UNDERSTANDING GENE REPLACEMENT THERAPY

What is a genetic disease?

A genetic disease is caused by a nonworking or missing gene or genes. A genetic disease can be passed down from one or both parents or can be a result of random errors in the body's genes.

What is a monogenic disease?

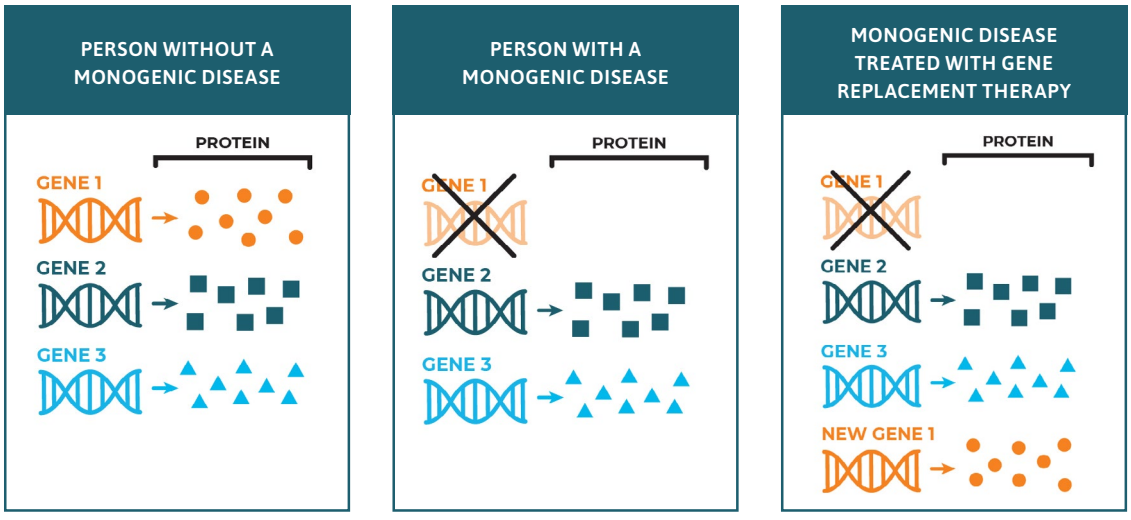
A monogenic disease is a disease caused by a single, nonworking or missing gene or gene pair. Gene replacement therapy is being studied for monogenic diseases, as the function of only one gene needs to be fixed.

What is the goal of gene replacement therapy?

Usually a person's own genes provide instructions to cells to make specific proteins.

In a person with a monogenic disease, there is one gene or gene pair that is missing or does not work right. This results in the protein being made incorrectly, made in short supply, or not made at all.

The goal of gene replacement therapy, a type of gene therapy, is to give cells a new, working copy of the missing or nonworking gene. This new gene may or may not become part of a person's DNA and is able to give the body instructions for making a particular protein the body needs.



How does gene replacement therapy work?

Gene replacement therapy starts with scientists creating a new, working copy of a missing or nonworking gene.

Then the new gene is placed inside a vector, which acts like an envelope and carries the gene to the right places throughout the body.

A vector can be created by making changes to a naturally occurring virus. A virus is selected as a vector because of its ability to enter the cells. One such virus, called an adeno-associated virus, or AAV, is commonly used because it is not known to cause sickness in people.

Next, the vector is placed in the body where it enters the cells and carries the new gene to the control center of the cells, also known as the nucleus.

Once inside the nucleus, the new gene tells the cells how to make the protein it needs.

Building a gene replacement therapy

What are the key components of gene replacement therapy?

There are 2 main parts to gene replacement therapy: genes and vectors.

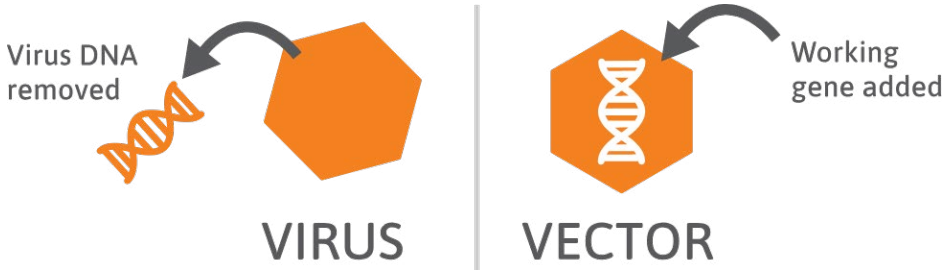
Genes

A new, working human gene is designed to give the cell the instructions it needs to make the protein that is missing or in short supply.

This new gene is created in a laboratory and is specific to the disease being treated. That is, scientists work to discover which gene needs to be replaced and figure out how to create the new, working gene. This is one reason why a single gene replacement therapy can take many years—even decades—to research and produce.

Vectors

Vectors are the delivery vehicles used to carry a new, working copy of the missing or nonworking gene into the right cells inside the body. These delivery vehicles are typically made from naturally occurring viruses. Viruses are used because they are very good at getting inside of cells. However, scientists remove DNA from the virus so that it won't make people sick when used as a vector.



A commonly used virus is the adeno-associated virus, or AAV. It was first discovered in 1965. It is used because it can get inside many different types of cells, such as those in the liver, kidney, eyes, and the central nervous system (*see diagram on next page*). There are several different types of AAVs, and each have a specific affinity for certain types of cells in people, allowing them to target different cells and tissues. AAV is also not known to cause illness in people. This makes the AAV a potentially promising vehicle for use in the treatment of a wide range of genetic diseases.

Building a gene replacement therapy (continued)

Vectors

Other viruses are also being researched as possible vectors for use in gene replacement therapy. Because each of these viruses have unique sets of characteristics, their use as a vector may be better suited for one genetic disease over another. For example, some viruses are naturally able to put genetic information into a person's DNA (integrating), while others leave it separate (nonintegrating).

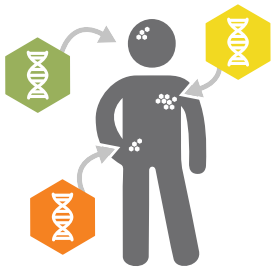
AAVs are capable of targeting many different cell types

- Integrating viral vectors could be important for genetic diseases that occur in cells that frequently copy themselves. This would enable the new cells to keep producing the genetic information with the intended effect
- Nonintegrating viral vectors could be better suited for use in cells that don't copy themselves often, such as brain or liver cells, because the new cells would not carry the new genetic information

Current gene replacement therapy advancements are the result of nearly a century of research.

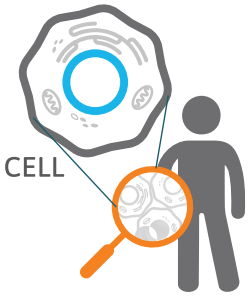
Definitions of key terms

Use this glossary of terms and images to better understand the meaning of common terms used when talking about genetic diseases and treatment.



Adeno-associated virus (AAV)

A type of virus that is able to get inside many different types of cells throughout the body, but not known to cause sickness in people. Because of this, it is a promising vector, or delivery vehicle, for gene replacement therapy.



Cell

Sometimes called the "building blocks of life," cells are the structural, functional, and biological units of life. They contain the nucleus at their center, which holds the cell's genetic materials and is where genes are delivered for gene replacement therapy.

Deoxyribonucleic acid (DNA)

The carrier of the body's genetic information, DNA is the template used by the body to make every substance in our body, such as proteins. It is made up of 2 strands of molecules that wind around each other in a double helix, a structure like a twisted ladder.

Gene

The basic units of heredity, and made up of DNA, genes carry the instructions cells need to make proteins used throughout the body.

Definitions of key terms (continued)

Gene addition

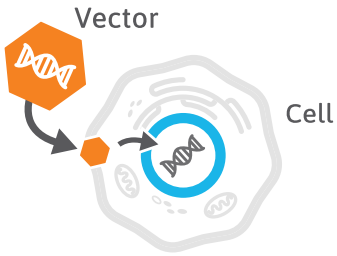
The addition of a new therapeutic gene that targets a specific cause of disease.

Gene editing

Also called genome editing, this treatment inserts, removes, or changes specific pieces of a person's existing DNA to correct a gene mutation.

Gene inhibition

This treatment deactivates, or silences, the expression of a mutant gene that codes for a toxic protein or too much protein.



Gene replacement therapy

This type of gene therapy uses a new, working gene to replace the function of a nonworking or missing gene. This gene then provides the instructions for the cells to make the missing or insufficient protein.

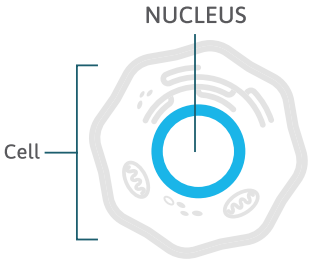
Gene therapy

A treatment strategy for disorders caused by a nonworking or missing gene and may involve the addition, inhibition, editing, or functional replacement of a gene.

Definitions of key terms (continued)

Genetic disease

This type of disease is caused by a missing or nonworking gene or genes. It may be inherited from one or both parents or happen due to random errors. Monogenic diseases are those caused by errors in a single gene.



Nucleus

This is the control center of a cell and is where all of the cell's genetic material, or DNA, is stored. This is also where the vector carries the new, working gene when undergoing gene replacement therapy.

Vector

A vehicle used to carry a working copy of a gene into the nucleus of a cell. It is usually made of a virus that has been changed so that it can no longer make a person sick.

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