The eye is an ideal target for gene therapy. It is relatively small and highly compartmentalized, and it is an immune-privileged organ with well-defined targetable diseases known to benefit from prolonged therapy. It is also fairly easy to distinguish both potential side effects and treatment benefits.

Gene therapy utilizes a viral vector to carry the desired genetic information—nucleic acids that encode a protein(s) of interest—to target cells; vectors that are successfully transduced into target cells utilize the cell’s machinery to express the protein(s) of interest. The goal of gene therapy is to provide a sustained therapeutic benefit via continual expression of the protein(s) that modulate the pathogenesis of the relevant disease. Although a full review of gene therapy is beyond the scope of this article, this brief review provides an overview of current avenues of gene therapy research, focusing on those that have progressed to clinical settings.

THE GENE THERAPY MOVEMENT
It has been more than a half century since the fundamental principles behind gene therapy were established. In the 1940s, nucleic acids were identified as the carriers of genetic information. The development of virus-based methods for delivering therapeutic genes to patients in the 1960s, coupled with the advent of recombinant DNA technology in the 1970s, kept the prospect of genetic medicine moving forward.

The culmination of decades of scientific efforts resulted in the first approved gene therapy clinical trial in 1990. The study, run by Blaese and colleagues at the National Institutes of Health, involved retroviral-mediated transfer of the gene encoding the enzyme adenosine deaminase into T cells of two children with severe combined immunodeficiency.

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A PRIMER ON VIRAL VECTORS
Viral vectors are a conduit for transferring genes to human cells. There are two main categories: integrating vectors and nonintegrating vectors. Integrating vectors insert themselves into the recipient’s genome; nonintegrating vectors usually form an extrachromosomal genetic element.

Transduction with lentiviral vectors is a commonly used method. Lentiviral vectors are integrating vectors capable of rapidly infecting dividing and nondividing cells. They have a relatively large transgene carrying capacity. AAV vectors, which are nonintegrating vectors, are among the most commonly used delivery systems for ocular gene therapy. AAV is a member of the Dependovirus group of the parvovirus family. Wild-type AAVs are not implicated in disease (only associated with mild immune responses) when unaccompanied by carrying the p53 gene, and it was approved by the State Food and Drug Administration of China for head and neck squamous cell carcinoma. Another significant step came in November 2012, when the European Medicines Agency first approved a gene therapy. Glybera, a designated orphan medication, is intended to treat lipoprotein lipase (LPL) deficiency, a rare inherited disorder. Patients with the disorder cannot produce enough LPL, an enzyme responsible for breaking down fats, and frequently experience life-threatening pancreatitis attacks. Glybera uses an adenovirus vector to add working copies of the LPL gene into muscle cells to enable production of the enzyme in muscle cells.
a “helper” adenovirus to coinfect cells.¹ AAV serotypes are determined by the sequence of their capsid proteins. Several AAV serotypes have been identified, but the most widely characterized and well-studied is AAV serotype 2 (AAV2).

**PROGRAMS ON THE RISE**

Gene therapy is quickly becoming a reality for patients with inherited retinal diseases, as a number of therapies are now in clinical trials.

Avalanche Biotechnologies, which announced a collaborative agreement with Regeneron last year,⁸ is a biotechnology company with several novel gene therapies in the pipeline. It has developed a technology platform called Ocular BioFactory, wherein libraries of non-naturally occurring viruses are created through mutagenesis. These libraries are screened for favorable properties, and, through a process of directed evolution, viral vectors with advantageous properties are produced. Its lead product, AVA-101, utilizes an AAV vector. Avalanche is developing its lead product to be delivered as a single subretinal injection for the treatment of wet age-related macular degeneration (AMD). The AAV2 vector used by AVA-101 contains a gene encoding sFLT-1, which is a naturally occurring antangiogenic protein. When sFLT-1 is expressed by host retinal cells, it inhibits the formation of new blood vessels, thereby reducing pathologic neovascularization.⁹ AVA-101 is currently being studied in a phase 1/2a trial;¹⁰ top-line results are expected in mid-2015.

Spark Therapeutics’ most advanced product candidate for inherited retinal therapies, SPK-RPE65, which utilizes an AAV vector, is currently in phase 3 development. Researchers are investigating the product as a treatment for inherited retinal dystrophies caused by mutations in the RPE65 gene; earlier trials demonstrated the therapy’s safety and efficacy.¹¹ Mutations in RPE65 are linked to ocular disease including subtypes of Leber congenital amaurosis (LCA) and retinitis pigmentosa.¹² Spark has received orphan product designation in both the United States and the European Union for the treatment of patients with LCA due to RPE65 mutations. Last year, SPK-RPE65 also received breakthrough therapy designation from the US Food and Drug Administration (FDA) for the treatment of nystagmatopia (night blindness) in patients with LCA.¹³ A phase 3 trial of the safety and efficacy of gene therapy to address RPE65 mutations in subjects with LCA is ongoing, with data expected to be released in the second half of 2015.¹²

The Applied Genetics Testing Corporation (AGTC) has developed an AAV-vector–manufacturing platform and currently has five ongoing ophthalmic development programs in multiple indications.¹⁴ AGTC is developing gene therapy for X-linked juvenile retinoschisis (XLRS), an inherited, early-onset retinal degenerative disease caused by mutations in the RS1 gene; it has received orphan designations for this indication in both the United States and the European Union.¹⁴ Initial clinical data are expected to be released in the second half of 2015.

Achromatopsia is an inherited condition associated with visual acuity loss, light sensitivity, and reduced (sometimes complete) loss of color discrimination. Although several genes can cause the disease, the most common are CNGB3 and CNGA3. AGTC is working on a program based on these genes: the therapy for CNGB3 has received orphan designation in the United States and the European Union, with initial clinical data anticipated late in 2015, and the therapy for CNGA3 is slated to begin investigational new drug application–enabling studies in the second half of 2015.¹⁴

Genzyme, a division of Sanofi, in-licensed AGTC’s AAV program for wet AMD in 2004.¹⁵ The two companies are now working independently on their own AAV initiatives. Genzyme’s intravitreal injection of AAV2-sFLT01 is currently being studied in a phase 1 trial.¹⁶

Oxford Biomedica is widely known for its LentiVector platform, which is based on the recombinant equine infectious anemia virus (EIAV). EIAV can be used in many therapeutic areas but has specific advantages in neurologic and ocular disorders. The company has five ocular therapies, three of which are in active clinical trials: RetinoStat in a phase 1 study for treatment of wet AMD¹⁷,¹⁸ StarGen in a phase 1/2a trial for treatment of Stargardt disease¹⁹,²⁰ and UshStat in a phase 1/2a study for treatment of Usher syndrome 1B.²¹,²² Oxford Biomedica announced a collaboration with Sanofi last year.²³

NightstaRx recently received orphan drug designation from the FDA and the European Medicines Agency for its lead program, AAV2-REP1, an AAV vector–based gene therapy to treat choroideremia,²⁴ a rare X-linked hereditary retinal dystrophy. Initial findings of the phase 1/2 trial reported that, 6 months after treatment with
the therapy, the first six subjects showed subjective improvement in their vision in dim light.25 The trial is ongoing, with the next six subjects receiving a higher dose of the viral therapy.26

CONCLUSION

Vision loss from retinal disease is increasing. However, with a number of gene therapies moving forward in the clinic, there may soon be novel therapeutic options for these complex diseases. The approval of the first gene therapy in the European Union is a positive indicator for an approval in the United States. These new technologies have the potential to become life-changing options for thousands of patients with inherited ocular diseases.

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