CHAPTER 20

Gene Therapy

This chapter includes a related video. Go to www.aao.org/bcscvideo_section12 or scan the QR code in the text to access this content.

Highlights

- Gene therapy is a quickly evolving field that offers great potential for the treatment of progressive, visually debilitating inherited retinal diseases.
- Although currently approved (and soon to be approved) gene therapies have targeted inherited retinal diseases, studies investigating treatment of age-related macular degeneration are also under way.
- Gene augmentation therapy involves replacement of mutated genes in affected cells or tissues with a normal, functional copy of the gene.

Introduction

The last decade has fostered major advancements in the field of gene therapy, including promising new treatments for cancer, heart disease, and diabetes. The eye is also a potential target for gene therapies, given that the retina is an immune-privileged tissue with low risk of systemic dissemination and only small amounts of vector are needed to achieve a therapeutic response. Inherited retinal diseases (IRDs), a rare and diverse group of disorders causing progressive photoreceptor cell death and vision loss, are considered particularly amenable to gene therapies, as mutations in more than 300 disease-related genes, all critical to retinal function, have been identified. Currently, approximately 200,000 people in the United States and 4.5 million people worldwide are affected by these progressively debilitating visual disorders.

In general, approaches to and applications of gene therapy vary depending on the different nucleic acids used and how they are delivered. For IRDs, investigational therapies involve modifying the genome of retinal cells primarily through the introduction of normal genes or the inactivation of disease genes (Table 20-1). In contrast, gene therapies under investigation for neovascular age-related macular degeneration use vector systems to express antiangiogenic proteins that block the vascular endothelial growth factor pathway (Table 20-2).

Although RNA and compound therapies are available, most gene therapies, such as voretigene neparvovec-rzyl, are DNA based. Common types of DNA therapy include gene augmentation, optogenetics, and genome editing.

Table 20-1 Gene Therapy Trials for Inherited Retinal Diseases[a]

Target Disease	Sponsor	Viral Vector	Gene Delivered	NCT #
Achromatopsia	AGTC	AAV2 — subretinal	*CNGA3*	NCT02935517
	AGTC	AAV2 — subretinal	*CNGB3*	NCT02599922
	MeiraGTx UK II Ltd	AAV2/8 — subretinal	*CNGA3*	NCT03758404
	MeiraGTx UK II Ltd	AAV2/8 — subretinal	*CNGB3*	NCT03001310
Choroideremia	Spark Therapeutics	AAV2 — subretinal	*CHM*	NCT02341807
	Biogen	AAV2 — subretinal	*CHM*	NCT03496012
Retinoschisis	AGTC	AAV2 — intravitreal	*RS1*	NCT02416622
	NIH/NEI	AAV8 — intravitreal	*RS1*	NCT02317887
Stargardt disease	Sanofi	Lentivirus — subretinal	*ABCA4*	NCT01367444
Usher syndrome 1B	Sanofi	Lentivirus — subretinal	*MYO7A*	NCT01505062
X-linked RP	AGTC	AAV2 — subretinal	*RPGR*	NCT03316560
	MeiraGTx UK II Ltd	AAV2/5 — subretinal	*RPGR*	NCT03252847
	Biogen	AAV8 — subretinal	*RPGR*	NCT03116113

AAV = adeno-associated virus; AGTC = Applied Genetic Technologies Corp; NCT = National Clinical Trial; NEI = National Eye Institute; NIH = National Institutes of Health; RP = retinitis pigmentosa.

[a]Data from National Institutes of Health. Clinicaltrials.gov website. Accessed July 2020.

Table 20-2 Gene Therapy Trials for Age-Related Macular Degeneration

Target Disease	Name/Sponsor	Vector	Mechanism of Action
Neovascular AMD	RGX-314 RegenxBio	AAV8 — subretinal/ suprachoroidal	Encodes anti-VEGF Fab protein similar to ranibizumab
Neovascular AMD	ADVM-022 Adverum Biotechnologies	AAV2 — intravitreal	Promotes production of aflibercept protein
Neovascular and nonneovascular AMD	AAVCAGsCD59 Hemera Biosciences	AAV2 — intravitreal	Soluble form of CD59 inhibits MAC formation

AAV = adeno-associated virus; AMD = age-related macular degeneration; MAC = membrane attack complex; VEGF = vascular endothelial growth factor.

Adapted with permission from Sabbagh O, Mehra A, Maldonado RS. Gene therapy in AMD: promises and challenges. *Retina Specialist.* Published March 21, 2020. Accessed February 13, 2022. https://www.retina-specialist.com/article/gene-therapy-in-amd-promises-and-challenges

See also Part III, Genetics, and the online appendix in BCSC Section 2, *Fundamentals and Principles of Ophthalmology,* for additional discussion and a genetics glossary.

Gene Augmentation Therapy

Augmentation is the most straightforward gene therapy. Often referred to as *gene replacement therapy,* gene augmentation involves the introduction of a normal, functional copy of a protein-coding gene into a host cell to replace a mutated gene (Fig 20-1). The normal copy then typically remains in an episomal state while promoters and enhancers facilitate its expression. This type of therapy is useful mainly for recessively inherited retinal

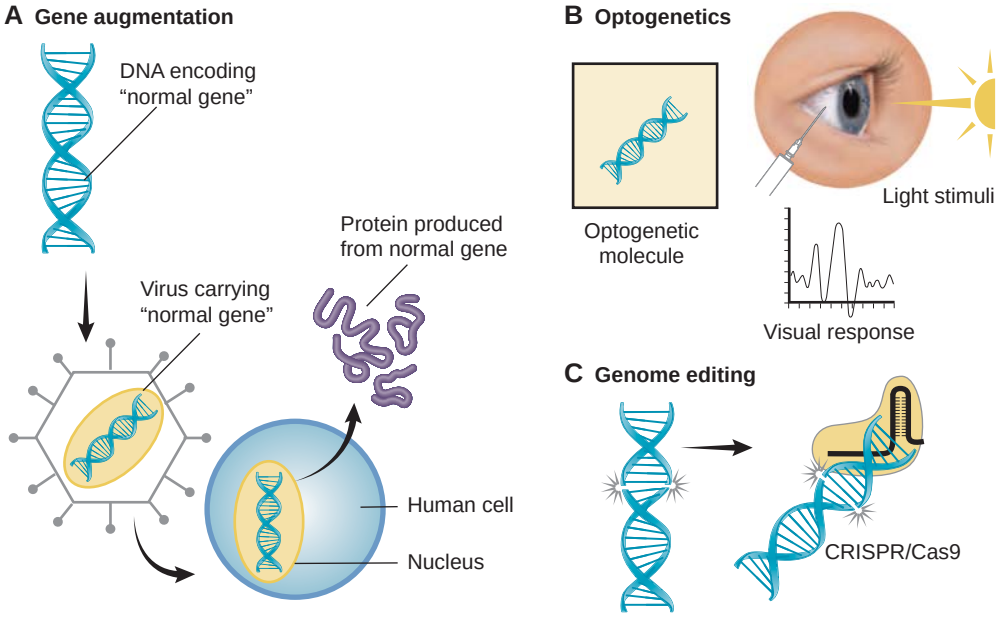

Figure 20-1 Three types of gene therapy: gene augmentation **(A),** optogenetics **(B),** and genome editing **(C).** *(Illustration by Cyndie C. H. Wooley. Part A modified from Kay C. Gene therapy: the new frontier for inherited retinal disease.* Retina Specialist. *Published February 20, 2017. Accessed February 13, 2022. https://www.retina-specialist.com/article/gene-therapy-the-new-frontier-for-inherited-retinal-disease)*

diseases, in which neither of the 2 mutated alleles can produce functional gene products. Delivery of a correct copy of the gene is expected to restore production of normal proteins, overriding the defective or missing proteins and modulating the disease phenotype.

Autosomal dominant IRDs are not amenable to gene replacement therapy because the mutant gene product continues to interact or interfere with normal protein function, even when the protein has come from an exogenous source. In patients with a dominant disease, gene editing is used instead to inactivate the mutant protein or ablate the mutant gene at the DNA level, providing longer-term treatment (see the section Genome Editing).

In gene augmentation therapy, DNA may be delivered into the host cell by several therapeutic vectors; however, adeno-associated viral (AAV) vectors are most often used because of their high tropism for retinal cells and their low immunogenicity. Other vectors under study include lentiviruses and nanoparticles, which have larger cargo capacities to accommodate larger genes.

For vector delivery into the eye, intravitreal, subretinal, or suprachoroidal options are available. Intravitreal injections, administered during an in-office visit, facilitate targeting of the inner retina and have a relatively low complication rate. Subretinal delivery enables vector transduction in retinal pigment epithelium cells and/or photoreceptors but requires a vitrectomy and retinotomy, limiting treatment to only a localized area of the retina. Suprachoroidal delivery, another in-office procedure, potentially allows widespread delivery throughout the eye and is an attractive route for treating neovascular age-related macular degeneration and other conditions affecting the choroid.

In 2017, the US Food and Drug Administration approved the first in vivo gene replacement therapy (ie, voretigene neparvovec-rzyl) for treatment of *RPE65*-related retinopathies

in patients with confirmed pathogenic variants in both alleles. These patients typically have autosomal recessive Leber congenital amaurosis or retinitis pigmentosa and experience progressive vision loss, which may be severe in early childhood. Voretigene neparvovec-rzyl delivers a normal copy of the gene encoding the human RPE65 protein to the retinal cells of individuals with a reduced or absent level of the biologically active protein. In a phase 3 trial, voretigene gene replacement therapy improved not only participants' ability to navigate in dim light but also their full-field light sensitivity threshold and visual field (Video 20-1).

VIDEO 20-1 Voretigene gene replacement surgery.
Courtesy of Audina M. Berrocal, MD.

Optogenetics

Although gene augmentation therapy is an attractive approach in patients with a known genotype or early-stage IRD, it is not suitable for those with more advanced disease (ie, in patients who have lost most of their photoreceptors). For these patients, optogenetics is an alternative treatment involving the genetic introduction of light-sensitive proteins into retinal cells to monitor or control neural activity (see Fig 20-1). This strategy is often used to convert secondary or tertiary neurons into "photoreceptors" or to restore the sensitivity of degenerating photoreceptors.

Genome Editing

Another emerging DNA therapy is gene editing using CRISPR/Cas9–based technology (see Fig 20-1). With this technique, clustered, regularly interspaced, short palindromic repeats (CRISPR) are complexed with a CRISPR-associated (Cas) nuclease to create controlled or targeted breaks in DNA sequences. This technique is especially useful in treating dominant IRDs.

Current Limitations

Although gene therapy holds tremendous promise for treating retinal diseases, many challenges must be overcome before it can be broadly implemented. They include the rare and heterogenetic nature of IRDs; the large size of affected genes, which can exceed the cargo capacity of AAV vectors; the inaccessibility of the target tissue (eg, the retina and/or retinal pigment epithelium); the lack of long-term safety data; and cost. Despite these obstacles, the number of retinal gene therapy trials is expected to increase dramatically over the coming years.

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Additional Materials and Resources

Related Academy Materials

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Online Resources

Visit the **Ophthalmic News and Education (ONE®) Network** at aao.org/retina-vitreous to find relevant videos, podcasts, webinars, online courses, journal articles, practice guidelines, self-assessment quizzes, images, and more. The ONE Network is a free Academy-member benefit.

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Basic Texts and Additional Resources

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