selection and the clinician's experience with the procedure.

Can Researchers Control Toxicity?

It is worth restating that viral vectors introduce toxic viruses into the ocular microenvironment. The eye's immunologic privilege mitigates some of that toxicity but not all of it. Researchers must continue refining their formulations and dosages to ensure acceptable toxicity levels. Failure to do so can result in severe inflammation, high toxicity and, in some cases, increased vision loss. The patient's condition, age, the severity of vision loss and riskiness of the procedure should all contribute to the decision to move forward with viral or non-viral vector strategies.

THE BOTTOM LINE

A bevy of new drug developers and billions in financial investment have demonstrated massive industry confidence in gene therapy to treat ocular diseases, cancers and viral infections, and innovative approaches have the potential to unlock even more exciting new treatments. For example, administering injections into the suprachoroidal space is a novel targeted approach that promises to deliver drug concentrations 10 times greater than currently available while avoiding specific adverse effects.[6] Its viability as a therapeutic approach will, of course, depend on the disease target and the patient. Likewise, further research into more robust, more effective non-viral vectors has the potential to add new therapies and alleviate concerns about toxicity and other side effects.

While gene therapy may offer game-changing new solutions, it is not without risk. Choosing the right treatment path and delivery method for each patient is essential to controlling immunologic response, reducing toxicity and improving vision. Drug developers and their laboratory partners cannot afford to overlook or underestimate the challenges inherent in each step.

ABOUT THE COMPANY

As a global company with operations across Asia, Europe and North America, WuXi AppTec provides a broad portfolio of R&D and manufacturing services that enable the global pharmaceutical and healthcare industry to advance discoveries and deliver groundbreaking treatments to patients. Through its unique business model, WuXi AppTec's integrated, end-to-end services include chemistry drug contract research, development and manufacturing organisation services; biology discovery; preclinical testing and clinical research services; and cell and gene therapy contract testing, development and manufacturing organisation services, helping customers improve their productivity in advancing healthcare products through cost-effective and efficient solutions. WuXi AppTec received an AA ESG rating from MSCI in 2021 and its open-access platform is enabling more than 5,600 collaborators from over 30 countries to improve the health of patients – and to realise the vision that "every drug can be made and every disease can be treated".

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