THE ROLE OF CFTR MUTATIONS IN CAUSING CYSTIC FIBROSIS (CF)
Program objectives

Increase your knowledge of:

• The importance of CFTR protein regulation in the body

• How $CFTR$ mutations are inherited, and how they affect CFTR protein quantity and/or function and total CFTR activity

• The links between $CFTR$ mutations, CFTR activity, and CF disease development

CFTR, cystic fibrosis transmembrane conductance regulator.
CFTR PROTEINS IN NORMAL CELLS
CFTR proteins: An important regulator of fluid and ion balance in organs throughout the body

- CFTR proteins are found on epithelial cell surfaces in organs throughout the body\textsuperscript{1-4}
- Normally, CFTR protein channels transport ions, such as chloride and bicarbonate, through the epithelial cell surface in these organs\textsuperscript{1-4}
- Maintaining water and salt balance at the epithelial cell surface requires an adequate quantity and function of CFTR proteins\textsuperscript{5}

• **Total CFTR activity** can be defined as total ion transport mediated by CFTR protein channels at the cell surface. It is dependent on CFTR protein **quantity** and **function**\textsuperscript{6,7}

CFTR proteins reach the membrane through a multi-step process

References:
CFTR MUTATIONS AND THEIR EFFECTS ON CFTR PROTEIN ACTIVITY
**CFTR mutations are inherited genetically**

- If a person inherits 2 copies of a disease-causing CFTR mutation (one from each parent), CFTR protein dysfunction can occur:
  - CFTR protein dysfunction impairs cellular chloride transport
  - CF disease can be the result

**CFTR mutations may affect CFTR quantity and/or function, reducing total CFTR activity**

**Spectrum of phenotypes associated with total CFTR activity**

- People with 2 CFTR mutations resulting in loss of CFTR activity generally have a CF phenotype, which may include:
  - Elevated sweat chloride (>60 mmol/L)
  - Pancreatic insufficiency
  - CBAVD
  - Lung function decline over time
  - *Pseudomonas aeruginosa* colonization

CBAVD, congenital bilateral absence of vas deferens.

**References:**
Different *CFTR* mutations produce different effects on *CFTR* protein quantity and function

*CFTR* mutations are grouped into classes according to their effects on *CFTR* protein synthesis, trafficking, or function

Classes I-V comprise the 25 most common mutations in the US CF patient population

Examples of *CFTR* mutations that result in defective biosynthesis of the *CFTR* protein

**CFTR quantity**

- Defective synthesis yields no functional *CFTR* protein

**CFTR function**

- Channel-open probability: Little to none
- Conductance: Little to none

**Total CFTR activity**

Little to none

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An absence of *CFTR* protein…

…regardless of function since few to no *CFTR* proteins reach the surface…

…results in little to no total CFTR activity

### Examples (Class I)

<table>
<thead>
<tr>
<th>Examples (Class I)</th>
<th>Type</th>
<th>US prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G542X</td>
<td>Nonsense</td>
<td>4.7</td>
</tr>
<tr>
<td>1717-1G→A</td>
<td>Splice defect</td>
<td>1.6</td>
</tr>
<tr>
<td>3659delC</td>
<td>Frameshift</td>
<td>0.7</td>
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</tbody>
</table>

**References:**

Examples of CFTR mutations that result in defective processing and trafficking of the CFTR protein

Significantly reduced CFTR protein…...regardless of function since few to no CFTR proteins reach the surface... ...results in little to no total CFTR activity

<table>
<thead>
<tr>
<th>Examples (Class II)</th>
<th>Type (^4)</th>
<th>US prevalence (%) (^5)</th>
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</thead>
<tbody>
<tr>
<td><em>F508del</em></td>
<td>Amino acid deletion</td>
<td>86.4(^a)</td>
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<tr>
<td><em>N1303K</em></td>
<td>Missense</td>
<td>2.4</td>
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</tbody>
</table>

\(^a\)Homozygous and heterozygous.

**Example of CFTR mutations that reduce channel-open probability in the CFTR protein**

![Diagram showing the relationship between CFTR quantity, CFTR function, and total CFTR activity.]

Although CFTR protein quantity may be normal...

...function is severely reduced due to decreased channel-open probability...

...and results in little to no total CFTR activity

<table>
<thead>
<tr>
<th>Examples (Class III)</th>
<th>Type</th>
<th>US prevalence (%)</th>
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</thead>
<tbody>
<tr>
<td>G551D</td>
<td>Missense</td>
<td>4.4</td>
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</table>

**References:**

Example of CFTR mutations that result in a CFTR protein with defective conductance

Although CFTR protein quantity may be normal…

…function is reduced due to decreased conductance…

…and results in some total CFTR activity

<table>
<thead>
<tr>
<th>Examples (Class IV)</th>
<th>Type</th>
<th>US prevalence (%)</th>
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</thead>
<tbody>
<tr>
<td>R117H</td>
<td>Missense</td>
<td>3.0</td>
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</table>
Examples of CFTR mutations that result in some functional CFTR at the cell surface

CFTR protein quantity is reduced... …even though CFTR function is not impaired... …and results in some total CFTR activity

<table>
<thead>
<tr>
<th>Examples (Class V)</th>
<th>Type</th>
<th>US prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3849+10kbC→T</td>
<td>Splice defect</td>
<td>3.0</td>
</tr>
<tr>
<td>A455E</td>
<td>Missense</td>
<td>0.6</td>
</tr>
</tbody>
</table>

THE IMPACT OF REDUCED CFTR ACTIVITY
Both *CFTR* mutations play a role in determining phenotype and disease severity

As CFTR activity declines, CF development becomes more likely

- **Normal:** No CF-causing mutation.
- **Some:** Classes IV-VI.
- **Little to none:** Classes I-III.

*CFTR genotype affects sweat chloride concentration, an indicator of underlying CFTR activity and a principle diagnostic marker for CF*¹

Summary

• CFTR protein is an important cellular regulator in organs throughout the body\textsuperscript{1,2}
  – *CFTR* mutations, which are acquired genetically, decrease CFTR protein function and/or quantity to reduce total CFTR activity
  – Loss of CFTR protein activity is the underlying cause of CF

• Different types of *CFTR* mutations vary in their effects on CFTR protein quantity and/or function, because they affect CFTR protein formation in different ways\textsuperscript{2,3}

• Both *CFTR* mutations play a role in determining phenotype or disease severity\textsuperscript{4}