GENETIC THERAPIES FOR CF: GLOSSARY OF KEY TERMS

Basal stem cells: These are a type of stem cell located in the bottom layer of the cell sheet that makes up the airway surface. Stem cells have the unique ability to self-renew and develop into other types of cells. In the lungs, basal stem cells serve as the raw material to replace other airway cells as they naturally age or are damaged. If the CFTR gene can be corrected in the DNA of basal cells, then the correct genetic instructions for making CFTR protein would be constantly supplied to the other cells on the airway surface, resulting in a permanent cure.

Cargo: The protein-making instructions that are carried by a vector to cells affected by CF. The cargo can be either DNA or RNA instructions for a normal and fully functional CFTR protein, or other molecules carrying instructions for editing DNA.

CFTR modulators: Modulators are oral medications that can help correct dysfunctional CFTR proteins, enabling them to move to the cell surface and work normally. CFTR modulators are generally classified into two types: potentiators and correctors, with each type working in a different way, necessitating the use of them in combination for most people. Modulators do not contain genetic material and are **not a form of genetic therapy**. Although they can significantly improve CFTR function, they are not a cure and need to be taken daily.

CFTR protein: The cystic fibrosis transmembrane conductance regulator (CFTR) protein sits on the surface of certain cells and controls the flow of chloride out of cells. Chloride, a key component of salt, can alter the mucus-water balance in the lungs and other tissues. Mutations in the CFTR gene can cause the CFTR protein to malfunction or not be made at all. CFTR mutations are grouped into different classes or groups based on the way the mutations affect the CFTR protein.

Cure: A cure for CF refers to a permanent correction to the DNA in the stem cells of a person with CF, which could be achieved through either gene editing or integrating gene therapy. Temporary therapies that require redosing, such as RNA therapy and non-integrating gene therapy, are not considered cures. Because CF affects multiple organs in the body, a cure for CF will need to be delivered systemically (to the whole body). Once cured, the cells in a person's body will permanently have the ability to make functioning CFTR protein; however, a cure will not reverse existing organ damage.

DNA: Deoxyribonucleic acid (DNA) is the molecule that stores all the genetic information needed for a person to develop and grow. Cells in the body contain the same DNA code, which serves as instructions to make proteins.

Gene: A gene is a specific sequence of DNA that carries the directions for making a specific protein. The CFTR gene provides the instructions to make CFTR protein. Cystic fibrosis is caused by mutations, or changes, in the CFTR gene.

Gene editing: Gene editing is a strategy to permanently make a change to the DNA in a cell, which could be used to correct any or all CFTR mutations (on a mutation-by-mutation basis). The gene editing machinery will need to be delivered to the stem cells to achieve a permanent therapeutic benefit.

Gene therapy: A new, correct copy of the CFTR gene (DNA) is delivered to cells. This can be achieved through two different strategies:

- **Integrating gene therapy**, in which the correct copy of the gene becomes a permanent part of a person's genome, or
- **Non-integrating gene therapy**, in which the correct copy of the gene is delivered to cells but is not permanent and will therefore require redosing.

In both cases, the mutations in the CFTR gene still exist in the person's own DNA, but the cells can use the new, correct copy of the gene to make normal mRNA and healthy CFTR protein. This is also referred to as gene transfer or gene replacement.

Genetic therapies: Therapeutic approaches that fix the DNA (via gene editing) or replace the DNA (via gene therapy/gene transfer) or RNA (via RNA therapy).

mRNA therapy: A new, correct copy of CFTR mRNA is delivered to cells. The cells use the new, correct instructions in the mRNA to produce healthy CFTR protein. This treatment does not affect a person's DNA or CFTR mutations. mRNAs are naturally broken down quickly inside cells, so the treatment will likely need to be re-dosed regularly for it to continue to work.

RNA: Ribonucleic acid (RNA) is a molecule similar to DNA that serves as an intermediary to help transfer and process the genetic information contained in a specific sequence of DNA (a gene) to the cell machinery responsible for making proteins. There are several types of RNA, but messenger RNA (mRNA) is the one most well-known type of potential therapy for CF. mRNA is created by copying the genetic instructions for a specific protein contained in the DNA and acts as a template carrying the instructions from the CFTR gene to the protein-making machinery.

Vector: A vector is a delivery vehicle that takes genetic therapies into cells. Some commonly used vectors are viruses that have been altered so they do not cause disease in humans. The virus' genetic material is replaced with the desired genetic therapy cargo. Because the virus has been modified, it cannot replicate, and it may be cleared by the body once it has delivered the genetic therapy into the cell. Non-viral vectors can also be engineered and used to deliver genetic therapies.

March 2022

CYSTIC FIBROSIS FOUNDATION®