Cystic Fibrosis: Progress in Treatment Management

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Medical University of South Carolina
Disclosures

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Mpex Pharmaceuticals, Inc
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Savara Pharma
KaloBios
Cystic Fibrosis Foundation
National Institutes of Health

Consultant
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Vertex Pharmaceuticals, Inc
Novartis
Pharmaxis Limited

Speaker’s Bureau
Genentech
Pathogenesis of CF Lung Disease

Gene mutations → Abnormal CFTR
Pathogenesis of CF Lung Disease

- Gene mutations
- ↓ CFTR quantity
- Abnormal CFTR
- ↓ CFTR function
- Reduced ASL
Pathogenesis of CF Lung Disease

- Gene mutations
  - ↓ CFTR quantity
  - ↓ CFTR function
  - Reduced ASL
  - Impaired MCC

→ Obstruction
Airway Mucous Plugging in Cystic Fibrosis

Used with permission – J. Wagener, 2004.
Pathogenesis of CF Lung Disease

Gene mutations

↓ CFTR quantity
↓ CFTR function

Reduced ASL
Impaired MCC

Obstruction
Infection
Respiratory Infections in CF Patients

Overall Percentage in 2006:

- *P. aeruginosa* 55.0%
- *H. influenza* 16.9%
- *B. cepacia complex* 2.9%
- *S. aureus* 51.5%
- *S. maltophilia* 12.6%
- *MRSA* 18.9%
Pathogenesis of CF Lung Disease

- Gene mutations
  - Decreased CFTR quantity
  - Decreased CFTR function
- Reduced ASL
- Impaired MCC
- Obstruction
- Infection
- Inflammation
Inflammation in Bronchioalveolar Lavage Fluid

Control

Cystic Fibrosis

Used with permission - J. Wagener, 2004.
Pathogenesis of CF Lung Disease

- Gene mutations
  - ↓ CFTR quantity
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- Reduced ASL
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- Inflammation
Pathogenesis of CF Lung Disease

Gene mutations

\[ \downarrow \text{CFTR quantity} \]

\[ \downarrow \text{CFTR function} \]

Reduced ASL

Impaired MCC

Obstruction

Infection

Inflammation

Progressive, irreversible lung damage

Respiratory failure
Chronic Therapies for Maintenance of Lung Health

<table>
<thead>
<tr>
<th>A: Strong Recommendation for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inhaled tobramycin</td>
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</tr>
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<td>• Inhaled β-agonists</td>
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<table>
<thead>
<tr>
<th>D: Recommendation against:</th>
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<tbody>
<tr>
<td>• Oral steroids</td>
</tr>
<tr>
<td>• Age 6-18</td>
</tr>
<tr>
<td>• Inhaled steroids</td>
</tr>
<tr>
<td>• Anti-Staph abx</td>
</tr>
</tbody>
</table>

Insufficient Evidence to make a recommendation:

• Other aerosolized antibiotics
• N-acetyl cysteine
• Cromolyn

• Inhaled anticholinergics
• Leukotriene modifiers
• Oral steroids (age>18)

Flume et al, Am J Respir Crit Care Med 2007; 176: 957–969
### Chronic Therapies for Maintenance of Lung Health

**A** Strong Recommendation for:
- Inhaled tobramycin
- Mod-severe dz
- Inhaled aztreonam
- Mod-severe dz
- Dornase alfa
- Mod-severe dz
- Ivacaftor (G551D)

**B** Recommendation for:
- Inhaled tobramycin
- Mild-asx dz
- Inhaled aztreonam
- Mild-asx dz
- Dornase alfa
- Mild-asx dz
- Hypertonic saline
- Macrolides (with PA)
- Ibuprofen (<18 yrs)

**D** Recommendation against:
- Oral steroids
- Age 6-18
- Inhaled steroids
- Anti-Staph abx

**Insufficient Evidence to make a recommendation:**
- Other aerosolized antibiotics
- Chronic oral anti-Staph
- N-acetyl cysteine
- Cromolyn
- Inhaled β-agonists (chronic)
- Inhaled anticholinergics
- Leukotriene modifiers
- Oral steroids (age>18)
- Macrolides (without PA)

Flume et al, Am J Respir Crit Care Med 2007; 176: 957–969
Challenges in the Treatment of CF Lung Disease

- Gene mutations
  - ↓ CFTR quantity
  - ↓ CFTR function

- Reduced ASL
- Impaired MCC

- Dornase alfa
- Bronchodilators
- Hydrators
- Infection
  - Antibiotics
- Inflammation
  - Ibuprofen, Macrolides

Progressive, irreversible lung damage

Respiratory failure
Challenges in the Treatment of CF Lung Disease

Gene mutations

↓ CFTR quantity
↓ CFTR function

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Bronchodilators
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Hydrators

Infection
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Progressive, irreversible lung damage
Respiratory failure
Challenges in the Treatment of CF Lung Disease

Gene mutations
- CFTR quantity
- CFTR function

Reduced ASL
- Impaired MCC

Progressive, irreversible lung damage
- Respiratory failure

Insert a normal gene
- Fix the CFTR defect

Bypass the function of CFTR

Obstruction
- Hydrators

Infection
- Antibiotics

Inflammation
- Ibuprofen, Macrolides

Dornase alfa
- Bronchodilators
Strategies to Treat Early Aspects of Pathogenesis of CF Lung Disease

• Replace the gene
  – Gene Therapy
Gene Therapy for CF

- UK Cystic Fibrosis Gene Therapy Consortium
- Multi-dose clinical trial of gene therapy
  - 130 patients age ≥ 12 years
- First study to look at a clinical benefit
- Expected completion in 2014

http://www.cfgenetherapy.org.uk/
Strategies to Treat Early Aspects of Pathogenesis of CF Lung Disease

• Replace the gene
  – Gene Therapy

• Bypass the effects of CFTR
  – alternate channels
    • Inhibit sodium absorption (ENaC)
    • Stimulate chloride secretion ($P_2Y_2$, CaCC)
Strategies to Treat Early Aspects of Pathogenesis of CF Lung Disease

• Replace the gene
  – Gene Therapy
• Bypass the effects of CFTR
  – alternate channels
• Correct the CFTR mutation
  – CFTR modulators
Challenges in the Treatment of CF Lung Disease

- Gene mutations
  - ↓ CFTR quantity
  - ↓ CFTR function
- Reduced ASL
- Impaired MCC
- CFTR Potentiators (e.g. ivacaftor)
- Dornase alfa
- Bronchodilators
- Hypertonic saline
- Bronchodilators
- Infection
  - Antibiotics
- Inflammation
  - Ibuprofen, Macrolides
- Progressive, irreversible lung damage
- Respiratory failure

Antibiotics
Hypertonic saline
Ibuprofen,
Ivacaftor in Patients with CF and G551D

Sweat Chloride
Normal: <40 mmol/L
CF: >60 mmol/L

Ramsey et al., NEJM 2011; 365: 1663-1672
Ivacaftor in Patients with CF and G551D

Ramsey et al., NEJM 2011; 365: 1663-1672
CFTR Modulation

- Ivacaftor for G551D
Important Questions

• Would earlier treatment prevent CF lung disease?
What might we expect from earlier treatment with ivacaftor?

**variable** | **CF-PI** | **CFTR-dysfunction**
--- | --- | ---
Age at diagnosis (yrs) | 0.2 | 11.3
Sweat chloride (mean) | 102.0 | 45.7
FEV\(_1\) (mean % pred) | 73% | 89%
*S aureus or P aeruginosa* | 100% | 65%
Clubbing | 71% | 27%

Goubau et al., Thorax 2009; 64: 683-691
Important Questions

• Would earlier treatment prevent CF lung disease?
• Will ivacaftor work for other CFTR gene mutations?
Ivacaftor Potentiation of CFTR Channels with Gating Mutations

What about ivacaftor for other gene mutations?

• Trial of ivacaftor in subjects with CF who have a non-G551D CFTR gating mutation¹

Clinicaltrials.gov: ¹NCT01614470;
CFTR Modulation

- Ivacaftor
  - G551D plus age 2-5 years
  - Other gating mutations
What about ivacaftor for other gene mutations?

- Trial of ivacaftor in subjects with CF who have a non-G551D CFTR gating mutation\(^1\)

- Trial of ivacaftor in subjects with R117H\(^2\)

Clinicaltrials.gov: \(^1\)NCT01614470; \(^2\)NCT01614457
CFTR Modulation

- Ivacaftor
  - G551D plus age 2-5 years
  - Other gating mutations
  - R117H
CFTR Gene mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>N</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔF508</td>
<td>31,073</td>
<td>67.7</td>
</tr>
<tr>
<td>G542X</td>
<td>1,075</td>
<td>2.3</td>
</tr>
<tr>
<td>G551D</td>
<td>987</td>
<td>2.1</td>
</tr>
<tr>
<td>W1282X</td>
<td>610</td>
<td>1.3</td>
</tr>
<tr>
<td>N1303K</td>
<td>593</td>
<td>1.3</td>
</tr>
<tr>
<td>R553X</td>
<td>430</td>
<td>0.9</td>
</tr>
<tr>
<td>Other</td>
<td>7,400</td>
<td>16.1</td>
</tr>
<tr>
<td>Unidentified</td>
<td>3,742</td>
<td>8.2</td>
</tr>
</tbody>
</table>

ΔF508 Mutations (%):
- Homozygous ΔF508: 48.3
- Heterozygous ΔF508: 38.8
- No ΔF508 or both unidentified: 12.9
What about ivacaftor for other gene mutations?

• Trial of ivacaftor in subjects with CF who have a non-G551D CFTR gating mutation¹

• Trial of ivacaftor in subjects with R117H²

• Not effective for dF508³

Clinicaltrials.gov: ¹NCT01614470; ²NCT01614457
³Flume et al., Chest 2012; 142: 718-724
CFTR Mutations and Quantity of CFTR

Challenges in the Treatment of CF Lung Disease

Gene mutations

↓ CFTR quantity

↓ CFTR function

Reduced ASL

Impaired MCC

Hypertonic saline

Dornase alfa
Bronchodilators
Obstruction
Hypertonic saline

Infection
Antibiotics

Inflammation
Ibuprofen, Macrolides

Progressive, irreversible lung damage

Respiratory failure

CFTR Correctors (e.g. VX809, VX661)
CFTR Corrector

Cellular Processing of F508del-CFTR

CFTR-mediated Cl⁻ Flux

Corrector molecules appear to hit an efficacy ceiling at 10-20% correction

Van Goor et al. Pediatr Pulmonol 2009; 44 (S32)
CFTR Corrector Monotherapy

CFTR Corrector + Potentiator

Van Goor et al. Pediatr Pulmonol 2009; 44 (S32)
Clinical Evaluation of Lumacaftor Alone and in Combination with Ivacaftor: Cohort 2 Study Design

**Lumacaftor Monotherapy**

- **F508del homozygotes**
  - n=23
  - Lumacaftor 200 mg qd
- **F508del heterozygotes**
  - n=21
  - Lumacaftor 400 mg qd
- n=21
  - Lumacaftor 600 mg qd

**Lumacaftor and Ivacaftor Combination**

- n=21
  - Lumacaftor 200 mg qd + ivacaftor 250 mg q12h
- n=21
  - Lumacaftor 400 mg qd + ivacaftor 250 mg q12h
- n=21
  - Lumacaftor 600 mg qd + ivacaftor 250 mg q12h

- n=17
  - Lumacaftor 600 mg qd
- n=6
  - Placebo
- n=21
  - Placebo + Placebo

n=number of patients randomized and dosed
Change in absolute FEV$_1$ % predicted in F508del homozygous patients

- **Monotherapy**
  - Placebo
  - VX-809 200mg ± ivacaftor 250mg
  - VX-809 400mg ± ivacaftor 250mg
  - VX-809 600mg ± ivacaftor 250mg

- **Combination**

* P < 0.05 within-group
** P ≤ 0.01 within-group
† P < 0.05 vs placebo
‡ P < 0.01 vs placebo

Boyle M, presented at NACFC 2012
Current Status for CFTR Modulators for dF508

- Phase 3 studies of lumicaftor (VX-809) + ivacaftor in subjects homozygous for dF508\(^1\)
- Phase 2 study of VX-661 +/- ivacaftor in subjects homozygous for dF508\(^2\)
  - Press release April 18, 2013

### Table: Dose of VX-661 vs Placebo

<table>
<thead>
<tr>
<th>Dose of VX-661</th>
<th>n</th>
<th>Absolute change in FEV(_1) (%)</th>
<th>Relative change in FEV(_1) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23</td>
<td>-0.4</td>
<td>0.03</td>
</tr>
<tr>
<td>10 mg</td>
<td>17</td>
<td>2.3</td>
<td>4.1</td>
</tr>
<tr>
<td>30 mg</td>
<td>17</td>
<td>3.4</td>
<td>5.4</td>
</tr>
<tr>
<td>100 mg</td>
<td>15</td>
<td>4.8*</td>
<td>9.0*</td>
</tr>
<tr>
<td>150 mg</td>
<td>16</td>
<td>4.5*</td>
<td>7.5**</td>
</tr>
</tbody>
</table>

*\(p=0.01\); **\(p=0.02\)
CFTR Modulation

- Ivacaftor
  - G551D plus age 2-5 years
  - Other gating mutations
  - R117H
- Homozygous dF508
CFTR Modulation

- Ivacaftor
  - G551D plus age 2-5 years
  - Other gating mutations
  - R117H
- Homozygous dF508
- Heterozygous dF508
Strategic Initiative for Next Generation Discovery

- **Vertex**
  - Combinatorial approach for synergy
- **Genzyme**
  - Mechanistic CFTR-target based approach
- **Pfizer**
  - Mechanistic and cell based, combinational therapy
- **Proteostasis**
  - CFTR interactome and folding environment
- **Reata**
  - Cell based NBD stabilization
- **McGill/Glaxo Smith Kline**
  - CFTR surface expression, mechanistic target based
What else is in the pipeline?
Challenges in the Treatment of CF Lung Disease

- Gene mutations
  - CFTR quantity
  - CFTR function
- Reduced ASL
- Impaired MCC
- Progressive, irreversible lung damage
- Respiratory failure

Gene Therapy
- CFTR Potentiators (e.g., ivacaftor)
- CFTR Correctors (e.g., VX809, VX661)

Hypertonic saline
- Mannitol

Infection
- Antibiotics
- Dornase alfa
- Bronchodilators
- Hypertonic saline
- Mannitol

Inflammation
- Ibuprofen, Macrolides

Obstruction
Inhaled Mannitol in CF

Challenges in the Treatment of CF Lung Disease

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- Hypertonic saline
  - Mannitol
- Dornase alfa
- Bronchodilators
- Obstruction
- Hypertonic saline
  - Mannitol
- More antibiotic choices
  - Change treatment strategy
- Infection
  - Antibiotics
  - Ibuprofen, Macrolides
- Inflammation
- Progressive, irreversible lung damage
- Respiratory failure

CFTR Correctors (e.g. VX809, VX661)
CFTR Potentiators (e.g. ivacaftor)
Gene Therapy
Mannitol
# Inhaled antibiotics targeting *Pseudomonas*

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>FDA Approved</th>
<th>Used Off-Label</th>
</tr>
</thead>
</table>
| Aminoglycosides  | TIS (TOBI<sup>®</sup>)  
Bethkis TIP (Powder) | Gentamicin |
| Beta-lactams     | AIS (Cayston<sup>®</sup>) | Ceftazidime |
| Fluoroquinolones | | |
| Polymyxins       | | Colistimethate |
What questions remain?

- Do we need more antibiotic choices for *Pseudomonas*?
- Do we have the optimal regimen?
- Should we exercise the same strategy for other pathogens?
# Inhaled antibiotics targeting *Pseudomonas*

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>FDA Approved</th>
<th>In Development</th>
<th>Used Off-Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>TIS (TOBI®)</td>
<td>Liposomal amikacin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td></td>
<td>Bethkis Bramitob</td>
<td></td>
<td></td>
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<tr>
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<td>Levofloxacin aerosol</td>
<td>Liposomal ciprofloxacin Ciprofloxacin powder</td>
<td></td>
</tr>
<tr>
<td>Polymyxins</td>
<td></td>
<td></td>
<td>Colistimethate</td>
</tr>
</tbody>
</table>
Dosing regimens

standard of care

intermittent monotherapy

continuous combination therapy

continuous monotherapy

Time (weeks)

0 4 8 12 16 20 24

A A A A A A

B B B B B B
Assessing combination inhaled antibiotic therapy by randomized controlled trial

US standard of care

TIS  Placebo  TIS  Placebo  TIS  Placebo
0  4  8  12  16  20  24

TIS  AIS  TIS  AIS  TIS  AIS
0  4  8  12  16  20  24

clinicaltrials.gov identifier: NCT01641822
# Inhaled antibiotics in CF

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Prophylaxis</th>
<th>Eradication</th>
<th>Suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
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Respiratory Infections in CF Patients

Cystic Fibrosis Foundation Patient Registry. 2006 Annual Data Report. Bethesda, MD.
Inhaled antibiotics targeting *Staphylococcus aureus*

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<th>FDA Approved</th>
<th>In Development</th>
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<tr>
<td>Glycopeptides</td>
<td></td>
<td>Vancomycin powder</td>
<td>Vancomycin IV solution</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Phase 2)</td>
<td></td>
</tr>
</tbody>
</table>

Clinicaltrials.gov identifier: NCT01746095
Inflammation in Bronchioalveolor Lavage Fluid

Control

Cystic Fibrosis

Used with permission - J. Wagener, 2004.
Inflammation in CF Airways

• Inflammation in the airways is exaggerated
• Neutrophil is the predominant WBC
• Inflammation:
  – Causes injury to the airways (neutrophil elastase)
  – Recruits more inflammatory cells to the airways
Approach to Reducing Injury from Inflammation in CF Airways

• Inhibit neutrophil migration to the airways
  – SB-656933\textsuperscript{1}

• Inhibit neutrophil elastase
  – Augmentation of alpha-1-antitrypsin\textsuperscript{2}

\textsuperscript{1} Clinicaltrials.gov: NCT00903201; J Cyst Fibr 2013; 12: 241-248
\textsuperscript{2} Clinicaltrials.gov NCT01531673
Challenges in the Treatment of CF Lung Disease

- Gene mutations
  - Reduced ASL
  - Impaired MCC

- CFTR quantity
- CFTR function

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Gene Therapy

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- Bronchodilators
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- Mannitol

- More antibiotic choices
- Change treatment strategy

- Infection
  - Antibiotics
  - Ibuprofen, Macrolides

- Obstruction
- Inflammation
- Alpha-1-antitrypsin
- Anti-Pseudomonas Ab
KB001-A renders PA non-toxic by binding to the PcrV protein on the tip of the TTSS on the surface of PA and therefore prevents PA from attacking host cells through its primary toxic mechanisms.

Clinicaltrials.gov identifier: NCT01695343
Conclusions

• We have made tremendous progress in the treatment of CF patients
  – Survival has improved
  – Yet, patients still die too young

• We need new medications
  – Recent developments offer huge potential
  – True example of personalized medicine
CFTR Modulation - this is the goal

- Ivacaftor
  - G551D plus age 2-5 years
  - Other gating mutations
  - R117H
- Homozygous dF508
- Heterozygous dF508
- Nonsense mutations
- Others
Conclusions

• But until that goal is reached:
  – We need to use current medications more effectively
    • Comparative effectiveness
      – Assess treatment regimens (e.g. strategy of inhaled antibiotics)
      – Personalize patient’s treatment regimen
    • Focus on adherence
      – Appreciate the treatment burden