CYSTIC FIBROSIS FOUNDATION®

UNDERSTANDING GENETIC THERAPIES

Genetic therapies – including mRNA therapy, gene therapy, and gene editing – could potentially benefit everyone with CF, regardless of mutation. Keep reading to learn how these exciting new therapies would work.

CF GENETICS: THE BASICS

Our cells contain DNA, a molecule that stores all of the genetic information needed to make proteins. Proteins are like tiny machines that do specific jobs within a cell, determining how the body looks, develops, and works. A gene is a specific sequence of DNA that carries the instructions for making a protein.

When making a protein, cells copy the DNA code into a molecule called messenger RNA (mRNA). The mRNA acts as a blueprint, carrying the instructions from the gene to the cellular construction site where the protein can be assembled.

Cystic fibrosis is caused by mutations in the gene that produces the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The faulty instructions caused by different mutations can result in different problems with the protein:

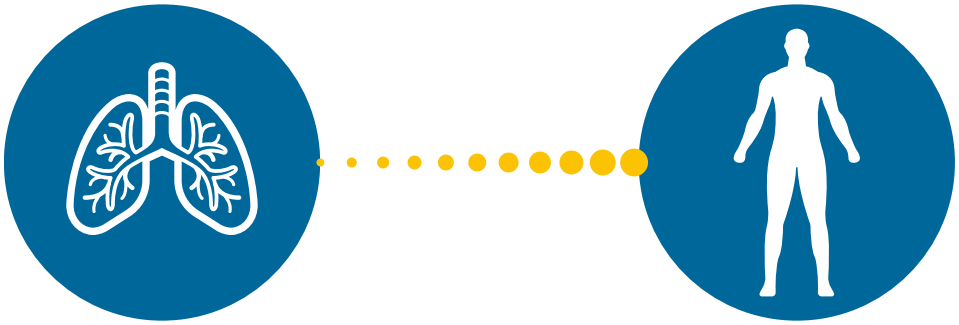
- Cells make CFTR protein that doesn't work correctly
- Cells make functional CFTR protein, but not enough of it to be effective
- Cells don't make CFTR protein at all

WHAT ARE GENETIC THERAPIES?

Genetic therapies could potentially benefit everyone with CF, regardless of their individual mutations. One strategy is to provide correct copies of the genetic instructions to cells, either through mRNA therapy or gene (DNA) therapy. Another approach is to correct the mutation in a person's own DNA, known as gene editing. Each of these approaches would allow cells to make functional CFTR protein.

Initially, genetic therapies will likely be delivered by inhalation and targeted to the lungs.

Eventually, the goal is to develop therapies that can be delivered to the entire body.



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HOW GENETIC THERAPIES COULD WORK FOR PEOPLE WITH CF

	What's happening in the cell?	Does it make a change to your DNA?	Could it work for all mutations?	How often do you take it?
mRNA Therapy	Correct copies of CFTR mRNA are delivered to cells. The cells use the new, correct instructions in the mRNA to produce healthy CFTR protein.	NO	YES	Frequent dosing (daily to weekly) – mRNA is quickly broken down inside cells and would need to be repeatedly re-dosed.
Non-Integrating Gene Therapy	A correct copy of the CFTR gene (DNA) is delivered to cells, but it is not permanent. The original mutated gene still exists in the person's own DNA. The cells use the new, correct copy of the gene to make healthy CFTR protein.	NO	YES	Less often than mRNA therapy – DNA copies may last longer than mRNA inside cells, but they aren't permanent and will likely need to be re-dosed. Early clinical trials for non-integrating gene therapies will focus on achieving a single effective dose before deciding how often to re-dose.
Integrating Gene Therapy	A correct copy of the CFTR gene (DNA) is delivered to cells and becomes a permanent part of a person's DNA. The original mutated gene still exists in the person's own DNA, but the cells use the new, correct copy of the gene to make healthy CFTR protein.	YES	YES	Unknown – Integrating gene therapies are permanent for the life of a cell. They may result in longer-lasting therapeutic benefit than non-integrating gene therapy. If the therapy can be delivered to lung stem cells, then integrating gene therapy could result in a permanent cure in the lungs.
Gene Editing	This strategy permanently makes a change to the DNA in a cell, which could be used to correct a person's CFTR mutation. The cells would permanently contain the correct instructions for making healthy CFTR protein.	YES	YES	Unknown – Gene editing therapies are permanent for the life of a cell. If the CFTR gene can be corrected in the DNA of lung stem cells, then gene editing could result in a permanent cure in the lungs.

WHAT THE FUTURE HOLDS

Genetic therapy research has come a long way, but we still have much more work to do.

Although clinical trials for RNA and gene therapies to treat CF are already underway, a trial for gene editing in CF is still several years away. Current and future clinical trials will help us answer important questions about how these genetic therapies could work in the real world, including how often they need to be dosed. These clinical trials will initially be focused on specific groups of people, such as those who are not eligible for CFTR modulators, before they are eventually expanded to others.

Additionally, further research is needed to understand how genetic therapies can be delivered to other organs beyond the lung, which would ultimately allow all people with CF – including those who have received a lung transplant – to benefit.

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For more information visit cff.org/genetictherapies

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