WHITE PAPER

AAV vectors: Pursuing a one-time therapy for ocular diseases

The approval of Luxturna® (voretigene neparvovec-rzyl) by the FDA in 2017 marked a pivotal moment for the gene therapy field. The one-time adeno-associated virus (AAV) vector-delivered gene therapy, which is used to treat children and adults with a rare condition leading to blindness, was the first approved gene therapy for an inherited disease. Notably, it was also the first AAV-based product to be approved for use in the United States.

Luxturna's landmark approval stemmed from decades of work initiated by Dr. Jean Bennett and Dr. Albert Maguire at the University of Pennsylvania. During this time, they published multiple research findings showcasing the potential of retinal gene therapy in animal models, including the successful restoration of vision in dogs with an inherited retinal degenerative disease.[1] Not only did this study mark the first cure for retinal degenerative disease in a large animal model, but it also provided proof of concept that AAV vectors could selectively and therapeutically deliver a defective gene to target cells in the eye.

We recently spoke to Professor Dominik Fischer, a Consultant Ophthalmic Surgeon at the Oxford Eye Hospital and Professor of Ophthalmology at the University of Oxford, who discussed the benefits of developing AAV gene therapies to treat ocular disorders and the significance of ensuring long-term gene expression is maintained in transduced cells.

Authors

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Durability of ocular-directed AAV therapies

AAV vectors are currently the go-to vector system for the vast majority of gene therapy research projects and clinical trials. "The genetic simplicity, robustness, and low immunogenicity of AAVs make them the gold standard vector for retinal gene transfer," explained Prof. Fischer. He adds that the virus is also considered relatively safe and can transduce a multitude of tissues and cell types, including photoreceptors.

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The eye is an ideal target for AAV-based gene therapy due to its immune-privileged status and compartmentalized anatomy. The presence of the blood-retinal barrier (BRB) means that the introduction of foreign substances is less likely to cause an immune reaction, while the enclosed nature of the eye means the risk of systemic dissemination of a locally administered vector is reduced. But as more gene therapies enter the clinic, confidence in the long-term durability of effect is of paramount importance. "From a clinical perspective, the main question for patients is: 'How long will the treatment work for?'" explained Prof. Fischer.

In principle, gene therapies should last for a lifetime but the innate features of AAVs have raised concerns relating to their long-term durability. Specifically, because the viral genome remains episomal in the nucleus there is a possibility that transgene expression could wane over time in dividing cells. This is further compounded by the fact that it is currently unknown whether AAV vectors can be safely readministered without triggering a relevant immune response.

Prof. Fischer reasons that transduced cells in the eye will likely demonstrate a sustained treatment effect because the target cells are largely post-mitotic. This hypothesis was supported by a recent review of the literature that found that recombinant AAV (rAAV)-derived genetic material can persist for years as transcriptionally active episomes.[2] And in preclinical canine disease models, treatment effects were found to last almost a decade—which is considered the late stage of life—with earlier intervention resulting in more pronounced effects.[2] "All the evidence supports the idea that gene therapy lasts a lifetime, but at this stage, it still remains a hypothesis," noted Prof. Fischer. He added that persistence is likely dependent on a wealth of factors, including disease stage, vector serotype, surgical procedure, and dosage.

Maximizing treatment effect while managing toxicity

Dosage is known to be one of the major limitations of AAV vector-based gene therapies. Many completed and ongoing AAV-based clinical trials administer large numbers of viral particles to ensure enough target cells are transduced. For instance, the recommended dose of Luxturna is 150 billion vector genomes for each treated eye, which equates to maybe a hundred thousand virus particles per targeted cell. "This is an unacceptable ratio, but that's the level of effectiveness that we're dealing with," said Prof. Fischer. " And it's still better than most other vectors for our purposes."

Various engineering approaches are being explored to enhance the properties of viral vectors and thereby reduce the required dosage. These include optimizing the transgene cassette or reengineering the capsid to improve transduction efficiency or vector tropism. Notably, methods for vector optimization may vary depending on the target cell population. "If you're targeting the ganglion cells, the retinal pigment epithelium, or photoreceptors, they each have unique characteristics and thereby you need to optimize your delivery to make it more targeted to specific cells," explained Prof. Fischer. Another way to improve the treatment effect is to genetically modify the viral capsid so it can escape the host's immune response. Research suggests that inflammatory reactions following ocular gene therapy are generally mild and can usually be controlled with topical, local, or systemic steroids.[3]

Approaches to improve the future of AAV gene therapies

While efforts are ongoing to optimize AAV vectors for improved efficiency, Prof. Fischer believes there should be more focus on understanding the immune response to gene therapies. "This is even more important now that gene therapy is going mainstream," he explained. "If you're treating prevalent diseases where treatments already exist, it's a different ball game than treating orphan diseases leading to blindness but without alternative treatment options. You need to be acutely aware of what you're doing, the risks involved, and how to manage them."

Other important factors to consider are the challenges of transitioning from preclinical to clinical trials. "I advise a lot in clinical trial design and it's very exciting, but it's also very challenging," said Prof. Fischer. "A lot of this is pioneering work which requires you to start from scratch. And that means even basic questions such as how to measure therapeutic effectiveness are asked. It may sound trivial, but it's not. You have to marry the mechanism of action with what you know about the disease's impact on vision, and you also have to understand the regulatory landscape." In addition, developing a business model requires considerable attention, especially when focusing on rare diseases.

The field has ultimately shown that gene therapy can and does work in eye diseases. Yet, there is still room for more innovation and improvement. “We need the next generation vector, and we need to make a big step in improving efficiency and transducing the target cells,” concluded Prof. Fischer. “We need to have a clear path forward to push these innovations at pace while keeping the patient safe.”

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Meet the expert

Professor Dominik Fischer

Professor Fischer is appointed Ophthalmic Surgeon at the Oxford Eye Hospital and full Professor of Ophthalmology at the University of Oxford. He holds second appointments as Professor at the University of Tübingen (Germany) and the University of Lausanne (Switzerland).

After receiving his MD (summa cum laude) for research performed as Visiting Scholar at the University of Pennsylvania, he completed his specialty and subspecialty training with Ulrich Bartz-Schmidt and Eberhart Zrenner in Tübingen and received his second doctorate (DPhil) for developing a new form of retinal gene therapy with Robert MacLaren at Oxford. He is the recipient of more than 25 awards, among them the Leonhard Klein award for the advancement of vitreoretinal surgery and the Senator H. Wacker award for scientific contributions to the field of retinal disease.

Professor Fischer continues to lead clinical trials in Oxford and Tübingen and is Chief Investigator of the first global post approval safety study for ocular gene therapy. As key opinion leader in the field, he serves on the advisory board of patient advocacy groups, academic institutions, biotech, and pharmaceutical industries and has been expert advisor to governmental regulators. He has given more than 100 invited lectures across the world and published extensively on topics including neuroscience, vision, retinal disease, and novel therapeutics.

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