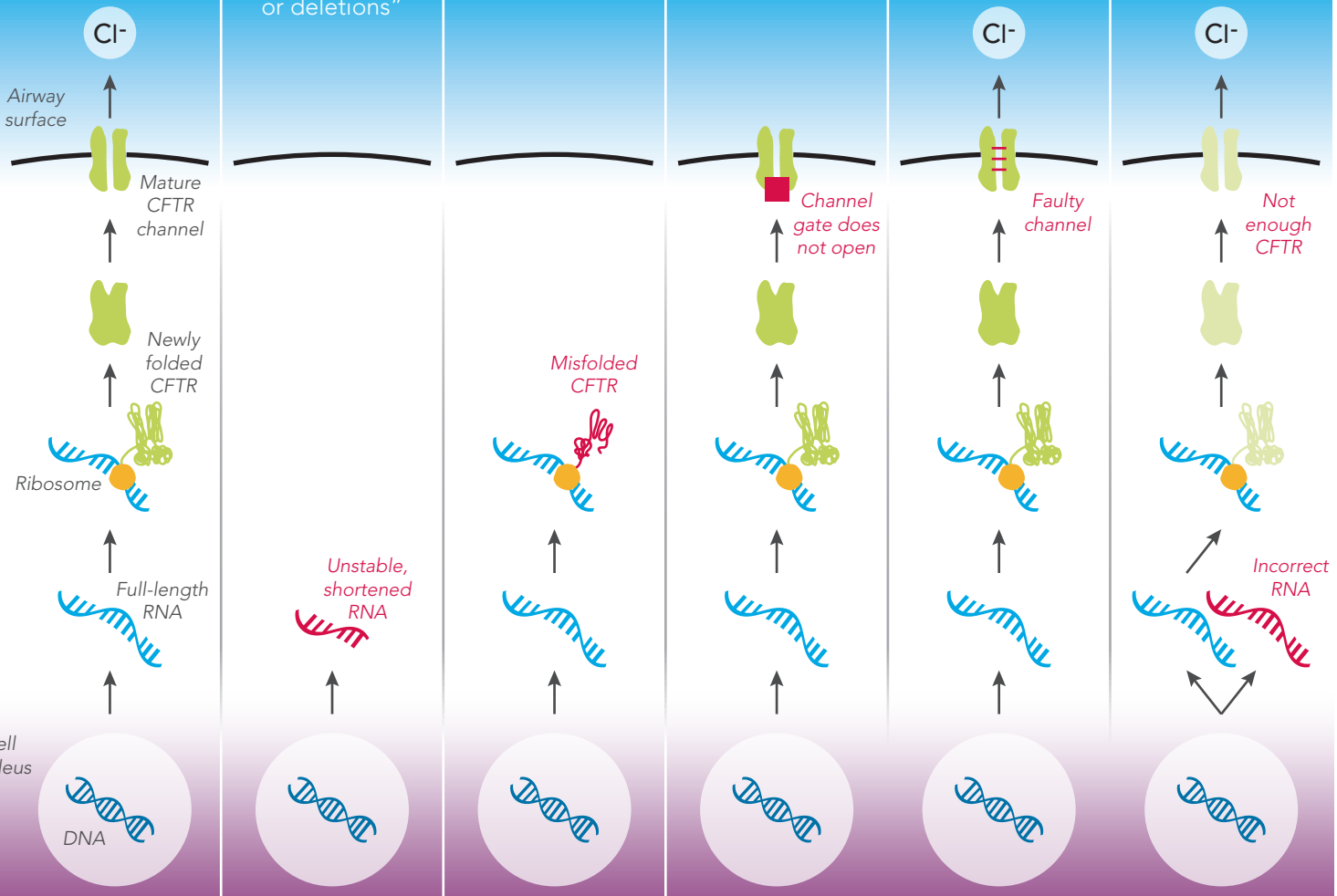
# CFTR MUTATION CLASSES

| | Normal | Class I | Class II | Class III | Class IV | Class V |
|---|---|---|---|---|---|---|
| **DESCRIPTION** | 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<br>W1282X<br>R553X**<br>aka "nonsense mutations, splice mutations or deletions" | **F508del<br>N1303K<br>I507del** | **G551D<br>S549N**<br>aka "gating mutations" | **D1152H<br>R347P<br>R117H** | **3849+10kbC→T<br>2789+5G→A<br>A455E** |

## WHAT'S HAPPENING IN THE CELL




## POTENTIAL THERAPIES

| Class I | Class II | Class III, IV, V |
|---|---|---|
| Read-through compounds may allow production of full-length CFTR for nonsense mutations | Correctors such as lumacaftor or tezacaftor help defective CFTR fold correctly | Potentiators such as ivacaftor help open the CFTR channel, and also help increase the function of normal CFTR |

# KNOW YOUR MUTATIONS:
## A CFTR Mutation Fact Sheet

CYSTIC FIBROSIS FOUNDATION

Cystic fibrosis is caused by mutations, or changes, in the CFTR gene. This gene provides the code that tells the body how to make the cystic fibrosis transmembrane conductance regulator (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. In the future, mutations may also be classified by "theratype," meaning which type of CFTR modulator therapy they respond to best. This is because mutations within the same class may respond to therapies differently, and not every mutation can be neatly assigned to one mutation class.

Certain types of CFTR mutations are associated with different disease complications. For example, some mutations are more likely to affect the pancreas than others. However, this correlation is not perfect, and knowing an individual's CFTR mutations cannot always tell you how severe that person's CF symptoms will be.

Although the potential therapies described on this sheet can be very effective for some people with CF, others may not experience the exact same benefit. Researchers continue to work in the lab and in clinical trials to find the best therapeutic approaches to target specific CFTR mutations or classes of mutations to improve the health of all individuals living with CF.

## How is CFTR made?

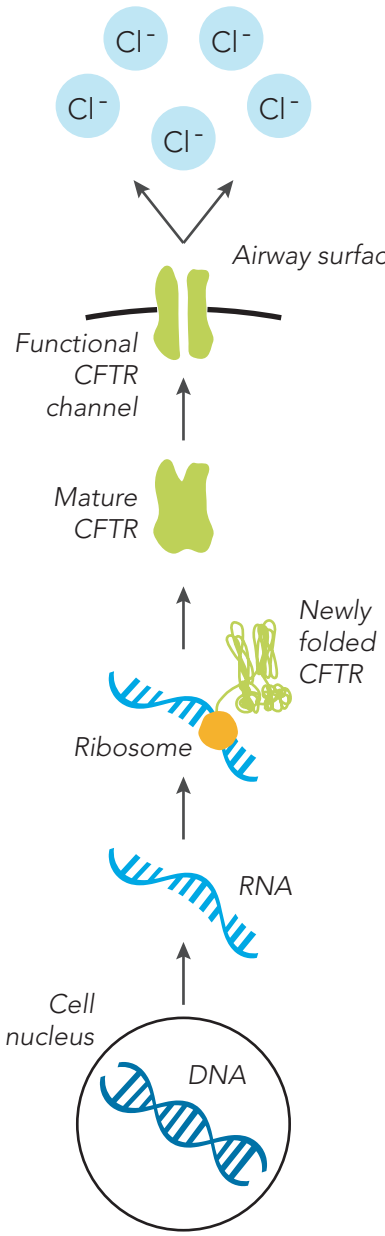
Once at the cell surface, the CFTR protein functions as a chloride channel. This channel helps maintain the right balance of fluid in the airways.

Once complete, the CFTR protein moves through the cell to the cell surface. This process is called trafficking.

Ribosomes are tiny molecular machines that read the instructions in the RNA and use them to make the CFTR protein. This process is called translation.

RNA is created by matching the coded instructions in the DNA. This process is called transcription. RNA acts as a template to make proteins.

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




## Potential therapies for CFTR mutations

Potentiators are drugs that help open the CFTR channel at the cell surface and increase chloride transport.

Correctors are drugs that help the defective CFTR protein fold properly so that it can move to the cell surface.

Read-through compounds aim to allow full-length CFTR protein to be made, even when the RNA contains a mutation telling the ribosome to stop.

RNA therapies aim to either fix the incorrect instructions in defective RNA, or provide normal RNA directly to the cell.

Gene-editing techniques aim to repair the underlying genetic defect in the CF gene DNA. Gene replacement techniques aim to provide a correct copy of the CF gene.