CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

Applications of Gene Therapy in Cystic Fibrosis

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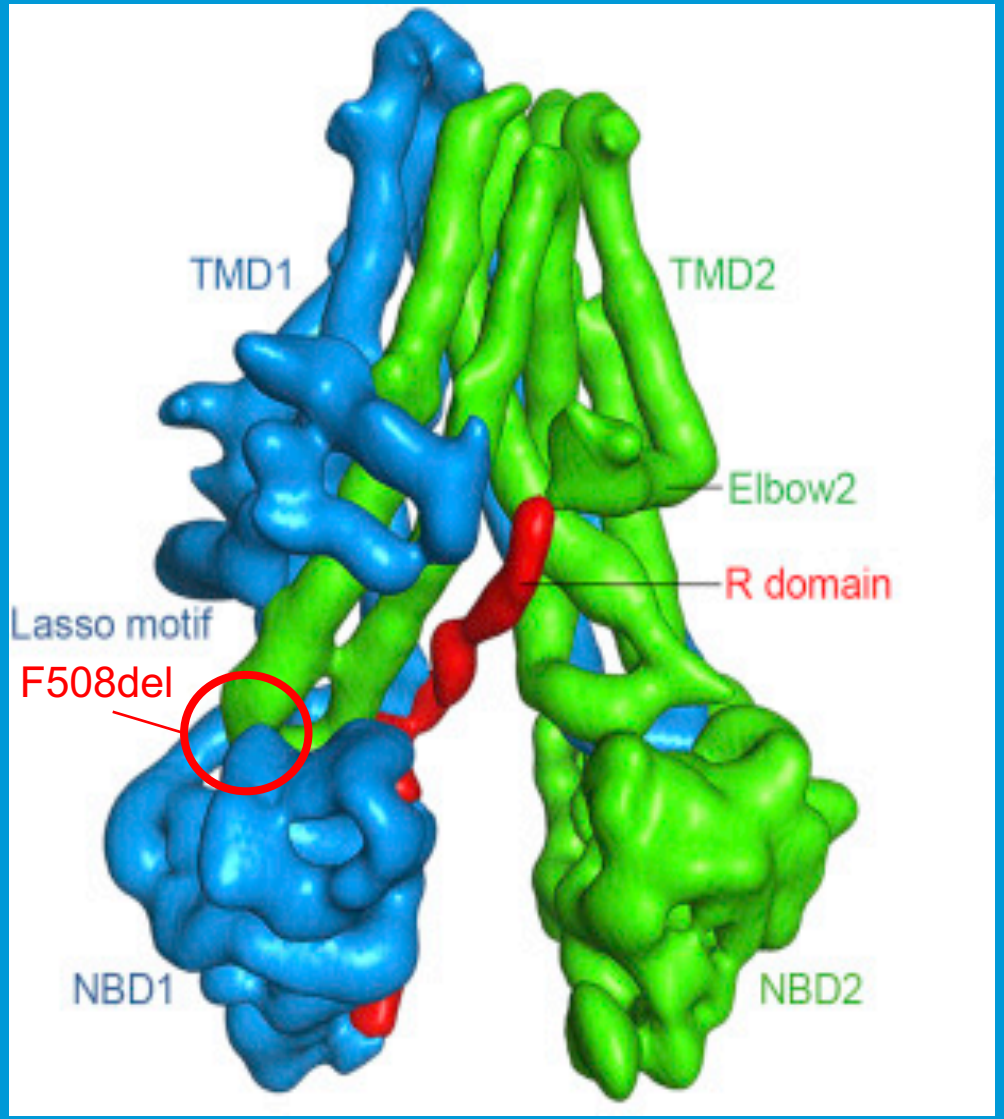
Our Mission

To cure cystic fibrosis and to provide all people with the disease the opportunity to lead full, productive lives by funding research and drug development, promoting individualized treatment, and ensuring access to high-quality, specialized care.

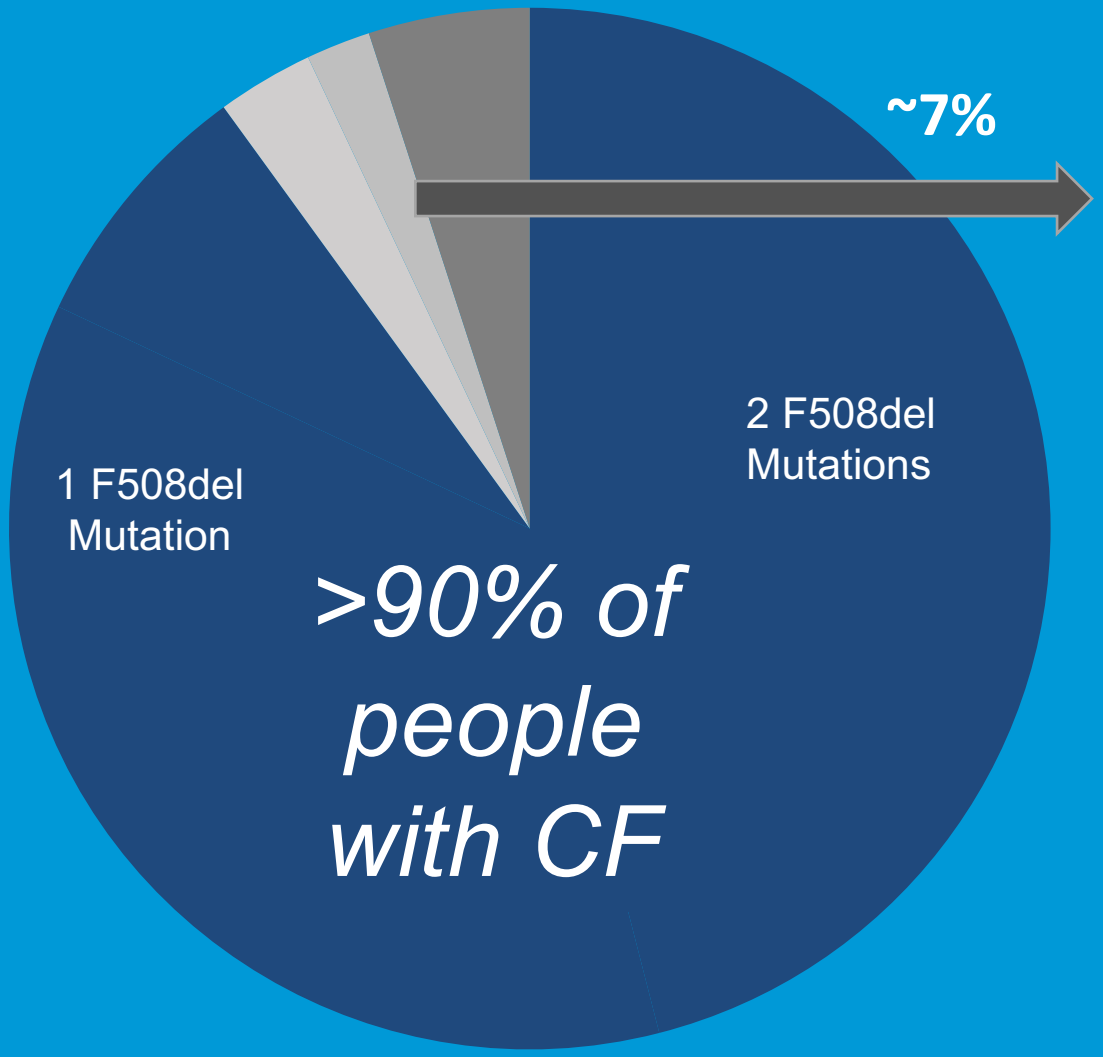
CFTR ► CF

- What is CFTR and what does it do?
- Cystic fibrosis transmembrane conductance regulator (CFTR)
- Chloride and bicarbonate channel
- Salt, water, mucus regulation
- CFTR modulators restore function by directly targeting the protein



F Liu, Zhe Zhang, L Csanády, DC. Gadsby, J Chen
Molecular Structure of the Human CFTR Ion Channel Cell Vol 169, Issue 1, 2017, 85–95.e8

Predicted CFTR Modulator Coverage (2020)



- Two mutations, no protein
- No F508del/rare mutation
- Other

<u>Kalydeco, Orkambi, Symdeko, Triple Combination</u>

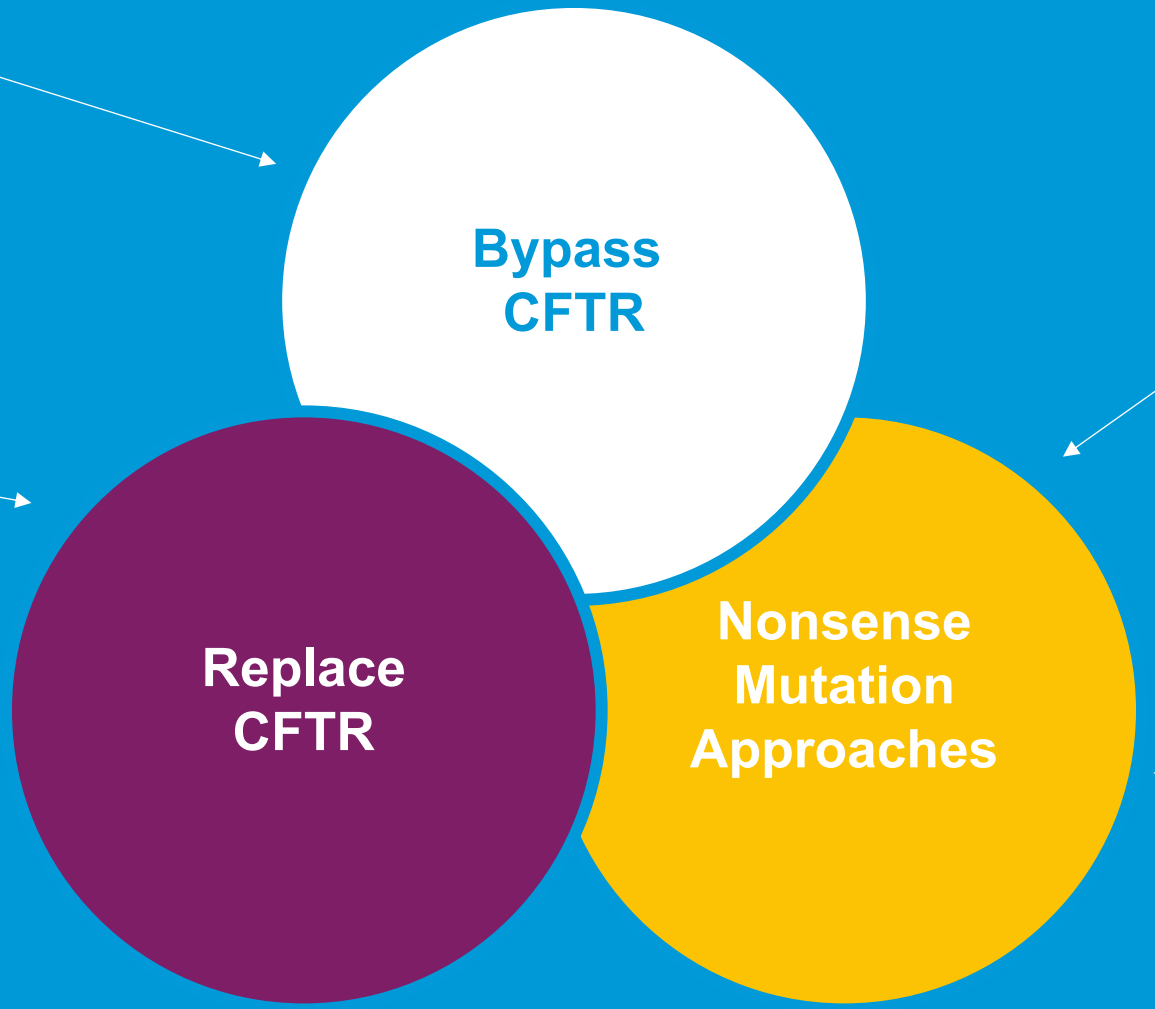
- F508del/F508del
- F508del/minimal function
- F508del/partial function
- Gating

Strategies to Treat the Remaining 7%

Modulate Other Ion Channels
- Spyryx
- Ionis
- Enterprise
- AstraZeneca*
- Boehringer-Ingelheim*

mRNA
- Arcturus
- Translate Bio*
- Moderna*

DNA
- TaleeBio
  - AAV
  - Lentivirus
- 4D Molecular
  - AAV



Small-Molecule Screening
- UAB-SRI
- Icagen
- CFFT Lab
- Eloxx*

Other Approaches
- ReCode
- Ionis

* Not funded by the CFF

The Pace of Discovery is Accelerating

Our medical scientific budget is growing

$89M in 2012 →$188M in 2018

Developing research programs focused on gene therapy

1. 2015 - Repairing *CFTR* Genetic Mutations for Research Tools and Therapeutics
   2015 - Delivery Approaches for *CFTR* Gene Replacement and Repair Technologies

2. 2018 - Advancing Gene Editing Technologies and Tools for Cystic Fibrosis
   2019 - Overcoming Obstacles for Nucleic Acid Delivery for Cystic Fibrosis (planned)

Therapeutic Development Award Program

- Early stage investments that fill the gap between basic research and phase 3 clinical trails
- Matching award program whereby funds will be awarded only if they are matched by the recipient
- The number of industry collaborations is growing
  - 6 programs in 2012
  - 39 programs in 2017

4D Molecular Therapeutics
AAV gene delivery to the lung

Arcturus Therapeutics
CFTR mRNA delivery to the lung

Therapeutic Development Award Guidelines

- Component 1 (preclinical)
  - Typically up to $600K over 2 years
  - IND-enabling studies including GLP toxicology
  - May include screening and optimization efforts for lead product selection
- Component 2 (clinical)
  - Typically up to $3M over 2 years
  - Clinical studies to involve people with CF (Phase 1-2)
- Not included
  - Healthy volunteer Phase 1 studies
  - CMC or drug manufacturing

On the Horizon…

- Aggressively pursuing research programs to ensure that 100% of people with CF have access to CFTR-based therapies
  - Small molecules
  - Gene therapy approaches
  - mRNA therapy
  - Gene editing
  - Antisense Oligonucleotides

“Until CF stands for Cure Found.”