Roadmap to a Cure: Advancing New CF Treatments

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Roadmap to a Cure:
Advancing New CF Treatments
Mucociliary clearance and obstruction

- CFTR
- Periciliary Liquid (PCL)
- Surface Epithelial Cells
- Tenacious Mucus
- Cytoplasmic CFTR

(normal)

(CF)
CF is Not One Genetic Disorder

**CFTR mutation classes**

- **Normal**
- **Class I synthesis**
- **Class II maturation**
- **Class III regulation**
- **Class IV conductance**
- **Class V quantity**

**‘severe’ mutations**
- pancreatic insufficiency
- decreased survival

**‘mild’ mutations**
- pancreatic sufficiency

So, there must be mutation specific treatment approaches

Reduced Quantity

- Little to no CFTR
- Some CFTR

Reduced Function

- Gating
- Conductance

Normal CFTR quantity and function

Class I
Class II
Class V

Little to no CFTR
Some CFTR

Correctors
Potentiators

Treatment approaches

How Much CFTR is Enough? The Ivacaftor – G551D Benchmark

Adapted from Accurso et al New Engl J Med 2010
Ivacaftor has a profound impact on lung function in patients with G551D (Class III) mutations.

J Davis, AJRCCM, 2012
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203188Orig1s000SumR.pdf.
The ivacaftor effect persists for many months

See: McKone et al. NACFC 2013 Poster #227
Are there other patients with CF who may benefit from ivacaftor monotherapy?

- Other Class III mutations
- Infants and toddlers with G551D
- Mutations, like R117H, that result in residual CFTR function
**Progress Towards Our Goal**

Ivacaftor G551D 4.4%*

95.6% Remaining

*- at some point in their lives (no data in infants and young children)

Cystic Fibrosis Foundation Patient Registry, 2012
CFTR proteins with Class II mutations do not reach the cell surface

Cultured F508del/F508del-human bronchial epithelial cells

Normal CFTR

F508del Class II mutation

Van Goor et al., PNAS 2011
Lumacaftor increases the amount of F508del-CFTR at the cell surface

Cultured F508del/F508del-human bronchial epithelial cells

untreated + lumacaftor

Van Goor et al., PNAS 2011
The function of lumacaftor corrected F508del-CFTR can be further enhanced by a CFTR potentiator.
Phase 2: lumacaftor with and without ivacaftor in F508del homozygotes

Boyle et al. NACFC 2012

Diagram showing the change in FEV₁ from baseline with placebo and active treatment over different study days.
Lumacaftor + ivacaftor Phase 3 studies: VX809-103 & 104, TRAFFIC & TRANSPORT

Randomized, placebo-controlled double-blind Phase 3 studies in F508del homozygotes

TRAFFIC (103)
TRANSPORT (104)

- Lumacaftor 600mg QD + ivacaftor 250mg q12h
- Lumacaftor 400mg q12h + ivacaftor 250mg q12h
- Placebo

Rollover/Extension
Up to 96 Weeks

- Lumacaftor 600mg QD + ivacaftor 250mg q12h
- Lumacaftor 400mg q12h + ivacaftor 250mg q12h

Primary Endpoints:
- Relative change in FEV₁ % predicted through Week 24 compared to placebo

Examples of Key Secondary Endpoints:
- Absolute change in body mass index (BMI) from baseline at Week 24
- Number of pulmonary exacerbations through Week 24
- Safety and tolerability assessments

Study Status: Enrollment is completed

Kindly provided by Vertex Pharmaceuticals, Inc.
CFTR Correctors

- **Good news:** significant progress in patients who have two F508del mutations

- **Ongoing challenges:**
  - Correction is a multi-step process which may require more than one drug
  - If a patient has only one F508del mutation (i.e., F508del heterozygote), the overall clinical response is often reduced.
Strategic planning for back-up correctors began 4 years go

- Reviewed lessons learned from first generation correctors
- Created road map for more robust second generation compounds
- Strong partners in place

- Amazing progress
  - Novel screens developed
  - Up to 6 million compounds will be reviewed
Remaining CFTR Genotypes

- G551D, R117H, F508del: 90.1%
- Remaining: 7.1%
- Nonsense Mutations: 8.8%
- Remaining: 2.8%
Class I Nonsense Mutations

Adapted from Schmitz A, Famulok M. Nature 2007
Inhaled aminoglycosides may affect ataluren response

- Patients NOT receiving inhaled aminoglycosides:
  - Week 48 $\Delta = 5.7\%$
  - $p = 0.008^*$

- Patients receiving inhaled aminoglycosides:
  - Week 48 $\Delta = -1.4\%$
  - $p = 0.43^*$

In 2014, PTC is initiating an ataluren Phase 3 efficacy and safety trial in patients not receiving inhaled aminoglycosides.
Class I (nonsense mutation) next generation possibilities

• Cystic Fibrosis Foundation has initiated new discovery programs with both academic and industry partners

• With support from CFF, University of Alabama and Southern Research Institute, are currently screening approved drugs for read-through activity
100% of patients with CF should have two identified mutations – the Mutation Analysis Program

- Genetic testing is available free of charge to all U.S. patients with CF who do not have 2 identified mutations

- For more information, go to cff.org

http://www.cff.org/LivingWithCF/AssistanceResources/MAP
CFTR2: An Emerging Tool for Diagnosis, Prognosis, and Therapeutics (supported by CFF)

<table>
<thead>
<tr>
<th>CLINICAL FEATURE (RANGE IN INDIVIDUALS WITHOUT CF)</th>
<th>AVERAGE OF ALL PATIENTS WITH MUTATION R117H AND MUTATION F508DEL</th>
<th>AVERAGE OF ALL PATIENTS WITH AT LEAST ONE F508DEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweat Chloride (non-CF is less than 40mEq/L in children and older, less than 30mEq/L in infants)</td>
<td>60</td>
<td>99</td>
</tr>
<tr>
<td>Lung Function expressed as % predicted (non-CF 80%-120% predicted)</td>
<td><img src="image" alt="Lung Function Graph" /></td>
<td><img src="image" alt="Lung Function Graph" /></td>
</tr>
<tr>
<td>Pancreatic Insufficiency (less than 1% of non-CF expected to be PI)</td>
<td>28%</td>
<td>90%</td>
</tr>
<tr>
<td>Pseudomonas (less than 1% of non-CF expected to have Pseudomonas)</td>
<td>25%</td>
<td>54%</td>
</tr>
<tr>
<td>Average Age</td>
<td>22</td>
<td>16</td>
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</tbody>
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http://www.cftr2.org/
Our Goal: develop disease modifying therapies for 100% of patients with CF

• Other non-allele specific therapeutic approaches are being pursued to achieve this goal
  ➢ gene replacement
  ➢ gene repair
  ➢ mRNA replacement
  ➢ protein replacement

• An excellent example: UK Cystic Fibrosis Gene Therapy Consortium
Beyond CFTR: will we still need new therapies to treat symptoms of CF?

- Yes, because CFTR modulators are not expected to reverse existing organ dysfunction (lung, pancreas, liver, GI tract)

- Prevention of organ damage is critical until CFTR modulator therapy is available to 100% of patients in infancy
CFF Pipeline is critical to patients with CF.
Advances in antibiotics to treat *Pseudomonas aeruginosa* (Pa)

- Tobramycin inhalation solution approved
- Aztreonam for inhalation solution approved
- Dry powder tobramycin approved
- Dry powder colistimethate approved (EMA)
- US oral azithromycin study completed

Timeline:
- 1997
- 1999
- 2001
- 2003
- 2005
- 2007
- 2009
- 2011
- 2013

- Phase 3 study of inhaled levofloxacin completed
- Phase 3 multi-cycle study of liposomal amikacin for inhalation (LAI) in 206 patients is ongoing
- Inhaled aztreonam/tobramycin cycling study in process
Studying MRSA Interventions

• Three ongoing trials assessing MRSA treatment strategies

  • ‘Eradication’ of initial MRSA infection (Sponsor: CFFT)
    • STAR-Too study (M. Muhlebach and C. Goss)
    • Testing the efficacy and durability of an oral antibiotic regimen at 14 US sites

  • ‘Eradication’ of established MRSA infection (Sponsor: CFFT)
    • Persistent MRSA Eradication Protocol (E. Dasenbrook and M. Boyle)
    • Testing efficacy of 28 days inhaled vancomycin and oral antibiotics at 2 US sites

• Chronic suppression of established MRSA infection (Sponsor: Savara Corp)
  • Dry powder inhaled vancomycin (AeroVanc)
  • Testing change in sputum MRSA density and lung function
Advances in Anti-Inflammatory Therapies

Adapted from Ziady and Davis. Prog in Resp Res 2006

Konstan and Saiman
NACFC 2009; Plenary Session II
Reducing airway inflammation: the next steps

Points of future emphasis:

• Encourage innovation in this area
  • KB001A – targeting *P aeruginosa* Type III secretion pathway is currently in Phase 2 for CF\(^1\)
  • Alpha-1-antitrypsin development continues

• CFF is initiating a strategic planning process in 2014 to re-evaluate the approach to development of anti-inflammatory therapies

1- Milla et al Pediatr Pulmonol 2013
Thank You

• ...for watching
• Bonnie Ramsey
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• The CF Foundation