Opinion

Ocular gene therapy a cutting-edge treatment

Volume 12 Issue 3 - 2022

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Received: August 02, 2022 | **Published:** August 23, 2022

Introduction

The current dilemma of gene therapy for various diseases is questionable as there are different practitioners in the field. It does not proportionately narrow our focus to the disease based on diverse opinions regarding the outcome. Therefore, it allows us to do more research and functional assessments. Today, including considering where the problem remains before the feasible clinical trial. The most advanced therapies for retinal degenerative diseases, various retinitis pigmentosa (RP), are well established in many animal models. Alternatively, a huge range of programs was also presented as gene therapy for relatively rare disorders, age-related macular degeneration (ARMD), Leber congenital amaurosis (LCA), and glaucoma. Many groups are engaged in such treatments from a handful of research laboratories, namely small biotechs and pharmaceutical companies. The reason for this is perhaps the significant benefits the eye can get from gene therapy are why attracting researchers' interest in the field of gene therapy. The eye has now moved to center stage.

It is undeniable that ocular tissues can transduce easily. Over the last few years, the human eye has been evaluated with various viral and non-viral vectors and effective techniques. Where the two significant vectors to date are based on adenoviral vectors and lentiviruses, these vectors are prominently used in a clinical trial in current gene therapy and are reviewed as particular problems.[1,2] Although the transducing cells in the anterior chamber and retinal pigmented epithelium are lentivirus vectors, they are much less efficient at transducing retinal photoreceptors. The promising vehicle recently specified for gene delivery to retina and photoreceptor cells are AAV8 vectors. Recognition of such significant variants of AAV has further enlightened the use of the AAV vector platform. These vectors have a unique characteristic that might help target various cell types in the retina. A Novice mutation technique of capsid surface tyrosine has been generated with the help of a new AAV serotype. Recent research shows that a novel use of such double-tyrosine mutant AAV9 can significantly polish retinal gene delivery.[3] However; more research is needed to assess how efficient the tyrosine mutants and various serotypes are in large animal models and non-human primates. It remains to be seen how much more effective the multiple tyrosine mutants and different serotypes are in large animal models, including non-human primates. Another major problem that has yet to be resolved is how we can expand the capacity of AAV vectors to deliver a large number of genes to photoreceptors.

The eye is considered a practical site of gene delivery compared with most other organ systems because it is compartmentalized and small. It allows modest delivery of gene vectors to the target sites. Furthermore, the anatomy and blood-retinal barrier limit the extension of the vector outside the eye. Hence, reduce the severity of immune response to antibodies in the form of transferred gene vectors. Another benefit of retinal gene therapy is the stability of the target cell population. The structure of the cell lack division that allows the use of non-integrating vector systems for maintained transgene expression. Mutagenesis and oncogenesis are formed due injection of vectors into the host cell genome, which the use of non-integrating systems can therefore reduce. This particular problem shows that any insertional events arising from sub retinal delivery of AAV and HIV-1 vectors do not affect the incidence of ocular neoplasia in p53 tumor-suppressor gene knockout mice, which are highly susceptible to intraocular malignant transformation.[4]

Recently, various ocular diseases have been treated with gene therapy, namely corneal dystrophies and retinoblastoma. The most focused advancement is gene therapy for inherited retinal disorders (IRDs). These disorders can cause progressive deterioration of photoreceptor cells and loss of vision due to the alteration of genetic and phenotypical heterogeneous characteristics. The epidemiology of the disease is more prevalent in Europe and the United States. About 150 genes and 50 loci concomitant with retinal dystrophy have recently been known. As go through this particular issue, there has been enormous progress concerning gene therapy for the treatment of recessive IRDs.[5] More than 20 forms of degenerative retinal disease and clinical trials are anticipated in the recent future to review the concept of treatment of the loss-of-function disorder. However, many ambiguities are yet to be addressed before the commencement of conventional gene therapy treatment. However, the early clinical trials for particular therapy demonstrated clinical benefit and safety but needed enhancement of the level of rescue, which is still not effective in animal models. The prognosis of the effective treatment that mainly affects retinal pigmented epithelium and photoreceptors might be achieved with such therapy in the next decade. Nevertheless, the treatment of retinal dystrophies may be challenging to overcome due to the increase in the capacity of AAV or may need effective control of the expression of the transgene.

The higher genetic heterogenicity of dominant IRDs is a barrier to the therapies in treating the abnormal mutant genes. Over 150 mutations in the rhodopsin gene alone and more than 60 genes have been identified. However, there has been a vast development in the last few years concerning gene therapy for dominant disorders.[6] There have been various approaches known as suppression and replacement' strategies that involve small interfering RNA-based techniques to ablate mRNA from specific target genes in combination with delivery of resistant replacement transgenes appear to be very promising. Alternatively, modulation of oxidative stress, provision of neurotrophic and anti-apoptotic factors modulates apoptotic pathways, and modulation of the cellular response to the presence of aggregated proteins requires gene therapy approaches for dominant

retinitis pigmentosa. Such a neuroprotective technique aimed at postponing or halting retinal ganglion cell loss would also be valued to save vision in glaucoma and the review of this special issue to know the mechanism underlying retinal ganglion cell degeneration and enhance the existence of neurons in experimental models of optic nerve injury.[7]

Over the last few years, gene therapy has also revolutionized treatment for neovascularization in common ocular disorders associated with diabetic retinopathy and AMD. Long-term suppression of neovascularization and excessive vascular leakage due to gene transfer of anti-angiogenic proteins has potentially more significant suppression of neovascularization than intravitreal administration of anti-vascular endothelial growth factor (VEGF). A review of the studies in animal models of ocular neovascularization demonstrated more effective results with several transgenes.[8] The successful clinical mainstream gene practice has been dominating recently as two industry-sponsored clinical trials, one using an AAV vector to express a VEGF-binding protein and another using a lentiviral vector to express endostatin and angiostatin, have started recently.

The gene therapy discussed above is ineffective for patients suffering from retinal degeneration as they have lost most of their photoreceptors. Alternatively, the use of optogenetics to target genetically encoded light sensors to the cells in the remaining retinal circuitry, thus converting these cells into artificial photoreceptors.[9] If these artificial photoreceptors are connected to other cell types in the retinal circuit, the light would also modulate the activity of these cells. The current issue lies in choosing the correct sensor and targeting techniques so that the light-evoked retinal activity arising from artificial photoreceptors will be similar to the activity of normal retinas stimulated through normal photoreceptors. Another significant improvement for enhancing usefulness includes developing more-sensitive artificial photoreceptors that look as fast as normal photoreceptors, sensors that work at near-infrared wavelengths, effective dendritic localization signals, and vectors that can transduce bipolar cells effectively.

Hence, the current treatment regime of ocular disorders with gene therapy that is explored is still a tiny fraction. Many challenges are still unknown, for instance, treating inflammatory disorders illustrated as uveitis and graft rejection in corneal disease. A better understanding of ocular immunology urges to have tremendous potential in these conditions. Both aspects, including the development and application of vectors to transduce a gene, are effective enough to understand the mechanism of the disease, and it also enables us to design unique characteristics of vectors to develop limitations of the strategies. The most strategic treatment of novel gene therapy will be for AMD, which is a common reason for blindness globally. The optimistic prediction is that in the next decade, with improving knowledge of disease mechanisms, gene therapy will replace the treatment of such diseases with precise modulation of the alternative complement pathway. However, procrastination is difficult when gene therapy is applicable in clinics, but rapid advancement suggests that it is likely to be the leading ocular therapy for disorders.

Acknowledgements

None.

Conflicts of interest

None.

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