Cystic Fibrosis Drug Discovery and Development: More Than Venture Philanthropy

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Cystic Fibrosis Foundation
To advance drug development and a search for a cure, Cystic Fibrosis Foundation Therapeutics has contractual agreements with several companies to receive royalties related to drugs that are developed as a result of CFFT funding. Any royalties we receive are used in support of our mission.
Cystic Fibrosis Organ Involvement

• Recessive genetic disease
• Multiorgan involvement (sinus, lungs, pancreas, liver, intestinal tract, skin, reproductive tract, skeletal system)
• Morbidity and mortality today primarily linked to progressive loss of lung function

CFTR Gene, Protein and Mutations

• hCFTR encodes a 1480 aa ATP binding cassette transporter (2 transmembrane domains, 2 nucleotide binding domains) that differs from other members of the ABC family by the presence of a cytosolic regulatory domain.

• CFTR is a ATP, PKA-activated anion channel. Permeability I^->Cl^->>HCO_3^-.

• >1000 described mutations in hCFTR gene.

• Most prevalent mutation worldwide is loss of phenylalanine at position 508 (F508del CFTR).

• Genotype-phenotype relationship variable among target tissues (vas deferens > pancreas >> lung) suggesting likelihood of environmental and genetic modifiers.
CFTR “Broad” Mutation Classification

<table>
<thead>
<tr>
<th>Defect Classification</th>
<th>Normal</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect Result</td>
<td>No synthesis</td>
<td>Block in Processing</td>
<td>Block in Regulation</td>
<td>Altered Conductance</td>
<td>Reduced Synthesis</td>
<td></td>
</tr>
<tr>
<td>Types of Mutation</td>
<td>Nonsense; Frameshift</td>
<td>Missense; Amino Acid Deletion (ΔF508)</td>
<td>Missense; Amino Acid Change (G551D)</td>
<td>Missense; Amino Acid Change (R117H) (R347P)</td>
<td>Missense; Amino Acid Change (A445E) Alternative Splicing</td>
<td></td>
</tr>
</tbody>
</table>

* Some mutations exert multiple negative effects (e.g., F508del – processing and regulation)

Electrophysiological Impact of Mutations on CFTR Protein Function

Non-CF HBE

CF HBE

ASL

Cl$^{-}$ Cl$^{-}$ Cl$^{-}$ Cl$^{-}$ Cl$^{-}$ Cl$^{-}$

G551D CFTR

I$_{Cl}$ N x P$_o$ x g

F508del CFTR

Cl$^{-}$ Cl$^{-}$ Cl$^{-}$ Cl$^{-}$ Cl$^{-}$ Cl$^{-}$

airway lumen

<7 µm

airway lumen

CF HBE

<7 µm

Non-CF HBE
Discovery and Development of CFTR Modulators

VX-770 and VX-809 structures

VX-770 augments (G551D, F508del and wt) membrane resident CFTR open channel probability.

VX-809 rescues membrane trafficking of F508del CFTR

Restoration of channel function is reflected in tissue level function.

VX-809 effect magnified by VX-770 co-administration.

Van Goor F et al. PNAS. 2009.
Van Goor F et al. PNAS. 2011.

September 27, 2016
Phase 3 Clinical Trial Results of Ivacaftor (VX-770)

Phase 3 Clinical Trial Results of Lumacaftor + Ivacaftor (VX-809 + VX-770)

1. Significant increases in FEV₁ and BMI
2. Decreases in hospitalizations and need for IV antibiotics

Figures courtesy of Michael Boyle, MD
How to derisk pharmaceutical company involvement in an orphan disease?

Basic Tenets of Venture Philanthropy¹:
• Tailored financing
• Multi-year support
• Performance measurement
• Engagement
  • Organizational capacity building

Additional measures we’ve chosen to take:
• Non-monetary assistance
• Clinical Trial Infrastructure
• Patient Education

Impact = Innovation + Scale²

²http://ssir.org/articles/entry/when_innovation_goes_wrong
CFTR Toolbox

• CFTR functional and mechanistic assays
• Access to non-commercial resources
  • CFTR modulator panel
  • CFTR antibodies
  • CF human airway epithelia
• Independent testing
  • CFFTI lab
  • Chantest – a division of Charles River
Documenting Disease Liability of CFTR Variants

Welcome to the CFTR2 website

Our Purpose:
CFTR2 is a website that provides information for patients, researchers, and the general public about specific mutations in what is commonly referred to as the cystic fibrosis (CF) gene.

For each mutation or mutation combination included in the database, the website will provide information about:
1. Whether the mutation or mutation combination is CF-causing, and
2. Information about sweat chloride, lung function, pancreatic status, and Pseudomonas infection rate in patients in the CFTR2 database with this mutation or mutation combination.

Information on the CFTR2 website is being updated as further analysis is completed. The most up-to-date clinical information and results of functional testing are available on individual mutation pages. For a complete list of CFTR2 mutations and their characterizations, please visit CFTR2 Mutation List History.

This site is intended to do:
- This website provides information for members of the general public, including cystic fibrosis patients and their family members, about what is currently known about specific genetic mutations related to cystic fibrosis.
- Patients and their family members are encouraged to visit the section, “For patients and family members” first.
- This website also provides more in-depth research-related information for health care professionals and researchers.

This site is NOT intended to do:
- This website is not intended to help diagnose anyone with CF.
  - The information about groups of patients contained on this website should not be used to predict the clinical course of individual patients.
  - This website is not intended to provide medical advice to individual patients.
  - This website is not intended to provide information about pancreatitis, diabetes mellitus, or other diseases associated with CF.
- For more information about CF, click here.

Note: If you have questions about any of the information contained in this website, please consult your doctor.

http://cftr2.org/index.php
Cystic Fibrosis Foundation’s Therapeutics Development Network

- $12.8 M in FY2015
- 82 Research Sites
- 150 Investigators
- 330+ Research Coordinators
- Independent DSMB

TDN Leadership Team
- Mike Boyle, MD
- George Retsch-Bogart, MD
- Chris Goss, MD
- Nicole Hamblett
- Joe Pilewski, MD
- JP Clancy, MD
- Jill Van Dalfsen

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Expanding Clinical Trial Numbers

Number of Trials in TDN

- Studies in Start-Up
- Total Studies

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Percentage of Center Population Newly Enrolled in Interventional Studies By Trial Site (mid-2016)

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Clinical Trial Participation: Education and Facilitation

https://www.cff.org/Trials/finder
### Drug Development Pipeline

#### Restore CFTR Function
- Ivacaftor (Kalydeco®)
- Lumacaftor + Ivacaftor (Orkambi®)
- Ataluren
- Deuterated ivacaftor
- FIL169
- N9111S
- GBW251
- Riociguat
- PTI-428
- QR-010

#### Mucociliary Clearance
- Dornase Alpha (Pulmozyme®)
- Hypertonic Saline
- Inhaled Mannitol
- VX-271 (formerly P-1037)
- Oligo

#### Anti-Inflammatory
- ibuprofen
- CTX-4430
- GS-5745
- JBT-101
- LAU-7b

#### Anti-Infective
- Azithromycin
- Asteosan (Cayston®)
- Inhaled Tobramycin
- Inhaled Levodiloxacin
- Inhaled Liposomal Amikacin
- Tobramycin Inhalation Powder (Inhale™) / Pulmicort®
- Fosfomycin/Tobramycin Inhalation Solution (PTI)
- Vancomycin Inhalation Powder (AeroVanc™)
- Nitric Oxide (Inhaled)

#### Nutritional-GI
- Lipotropase
- Pancrelipase Enzyme Products
- Glutathione

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https://www.cff.org/Trials/pipeline

September 27, 2016
Thank You