Treating CF at the Source
Drugs that work on CFTR

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CF Education Day
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Targeting Primary Defects vs Secondary Pathophysiologies in CF Lung Disease

Primary Defects

- CFTR gene mutation
  - Gene therapy
  - Ivacaftor, VX-809, VX-661, Ataluren

Defective ion and fluid transport
  - Cl-/Na+ channel modulators

Defective CFTR protein

Secondary Pathophysiologies

- Infection
  - Anti-infectives

- Impaired mucociliary clearance
  - Mucolytic Treatment
  - Bronchiectasis, lung function loss

- Obstruction
  - Bronchodilators

- Inflammation
  - Anti-inflammatories

- Lung Transplant

Based on Amaral, et al. TIBS 2007
The steps from CF gene to CFTR protein

- **CF gene (chromosome #7)**
  - Codes for...
- **CFTR (cystic fibrosis transmembrane conductance regulator)**
  - Membrane protein that regulates salt transport
Phenotype Effects of Classes of CFTR Mutations

Normal

Class I

Class II

Class III

Class IV

Class V

I, II, III ("severe")

- Pancreatic Insufficiency
- Risk of:
  - Meconium ileus, DIOS
  - CFRD
  - Severe hepatobiliary disease

IV, V ("mild")

- Pancreatic Sufficiency
- Risk of:
  - Acute, recurrent pancreatitis
  - Chronic pancreatitis
What is a CFTR modulator, and why is it different from other CF therapies?

• Modulator – targets underlying defects in CFTR
  – Restore function (not replace)
• Addresses primary cause of CF
  – Not downstream symptoms
• Different defects – different targets – different strategies
  – Generally based on CF mutation class
Phenotype Effects of Classes of CFTR Mutations

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Ribosomal Translation of mRNA to Protein

Normal Translation

Ribosomes

Amino acid

mRNA

Normal Termination Codon

STOP

Full-length Protein
Effect of Stop Mutation

Premature Termination

Nonsense (Premature Termination) Codon

Normal Termination Codon

mRNA

Truncated Protein
Read-Through of CFTR Stop Mutations (Class I) with PTC124
PTC124-Mediated Increases in Epithelial Cell-Surface CFTR

Pre-treatment (Day 0)

End of PTC124 10-, 10-, 20-mg/kg Dose Level (Day 45)

Full-length Apical CFTR
Evidence of CFTR Abnormality: Nasal Potential Difference (NPD)

CF patients have:

- Higher basal NPD
- Greater decline in NPD after amiloride perfusion
- Lack of response to Cl⁻ free perfusion and isoproterenol
PTC124 (Ataluren) Improved NPD Chloride Secretion

Wilschanski M et al, Eur Respir J 2011;38:59-69
PTC 124 Increased Lung Function and Decreased Cough Frequency

Improved

* Paired t-test versus Day 1

Wilschanski M et al, Eur Respir J 2011;38:59-69
Phenotype Effects of Classes of CFTR Mutations

Normal

Class I
- Reduced Synthesis/Trafficking
- Increased Degradation
- Defective Regulation
- Abnormal Conductance
- Reduced Synthesis/Trafficking

Class II
- Abnormal Conductance

Class III
- Defective CFTR Channel

Class IV
- Correct Splicing
- Correct Splicing

Class V
- Correct Splicing
- Correct Splicing

I, II, III ("severe")
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Adapted from Hospital Practice, 1997
Potentiators Increase Gating of CFTR

- G551D is the most prevalent mutation with gating defect (~5%)
- VX-770 shown active both in vitro and in patients with G551D
VX-770 Restores Gating of G551D CFTR In Vitro

Ussing chamber studies using G551D/ΔF508-HBE

EC\textsubscript{50} = 240 nM

Single channel patch clamp studies in Fisher Rat Thyroid cells expressing G551D CFTR

Average data from 16 replicates

Change in Sweat Chloride after VX-770

**Part 1: 14-Day**

Mean Change from Baseline

![Graph showing sweat chloride levels for Placebo, 25mg VX-770, 75mg VX-770, and 150mg VX-770 over baseline at Day 7 and Day 14.]

- **Placebo**: Baseline to Day 7: -32.9 \( ^\ast \) *p ≤ 0.0001*, Day 14: -42.3 \( ^\ast \) *p ≤ 0.0001*
- **25mg VX-770**: Baseline to Day 7: -40.4 \( ^\ast \) *p ≤ 0.0001*, Day 14: -52.6 \( ^\ast \) *p ≤ 0.0001*
- **75mg VX-770**: Baseline to Day 7: -52.3 \( ^\ast \) *p ≤ 0.0001*, Day 14: -52.3 \( ^\ast \) *p ≤ 0.0001*
- **150mg VX-770**: Baseline to Day 7: -40.4 \( ^\ast \) *p ≤ 0.0001*, Day 14: -52.6 \( ^\ast \) *p ≤ 0.0001*

**Part 2: 28-Day**

Mean Change from Baseline

![Graph showing sweat chloride levels for Placebo, 150mg VX-770, and 250mg VX-770 over baseline at Day 3, Day 14, Day 21, and Day 28.]

- **Placebo**: Baseline to Day 3: -2.3 \( ^\dagger \) *p < 0.01*, Day 14: -4.8 \( ^\dagger \) *p < 0.01*, Day 21: -5.2 \( ^\dagger \) *p < 0.05*, Day 28: -5.2 \( ^\dagger \) *p < 0.05*
- **150mg VX-770**: Baseline to Day 3: -27.6 \( ^\dagger \) *p < 0.01*, Day 14: -32.4 \( ^\dagger \) *p < 0.01*, Day 21: -32.4 \( ^\dagger \) *p < 0.01*, Day 28: -32.4 \( ^\dagger \) *p < 0.01*
- **250mg VX-770**: Baseline to Day 3: -52.6 \( ^\dagger \) *p < 0.05*, Day 14: -52.8 \( ^\dagger \) *p < 0.05*, Day 21: -52.8 \( ^\dagger \) *p < 0.05*, Day 28: -52.8 \( ^\dagger \) *p < 0.05*

\( ^\ast \) *p ≤ 0.0001 within subject comparison

\( ^\dagger \) *p < 0.05 within subject comparison

Change in CFTR-Mediated Chloride Transport after VX-770

**NPD: Zero Chloride/Isoproterenol Response**

**Part 1: 14-Day**

<table>
<thead>
<tr>
<th>Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

* p < 0.005 (75mg) within subject comparison
† p < 0.010 (150mg) within subject comparison

**Part 2: 28-Day**

<table>
<thead>
<tr>
<th>Mean Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>-8.4 ‡</td>
</tr>
</tbody>
</table>

‡ p < 0.05 within subject comparison

Percent Change in FEV₁ from Baseline after VX-770

**Part 1: 14-Day**

% Change from Baseline in FEV₁

<table>
<thead>
<tr>
<th>14 day</th>
<th>Placebo</th>
<th>25mg VX-770</th>
<th>75mg VX-770</th>
<th>150mg VX-770</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Percent Change from Baseline [95% CI]</td>
<td>10.5 ‡</td>
<td>10.0 *</td>
<td>4.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Part 2: 28-Day**

% Change from Baseline in FEV₁

<table>
<thead>
<tr>
<th>Day 3</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>150mg VX-770</td>
<td>250mg VX-770</td>
<td></td>
</tr>
<tr>
<td>Mean Percent Change from Baseline [SD]</td>
<td>11.6 †</td>
<td>7.4 ‡</td>
<td>7.0</td>
</tr>
</tbody>
</table>

* \( p = 0.002 \) within subject comparison
‡ \( p = 0.008 \) within subject comparison
† \( p < 0.01 \) within subject comparison
‡ \( p < 0.05 \) within subject comparison

Changes from Baseline in Percent of Predicted FEV₁, Respiratory Symptoms, and Weight, and Time to the First Pulmonary Exacerbation, According to Study Group.

Changes from Baseline through Week 48 in Sweat Chloride, According to Study Group.

'Discover': 24-week randomized, double-blind, placebo-controlled trial; children 6-11 years old with at least one copy of G551D, (N = 52)

Primary endpoint:

• Ivacaftor was associated with improved lung function; relative improvement from baseline for FEV1 relative to the placebo group was 17.4% (p<0.0001)

Secondary endpoints:

• Those in the treated group through week 24 saw a drop of sweat chloride levels to 60 mmol/L from a base of 104 mmol/L; a significant drop was not observed in the placebo group
• Those in the treated group gained 3.7kg through 24 weeks compared to the placebo group that gained 1.8kg
Phenotype Effects of Classes of CFTR Mutations

I, II, III ("severe")
- Pancreatic Insufficiency
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Cystic Fibrosis Transmembrane Regulator (CFTR) Protein

- ~90% of CF individuals have at least one F508del allele
- F508del-CFTR has a protein-folding defect that
  - Inhibits intracellular trafficking
  - Enhances CFTR protein degradation
- Little to no functional F508del-CFTR reaches the cell surface

CFF Patient Registry 2008 (US)
BIOLOGY OF ΔF508 CFTR

normal

CF

Cl⁻

CFTR

Cl⁻

Golgi

ER

degrade

75%

degrade

99%

CFTR
A model for CFTR maturation and the influence of suppressor mutations in NBD1 and TMD2.

Effect of ΔF508 CFTR on ‘Destiny’

- ΔF508 CFTR – most common cause of CF
  - 80-90% of CF patients, 65-70% of CF chromosomes
  - Protein misfolding in the endoplasmic reticulum
    - Protein marked for degradation
    - Failure to ‘mature’ and reach plasma membrane

CFTR Correctors

CFTR correctors aim to increase the delivery and amount of functional CFTR protein to the cell surface, resulting in improved ion transport.

VX-809 resulted from a high-throughput screening and medicinal chemistry optimization program to generate F508del-CFTR corrector compounds.
VX-809 Improved F508del-CFTR Maturation and Cl\(^{-}\) Secretion *In Vitro*

**CFTR Maturation**
Western blot showing B- to C-band conversion with cultured human bronchial epithelia (HBE) from F508del homozygous CF donors

**Cl\(^{-}\) Secretion**
Ussing chamber studies with HBE from F508del homozygous CF donors (n=7)

CFTR-mediated Cl⁻ Transport:
Sweat Cl⁻ biomarker

Change from baseline in average sweat Cl⁻

Clancy JP et al, Thorax 2012;67:12-8
CFTR-mediated Cl⁻ Transport: Sweat Cl⁻ biomarker

Change from baseline at Day 28 – difference vs placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in Cl⁻ (mmol/L) (mean [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>VX-809 25 mg</td>
<td>+0.10 (n=16)</td>
</tr>
<tr>
<td>VX-809 50 mg</td>
<td>- 4.61 (n=16)</td>
</tr>
<tr>
<td>VX-809 100 mg</td>
<td>- 6.13* (n=15)</td>
</tr>
<tr>
<td>VX-809 200 mg</td>
<td>- 8.21† (n=16)</td>
</tr>
</tbody>
</table>

* P<0.05 vs placebo and within-subject
† P<0.01 vs placebo and within-subject
Linear trend test for dose-response: P=0.0013

Change in sweat chloride (mmol/L) (mean [95% CI])

<table>
<thead>
<tr>
<th>VX-809</th>
<th>25 mg</th>
<th>50 mg</th>
<th>100 mg</th>
<th>200 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0 (n=17)</td>
<td>0 (n=15)</td>
<td>1 (6%) (n=16)</td>
<td></td>
</tr>
<tr>
<td>Responder 20,* n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Responder 10,† n (%)</td>
<td>0</td>
<td>6 (40%)‡</td>
<td>6 (38%)‡</td>
<td></td>
</tr>
</tbody>
</table>

*≥20 mmol/L reduction vs baseline; †≥10 mmol/L reduction vs baseline; ‡P=0.02 vs placebo

Clancy JP et al, Thorax 2012;67:12-8
Combination Corrector-Potentiation Therapy: VX809-770 Program

**CORRECTOR:** Increases cell surface density and function of F508del-CFTR

**POTENTIATOR:** Increases channel opening of cell surface F508del-CFTR

Cells from one homozygous F508del donor tissue
### VX809-Ivacaftor Combination Trial

**Part 1 Sweat Chloride Results**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Within-Group Mean Change in Sweat Chloride From Baselines (Day 0 and Day 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 (n=20): VX-809 (200mg); VX-809 (200 mg) in combination with KALYDECO (150 mg)</td>
<td>Day 0 – 14: VX-809 Alone -2.24 mmol/L (p=0.163)</td>
</tr>
<tr>
<td>Arm 2 (n=21): VX-809 (200mg); VX-809 (200 mg) in combination with KALYDECO (250 mg)</td>
<td>Day 14 – 21: VX-809 in Combination with KALYDECO -9.10 mmol/L (p&lt;0.001)</td>
</tr>
<tr>
<td>Arm 3 (n=21): VX-809 placebo; VX-809 placebo in combination with KALYDECO placebo</td>
<td>-2.86 mmol/L (p=0.179)</td>
</tr>
</tbody>
</table>

8/17 Arm 2 patients had sweat Cl⁻ reduction >15 (4 of these >20)

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Vertex Press Release, 11/3/11