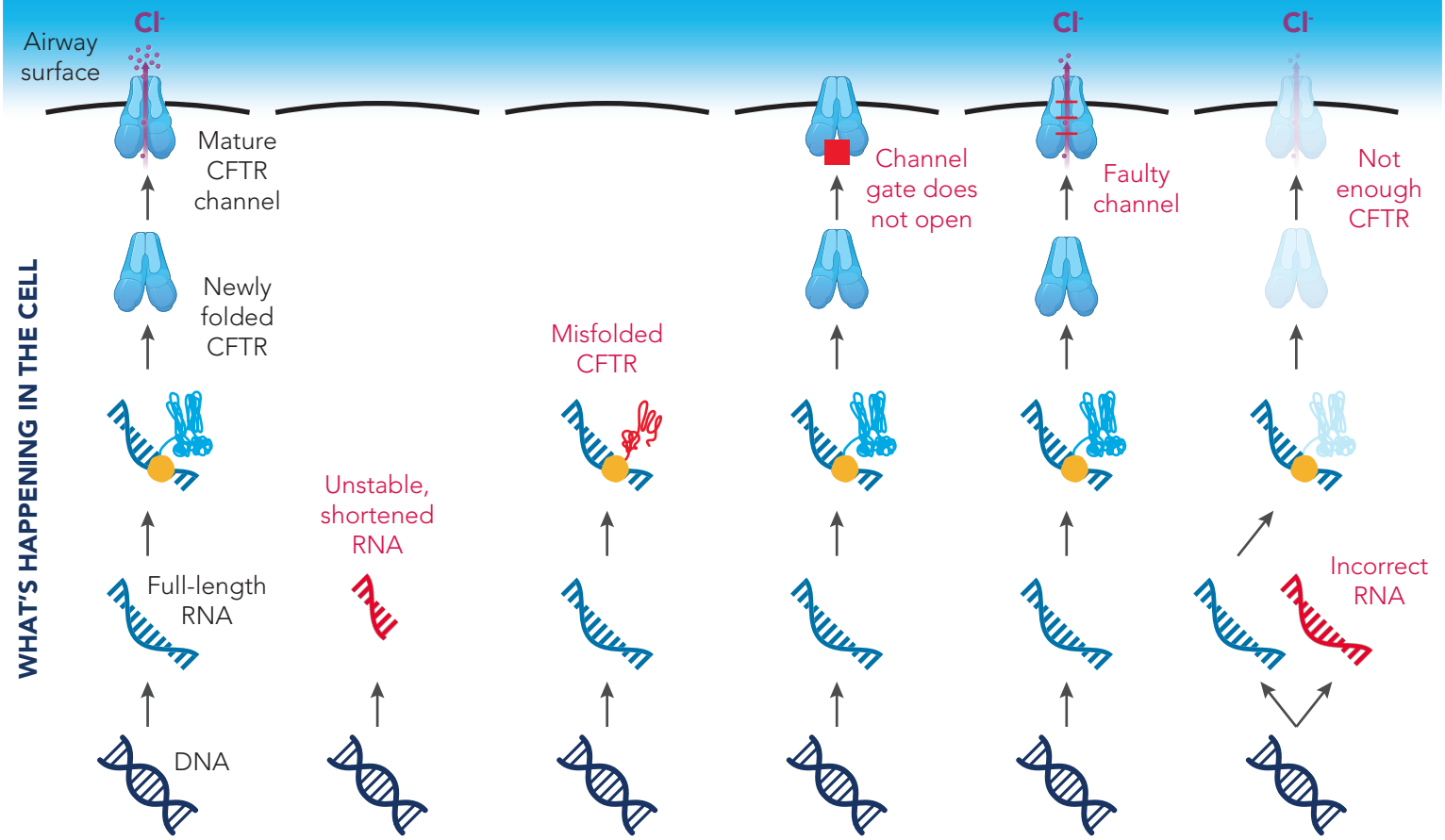
KNOW YOUR CFTR MUTATIONS

Normal	Class I	Class II	Class III	Class IV	Class V
CFTR protein is created, moves to the cell surface and allows transfer of chloride and water.	No functional CFTR is created.	CFTR protein is created, but misfolds, keeping it from moving to the cell surface.	CFTR protein is created and moves to the cell surface, but the channel gate does not open properly.	CFTR protein is created and moves to the cell surface, but the function of the channel is faulty.	Normal CFTR protein is created and moves to the cell surface, but in insufficient quantities.
% of people with CF who have at least one mutation in that class >	22%	88%	6%	6%	5%
MUTATION EXAMPLES	No mutation	**G542X** **W1282X** **R553X** aka "nonsense mutations," "splice mutations," or "deletions"	**F508del** **N1303K** **I507del**	**G551D** **S549N** aka "gating mutations"	**D1152H** **R347P** **R117H**	**3849+10kbC→T** **2789+5G→A** **A455E**



POTENTIAL THERAPIES

CFTR modulators help defective CFTR protein fold correctly and stay open at the cell surface, and can also help increase the function of normal CFTR

Genetic therapies, including RNA therapy, gene therapy, and gene editing, could potentially benefit any person with CF, regardless of their CFTR mutations

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KNOW YOUR MUTATIONS:
A CFTR MUTATION FACT SHEET

CYSTIC FIBROSIS FOUNDATION®

Cystic fibrosis is caused by mutations, or changes, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This gene provides the code that tells the body how to make the CFTR protein. The protein controls the salt and water balance in the lungs and other tissues. All people have two copies of the CFTR gene, and there must be mutations in both copies to cause CF. More than 1,700 mutations of the CFTR gene have been identified. Although some are common, others are rare and found in only a few people.

CFTR mutations are grouped into classes based on the way the mutations affect the CFTR protein. The reverse side of this sheet shows the most common CFTR mutation classes. These categories are helpful for understanding how CFTR modulator therapies tackle different problems with the faulty protein to restore CFTR function. However, the mutation classes and potential therapies described in this handout do not necessarily determine how much an individual will benefit from a CFTR modulator therapy.

Some people who are eligible for CFTR modulators based on their mutations may only experience a small benefit. Others may be unable to take them due to unwanted side effects or drug-drug interactions. In addition, some CFTR mutations don't produce any CFTR protein at all. These mutations do not respond to CFTR modulators because there is no protein for the modulators to work on. Compared to the general CF population, people of color with CF are more likely to have rare or nonsense mutations that do not respond to current modulators.

We are committed to addressing this disparity and ensuring that every person with CF has an effective therapy that corrects the underlying cause of their disease. The diagram below explains how currently available and potential therapies could restore CFTR function. Genetic therapies, including RNA therapy, gene therapy, and gene editing, could work for any person with CF, including those with nonsense, splicing, and other rare mutations.

HOW IS CFTR MADE?

Once at the cell surface, the CFTR protein functions as a chloride channel. This channel helps maintain the right balance of fluid in the airways.

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Once complete, the CFTR protein moves through the cell to the cell surface.

↑

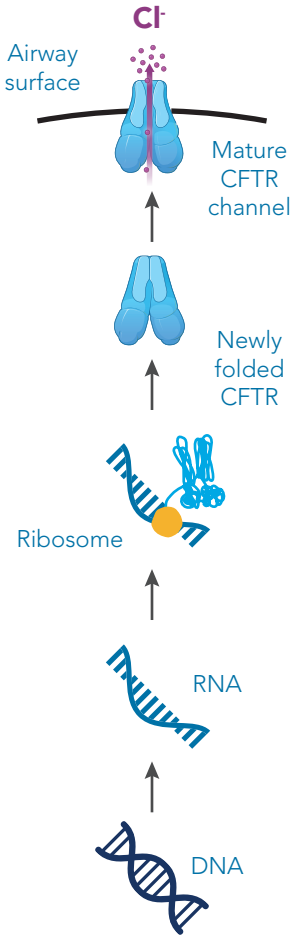
Ribosomes are tiny molecular machines that read the instructions in the RNA and use them to make the CFTR protein.

↑

RNA acts as a template to make proteins. RNA is created by copying the coded instructions in the DNA.

↑

DNA in the cell nucleus provides instructions to make proteins. The CFTR gene contains instructions to make the cystic fibrosis transmembrane conductance regulator (CFTR) protein.



TYPES OF THERAPIES

Potentiators, such as ivacaftor, are CFTR modulators that help open the CFTR channel at the cell surface and increase chloride transport.

Correctors, such as tezacaftor and elexacaftor, are CFTR modulators that help the defective CFTR protein fold properly so that it can move to the cell surface.

Antisense oligonucleotides (ASOs) and readthrough compounds are drugs that could help the cell overcome mutations in the RNA and make full-length CFTR protein.*

RNA therapies aim to either fix the incorrect instructions in defective RNA, or deliver a new, correct copy of CFTR RNA directly to the cell.*

Gene therapies aim to deliver a new, correct copy of the CFTR gene (DNA) to the cell. Gene editing techniques aim to correct CFTR mutations by making a permanent change to the existing DNA in a cell.*

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*These treatments are not yet available to people with CF.