Targeting CFTR to Treat Cystic Fibrosis: Small Molecule Therapy

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No disclosures.

Cystic Fibrosis Foundation Patient Registry 2013

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2013</th>
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</thead>
<tbody>
<tr>
<td>Total number of patient in Registry</td>
<td>21,488</td>
<td>28,103</td>
</tr>
<tr>
<td>Adults &gt; 18 years</td>
<td>39.7%</td>
<td>49.7%</td>
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<tr>
<td>Diagnosis by newborn screening</td>
<td>11.7%</td>
<td>62%</td>
</tr>
<tr>
<td>BMI percentile, median, age 2-19 years (50th)</td>
<td>44.1</td>
<td>53.3</td>
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<tr>
<td>BMI, age &gt; 20 years</td>
<td></td>
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<tr>
<td>Goal for men ≥ 23</td>
<td>21.5</td>
<td>22.8</td>
</tr>
<tr>
<td>Goal for women ≥ 22</td>
<td>20.5</td>
<td>21.6</td>
</tr>
<tr>
<td>FEV1, Median percent predicted Children, age 7-17 years, (100%)</td>
<td>85.4%</td>
<td>98%</td>
</tr>
<tr>
<td>FEV1, Median percent predicted Adults, age ≥ 18 years</td>
<td>55.9</td>
<td>66.8</td>
</tr>
</tbody>
</table>

Patient Registry 2013: Annual Report to the Center Directors @ CFF.org

Fundamental Treatment of Cystic Fibrosis: Managing Effects of CFTR Malfunction or Absence

- **Quarterly CF Center Visits**
  - Health assessment and surveillance
  - Education
  - Care coordination
- **Nutrition**
  - Pancreatic Enzyme Replacement Therapy
    - Proprietary formulations
    - Titrated to control steatorrhea (<2500 lipase units/kg/meal)
  - Supplement fat soluble vitamins
  - Daily caloric intake 120-200% of healthy population
- **Airway Clearance**
  - Mechanical therapies
  - Mucolytics
    - Pulmozyme
    - Hypertonic saline
- **Treatment of infection**
  - The CF exacerbation
  - Chronic pseudomonas infection
    - Inhaled tobramycin
    - Inhaled aztreonam
    - Oral antibiotics

Years of life expectancy are added through the consistent application of evidence-based care: nutrition, pulmonary care, special treatments for pseudomonas infected patients.
Cystic Fibrosis Transmembrane Conductance Regulator

Classic Cystic Fibrosis
- Elevated Sweat [Cl] (> 60 mmol/L)
- Chronic Rhinosinusitis
- Pulmonary Disease
- Congenital Bilateral Absence of the Vas Deferens (CBAVD)

Atypical Cystic Fibrosis
- Chronic Rhinosinusitis
- Pulmonary Disease, sometimes less severe
- Pancreatitis, not PI
- Varying sweat [Cl] values
- Congenital Bilateral Absence of the Vas Deferens (CBAVD)

The Basic Defect in Cystic Fibrosis
- No CFTR
  - Class I: no protein synthesis
  - Class II: defective protein
- Too Little CFTR
  - Function
    - Class III: defective channel regulation
    - Class IV: altered conductance
    - Class V: reduced synthesis
    - Class VI: accelerated turnover
Laying the Foundation for New Therapies

- Building a clinical trial network
  - Cystic Fibrosis Foundation Therapeutics Development Network
- Genotyping all patients with cystic fibrosis
  - Mutation Analysis Program
- Attract scientists to cystic fibrosis
  - Grants and conferences
- Partner with industry
  - Venture philanthropy

CFTR Modulation

- Potentiators
  - Make mutant CFTR work more efficiently
    - VX 770: Ivacaftor
- Correctors
  - Help mutant CFTR reach the cell surface
    - VX 809: Lumacaftor
    - VX 661
    - Ataluren: overcome “stop” codons

How does VX 770 (Ivacaftor) work? The drug increases the time that CFTR channels at the cell surface remain open. This permits chloride transfer in and out of the cell to balance the salt and water composition of fluids on epithelial surfaces.
Rescue of G551D CFTR

Long Term Effects of Ivacaftor

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect at 6 months</th>
<th>Absolute change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>Mean, 56 ± 18.8</td>
<td>2.5 (1.9-3.1), p &lt;0.001</td>
</tr>
<tr>
<td>Sweat Chloride</td>
<td>Mean, -49 ± 23.1</td>
<td>-53.8 (-57.7 -- -49.9), p &lt;0.001</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>Mean, 2.7 ± 1.0</td>
<td>+0.3 (0.2-0.3), p &lt;0.001</td>
</tr>
<tr>
<td>Hospitalization (%)</td>
<td>9%</td>
<td>Down from 25%</td>
</tr>
<tr>
<td>Culture P. aeruginosa</td>
<td>35%</td>
<td>Down from 55%</td>
</tr>
<tr>
<td>Duodenal pH</td>
<td>More alkaline</td>
<td></td>
</tr>
<tr>
<td>Sputum microbiome</td>
<td>More diverse</td>
<td></td>
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Rowe, Am J Respiratory Crit Care Med, 190:175-184, 2014
The GOAL Study: Longitudinal cohort study of 151 patients

Ivacaftor is Effective Treatment for 12-14% of Cystic Fibrosis Patients

- Class 3 Mutations
  - Approved for 9 of 10 known gating mutations
- Class 4 Mutations
  - Approved for R117 H
- Class 5 Mutations
  - ‘Trial of one’ data
- Under FDA review for children age 2-6 years.

The Challenge of del508F CFTR

- 50% of CF patients are homozygous for del 508F.
- 40% of CF patients are heterozygote for del 508F.
- Intracellular processing leads to improper folding and degradation
- del508F-CFTR that does reach the cell membrane, exhibits defective gating
- del508F-CFTR has a rapid turnover in the cell membrane.
The Small Molecules

IVACAFTOR

LUMACAFTOR


Lumacaftor/Ivacaftor
del508F/del508F

FDA Review and Approval Process

• FDA decision on Ivcaftor/Lumacaftor combination product due on July 5, 2015.
• FDA Advisory Board, May 12, 2015
• Challenges to approval
  – Effect on FEV1 small
  – Reduced frequency of exacerbations may be primary benefit
  – Patient engagement and perception of benefit
Second Modulator Combination Therapy in Phase 3 Trials
VX 661 + Ivacaftor
VX 661
Works like Lumacaftor
Has a longer half-life
Does not degrade Ivacaftor
Does not cause bronchospasm

Patients with no CFTR to repair.
10% of CF patients have nonsense mutations that do not produce CFTR.
Revisiting Ataluren
How Should Ataluren Work? Why Didn’t It Work?

• The small molecule locks on the ribosome to promote read-through of stop signals on the mRNA. Drug facilitated read-through allows translation of a full length protein.
• Tobramycin had been shown to induce read-through of the stop codon in CF patients with the nonsense mutation, W1282X.
• Tobramycin competes with Ataluren for binding on the ribosome.

Limitation of the Small Molecule Approach to CF

• Increase CFTR activity is relatively modest.
• Established CF morbidities are not reversed.
• Update Cystic Fibrosis chronic care guidelines to include recommendations for Ivacaftor.  
  — Indications are a moving target: Ivacaftor indications have been extended.
• Daily therapy, lifelong is required.
• Therapy is costly.

Other Approaches

• Gene-specific RNA replacement therapy
• Edit CF gene in lung or pancreatic cells
• Deliver new genes to cells
• Create better anti-inflammatory therapy
• Activate other cell surface ion channels to offset effect of CFTR.
Goal for Cystic Fibrosis Care

Continuously refine and replace existing therapies until a safe, effective, permanent cure is available for all individuals with cystic fibrosis.