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Recent Innovations in Gene Therapy for Retinal Disease

Adnan Mallick, MD[a,*], Peter Belin, MD[a], Ronni M. Lieberman, MD[b]

[a]Department of Ophthalmology, Hofstra Northwell School of Medicine, 600 Northern Boulevard #220, Great Neck, NY 11021, USA; [b]Department of Ophthalmology, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY 10029, USA

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• Macular degeneration • Retinitis pigmentosa • Stem cell transplantation

Key points

- Degenerative retinal diseases, such as retinitis pigmentosa (RP), Leber congenital amaurosis, and age-related macular degeneration (AMD), are the leading causes of incurable blindness in the developed world.
- Gene therapy in degenerative retinal disease is quickly moving from theory to clinical application.
- Gene therapy may substantially change the manner in which degenerative retinal disease is treated.

INTRODUCTION

Retinal degenerative diseases affect millions of people worldwide. Collectively, diseases such as retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), and age-related macular degeneration (AMD) are the leading causes of incurable blindness in the developed world [1]. More than 15 million people are blind or severely visually impaired because of AMD and RP [1,2]. These diseases target outer retinal cells, such as photoreceptors, retinal pigment epithelium (RPE), and choroidal endothelial cells. The ganglion, bipolar, amacrine, horizontal, and Müller glial cells, located in the inner retina, are typically spared in these diseases, which provides an opportunity to then replace the cells of the outer retina, potentially improving vision.

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*Corresponding author. *E-mail address:* amallick1@northwell.edu

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In recent years, research regarding management of incurable diseases using gene therapy has made significant progress. Although researchers were able to isolate certain genes from DNA as early as the 1970s, the first approved gene therapy trial in the United States took place in 1990 when William French Anderson treated a 4-year-old patient with adenosine deaminase severe combined immunodeficiency (ADA SCID) [3]. A subset of her T cells were removed, treated with a gammaretrovirus expressing the *ADA* gene, then the gene-corrected T cells were reintroduced into her. The patient showed improvement to a degree in which she no longer needed to be kept in isolation and was able to attend school without great risk of developing infection. This early success led to an increase in the number of gene therapy trials taking place in subsequent years.

Despite early success, several significant setbacks occurred in the 1990s, including a US gene therapy trial that led to the death of an 18-year-old with ornithine transcarbamylase deficiency secondary to a severe host immune response to the viral caspid [4,5]. As a result of this, attention was refocused on safety, paving the way for future studies. After Anderson's work, several others have demonstrated groundbreaking research in the utility of gene therapy, with more than 2300 clinical trials registered by 2016 [6]. This has led to the promise of treatments in various diseases, including human immunodeficiency virus, sickle cell, thalassemia, leukemia, and cystic fibrosis, in addition to several retinal diseases.

The eye is an ideal candidate as an organ for gene therapy because of its relative immune privilege. Kaplan and Streilein [7] demonstrated that the response to antigens in the eye is controlled due to anterior chamber–associated immune deviation (ACAID). The eye communicates with the immune system via the spleen to tolerate antigen-presenting cells, eliciting a transient suppression in cell-mediated immunity. Although the posterior segment of the eye does not display ACAID, the blood-retinal barrier still acts as a barrier between the retina and immunomodulators within the systemic circulation. In addition, there is ease of accessibility to intraocular structures to use developing therapies. Response to treatment also can be easily monitored by ophthalmic examination and testing of visual function. Gene therapy holds great potential for the treatment of retinal disease. For years, preclinical studies have shown the efficacy and potential of gene therapy in retinal disease with recent advancement into clinical trials. The aim of this review was to provide an up-to-date summary of gene therapy in retinal disease with a focus on degenerative disease. Emphasis is placed on recent and ongoing human clinical trials.

MECHANISMS OF GENE THERAPY

The goal of gene therapy is to identify a defective gene, then replace the gene or modify its nucleic acid polymers to treat a given disease. Early on, scientists focused on diseases caused by single-gene defects. In ophthalmology, there was much research in LCA, Usher syndrome (USH), choroideremia, and other monogenic diseases. As delivery techniques and methods of DNA editing have