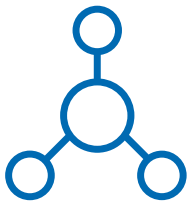
Gene Therapy

An Innovative Approach for Treating Rare Genetic Diseases

Genetic Diseases



Genetic diseases involve defects in functioning genes, which are made up of DNA and produce proteins—large complex molecules required for the structure and function of tissues and organs.[1,2]

Some genetic diseases are monogenic, meaning they are caused by an inherited defect in a single gene, making them an ideal candidate for gene therapy.[1,2]

Examples of Genetic Diseases

- 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 a genetic 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.[1,3,4]

Step 1

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

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

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.

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.

Step 3

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

Adeno-Associated Virus (AAV) Vectors

Some gene therapy delivery is accomplished with the use of a vector—often a virus engineered to carrying a functional human gene rather than one causing disease.[4]

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:[1,3–5]

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

An AAV serotype called AAV9 also has the unique ability to cross the blood–brain barrier.[3]

Advances in Gene Therapy

The concept of gene therapy was introduced in the 1970s and was first demonstrated to be effective in correcting a genetic defect in human cells in 1985.[1,6] Following decades of development, gene therapy research is now considered one of the most promising and active research fields in medicine.

In 2012, the first gene therapy was approved by the European Medicines Agency (EMA) to treat a rare genetic blood disorder,[6] 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.[7] As gene therapy research continues to advance, its potential to help patients with other genetic diseases grows.

A Timeline of Progress

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

1965: AAV is discovered.[8]

1972: Gene therapy is first suggested as a treatment for genetic disease.[9]

1990: A 4-year-old child with immunodeficiency is the first person to undergo experimental gene therapy.[10,11]

1999–2002: A number of individual gene therapy cases result in complications, and a death in a clinical trial sets back research.[12]

2003: China approves the first gene therapy in the world, with an indication for head and neck cancer.[13]

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.[3]

2012: The first gene therapy is approved by the EMA to treat a rare genetic blood disorder.[6]

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.[7]

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.[14]

2019: Several gene therapy clinical trials completed, ongoing, or approved worldwide. A major medical journal declares, "Gene Therapy Comes of Age."[15]

1. Global Genes. A Guide to Gene Therapy. https://globalgenes.org/wp-content/uploads/2016/03/Guide-to-Gene-Therapy_DIGITAL_spread-1.pdf. Date accessed: January 2022. **2**. National Human Genome Research Institute. https://www.genome.gov/For-Patients-and-Families/Genetic-Disorders. Date accessed: January 2022. **3**. 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*. 2016;241:94–109. **4**. NIH. How does gene therapy work? https://medlineplus.gov/genetics/understanding/therapy/procedures/. Date accessed: January 2022. **5**. Gray S, Woodard K, Samulski R. Viral vectors and delivery strategies for CNS gene therapy. *Ther Deliv*. 2010;1(4):517–534. **6**. National Organization for Rare Disorders. Glybera Becomes First-ever Gene Therapy Approved in Europe. https://rarediseases.org/glybera-becomes-first-ever-gene-therapy-approved-in-europe/. Date accessed: May 2020. **7**. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss [news release]. US Food and Drug Administration; December 19, 2017. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision- loss. Date accessed: May 2020. **8**. Hastie E and Jude Samulski R. 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. **9**. Freidmann T and Roblin R. Gene therapy for human genetic disease? Science. 1972;175(4025):949–955. **10**. Muul LM, Tuschong LM, Soenen SL, *et al*. Persistence and expression of the adenosine deaminase gene for 12 years and immune reaction to gene transfer components: long-term results of the first clinical gene therapy trial. Blood. 2003;101(7):2563–2569. **11**. Edelstein M, Abedi M, Wixon J. Gene therapy clinical trials worldwide to 2007—an update. *J Gene Med*. 2007;9:833–842. **12**. Keeler A, ElMallah M, Flotte T. Gene therapy 2017: progress and future directions. *Clin Transl Sci*. 2017;10(4):242–248. **13**. Zhang WW, Li L, Li D, *et al*. The first approved gene therapy product for cancer ad-p53 (Gendicine): 12 years in the clinic. *Hum Gen Ther*. 2018;29(2):160–179. **14**. Ginn S, Alexander IE, Edelstein ML, *et al*. Gene therapy clinical trials worldwide to 2012—an update. *J Gene Med*. 2013;15:65-77. **15**. Dunbar CE, High KA, Joung JK, *et al*. Gene therapy comes of age. *Science*. 2018;359(6372). Date accessed: May 2020.

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