Gene Therapy

An Innovative Approach for Treating Rare Genetic Diseases

Genetic Diseases

Genetic diseases involve defects in genes, which are made up of DNA and produce proteins—large complex molecules required for the structure and function of tissues and organs.[1]

Some genetic diseases are monogenic, meaning they are caused by an often inherited defect in a single gene, making them an ideal candidate for gene therapy.[2-4]

Examples of Genetic Diseases[2,5]

- Cystic fibrosis
- Duchenne muscular dystrophy
- Hemophilia
- Parkinson's disease
- Rett syndrome
- Spinal muscular atrophy

About Gene Therapy

Gene therapy for monogenic diseases addresses the root cause of disease by replacing the function of a missing or faulty gene. In one type of gene therapy, a new working copy of the gene restores the function of the protein.[3,6]

Step 1

A new working copy of a missing or defective gene is isolated.[3]

A virus is selected as a vector due to its ability to enter cells.[3]

The new working gene is placed inside the vector, which acts like an envelope to carry and deliver the functional gene to cells in the patient's body.[3]

Step 2

The vector is administered to the patient and enters the cells, where it breaks down, allowing the new working gene into the nucleus of the cells.[3]

Step 3

With the new gene in place, the cells begin producing the needed protein.[3]

Adeno-Associated Virus (AAV) Vectors

Some gene therapy delivery is accomplished with the use of a vector—often a virus engineered for carrying a functional human gene rather than one causing disease.[7]

Several vectors have been developed and studied to optimize the gene delivery process, but AAVs have emerged as among the most favorable. AAVs are not known to cause disease in humans, and they have the ability to:[1,8]

- Transfer genetic material into the cell's nucleus[3]
- Enter dividing and non-dividing cells[9]
- Target a variety of cells, including those in the central nervous system[8]

An AAV serotype called AAV9 also has the unique ability to cross the blood–brain barrier.[8]

Advances in Gene Therapy

The concept of gene therapy was introduced in the 1970s. Following decades of development, gene therapy research is now considered one of the most promising and active research fields in medicine.[1,10]

In 2012, the first gene therapy was approved by the European Medicines Agency (EMA) to treat a rare genetic blood disorder, and, in 2017, the first gene therapy was approved by the U.S. Food and Drug Administration (FDA) for a rare, inherited type of vision loss. As gene therapy research continues to advance, its potential to help patients with other genetic diseases grows.[6,11,12]

A Time Line of Progress

1909: The term "gene" is coined.[1]

1965: AAV is discovered.[13]

1972: Gene therapy is first suggested as a treatment for genetic disease.[1]

1990: A 4-year-old child with immunodeficiency is the first person to undergo experimental gene therapy.[1]

1999–2002: A number of individual gene therapy cases result in complications, and a death in a clinical trial sets back research.[1,14]

2003: China approves the first gene therapy in the world, with an indication for head and neck cancer.[1]

2009: Scientists show that an AAV vector has the potential to cross the blood–brain barrier, marking a major advance toward the treatment of genetic diseases with gene therapy.[15]

2012: The first gene therapy is approved by the EMA to treat a rare genetic blood disorder.[1]

2017: The US FDA approves two gene therapies. The first is used to treat acute lymphoblastic leukemia; the second for an inherited form of vision loss.[12,16]

2018: Despite past setbacks, numerous gene therapy approaches are showing promise with viable candidates; clinical studies continue to be conducted in a breadth of devastating genetic diseases.[10]

2018: Several gene therapy clinical trials completed, ongoing, or approved worldwide. A major medical journal declares, "Gene Therapy Comes of Age."[10]

References: 1. Global Genes. *A Guide to Gene Therapy.* Rare Toolkits. November 2016. Accessed February 22, 2022. https://globalgenes.org/wp-content/uploads/2016/03/Guide-to-Gene-Therapy_DIGITAL_spread-1.pdf **2.** Genetic disorders. National Human Genome Research Institute. Updated May 18, 2018. Accessed February 22, 2022. https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders **3.** American Society of Gene & Cell Therapy. 2000-2022. Accessed February 7, 2022. https://asgct.org/ **4.** What are single gene disorders. yourgenome. Updated July 21, 2021. Accessed February 24, 2022. https://www.yourgenome.org/facts/what-are-single-gene-disorders **5.** About Rett Syndrome. Rett Syndrome Research Trust. 2022. Accessed January 28, 2022. https://reverserett.org/about-rett-syndrome/ **6.** Wang D, Gao G. State-of-the-art human gene therapy: part II. gene therapy strategies and applications. *Discov Med.* Accepted manuscript. Published online May 21, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4440458/ **7.** How does gene therapy work? MedlinePlus. May 26, 2020. Updated April 12, 2021. Accessed February 22, 2022. https://medlineplus.gov/genetics/understanding/therapy/procedures/ **8.** Saraiva J, Nobre RJ, Pereira de Almeida L. Gene therapy for the CNS using AAVs: the impact of systemic delivery by AAV9. *J Control Release.* Accepted manuscript. Published online September 12, 2016. **9.** Wang D, Gao G. State-of-the-art human gene therapy: part I. gene delivery technologies. *Discov Med.* Accepted manuscript. Published online May 21, 2015. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4440413/ **10.** Dunbar CE, High KA, Joung K, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. *Science.* 2018;359(6372):eaan4672. **11.** Glybera becomes first-ever gene therapy approved in Europe. National Organization for Rare Disorders. November 2, 2012. Accessed February 22, 2022. https://rarediseases.org/glybera-becomes-first-ever-gene-therapy-approved-in-europe/ **12.** FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. US Food and Drug Administration. December 18, 2017. Updated March 16, 2018. Accessed February 22, 2022. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss **13.** Hastie E, Samulski RJ. Adeno-associated virus at 50: a golden anniversary of discovery, research, and gene therapy success—a personal perspective. *Hum Gene Ther.* 2015;26(5):257-265. **14.** Check E. A tragic setback. *Nature.* 2002;420(6912):116-118. **15.** Foust K, Nurre E, Montgomery CL, Hernandez A, Chan CM, Kaspar BK. Intravascular AAV9 preferentially targets neonatal-neurons and adult-astrocytes in CNS. *Nat Biotechnol.* Accepted manuscript. Published online July 2, 2010. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2895694/ **16.** FDA approval brings first gene therapy to the United States. US Food and Drug Administration. August 30, 2017. Updated March 26, 2018. Accessed February 22, 2022. https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states

03/2022 GL-UNB-22-0002

NOVARTIS | Reimagining Medicine