Potentiators and Correctors for the Treatment of Rare Diseases: Therapeutic Use of Ivacaftor in Cystic Fibrosis

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### Disclosures

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Cystic Fibrosis

- CFTR = cystic fibrosis transmembrane conductance regulator

- CFTR doesn’t work → cystic fibrosis
  - Genetic, 1:3,000 births
  - Autosomal recessive
  - Lungs, GI tract, pancreas, liver, vas deferens, sweat gland
  - 2,000+ mutations
  - Median predicted survival = 41 yrs
CFTR to CF – numerous targets

Loss of CFTR
Cl⁻ HCO₃⁻ Na⁺

CFTR modulators
Gene transfer
Gene/RNA editing

Hydrators
Mucolytics

Antimicrobials

Airway infection
Persistent inflammation
Thick mucus
Airway damage

Anti-inflammatories
Evidence-based medicine success

(2013 CFF Annual Report)
Current challenges

- Enzymes
- Vitamins
- Azithromycin
- High-calorie meals and snacks
- School/work
- Sports/play
- Homework
- Social life/friends
- Family time
- Rest
- Chest PT
- Modulators
- Nebulized antibiotics
- Albuterol
- rhDNase
Cystic fibrosis and CFTR

- Traffic ATPase
- Two transmembrane domains (TMDs)
- Two nucleotide binding domains (NBDs)
- One Regulatory domain (R domain)
- Anion channel
  - Cl-
  - HCO$_3$-
  - SCN-, GSH, others?

• How can we modulate CFTR?
  
  – Number of channels at the plasma membrane (N)
  
  – How much time each channel spends open vs closed (Po)
  
  – The size of each chloride channel (G)

\[(N \times Po \times G) = \text{total Cl- transport}\]
### Breakdown of CFTR mutations (>2000…)

**Gene transfer**
- DNA/RNA editing

**Suppressor:**
-_potentiator?

**Classes:**
1. **Class 1** biosynthesis
2. **Class 2** folding
3. **Class 3** gating
4. **Class 4** conductance
5. **Class 5** levels

**States:**
- **Closed**
- **Pore size**
- **Reduced amount at membrane**
What are CFTR modulators?

- Potentiator – improves gating (Po)
- Corrector – improves trafficking (N)

Spielberg DR and Clancy JP – Cystic fibrosis and its management through established and emerging therapies
*Ann Rev Genomics* (2016)
Summary of genotype groupings

- **F508del Homozygotes**: ~50% (12,944 in US)
- **F508del Heterozygotes**: ~40% (11,213 in US)
- **gating/R117H**: ~7%
- **other**: ~5%
Potentiating G551D CFTR (VX-770)

- 3rd most common disease-causing mutation (4%)
  - Higher in Ireland (5-10%)
  - Problem with open channel probability (gating)

- Strategy – increase Po
- Development
  - HTS
  - human AECs

• Airway surface liquid volume
  – Reduced ~50% in CF
  – Improved with VX-770

• Ciliary beat frequency (CBF)
  – Normalized with VX-770

Ivacaftor for gating mutations

G551D patients: STRIVE results: N=161 (>12 yr); FEV\textsubscript{1} = 63.6%; RDBPC

Ivacaftor: 48 weeks
Safety and efficacy

Placebo

FEV\textsubscript{1}

A new ‘benchmark’

Ivacaftor in young children

- Children age 6-11 yrs with G551D CFTR mutation (mean age 8.9 yr)
- 150 mg every 12 hr vs placebo

52 subjects (26 each group – 4 plac. withdrew)
- FEV$_1$ % predicted increase 12.5% (p<0.001)
- Weight +2.8 kg (p<0.001)
- SC -53.5 mM (p<0.001)
- Similar AEs

Davies, JC et al. Efficacy and safety of ivacaftor in patients 6 to 11 years with cystic fibrosis with a G551D mutation
Ivacaftor in very young children

- Children age 2-5 yrs with gating mutations (KIWI)
- Weight based dosing (50 mg or 75 mg every 12 hrs, 14 kg cutoff)

**Part A**
4 days
Short term safety

**Part B**
24 weeks
Longer term pharmacodynamics

9 subjects
34 subjects

- 33 completed study
- Similar exposure vs adults
- Common AEs: cough (56%), vomiting (29%)
- LFTs: 15% with 8 X ULN, 4 with study drug interrupted, 1 discontinued study drug
- Reduced SC (-46.9 mM), BMI Z score (+0.4) – p<0.001

Ivacaftor in non-G551D gating mutations (KONNECTION)

- Patients > age 6 yrs (mean age 22.8 yr)
- 150 mg every 12 hr vs placebo in eight week crossover trial

39 subjects
- FEV₁ % predicted increase 10.7% (p<0.001)
- BMI +0.7 kg/m² (p<0.001)
- SC -49.2 mM (p<0.001)
- CFQ-R +9.6 (p<0.001)
- Similar AEs

CFTR and R117H

- Age > 6 yrs with R117H mutation (KONDUCT)
- Partial function, gating AND conduction defects

Ivacaftor: 24 weeks
Safety and efficacy

Placebo

69 subjects
- Abs. increase FEV1 % pred = 2.1% (p=0.20)
- Rel. increase FEV1 % pred = 5.0% (p=0.06)
- CFQ-R increase = +12.6 (p=0.002)
- Sig. reduction in SC

- >18 yrs (n=50)
  - Abs. FEV1 % pred = +5.0% (p=0.01)
  - Rel. FEV1 % pred = +9.1% (p<0.01)

Class 3 and 4
Gating and conductance
Barack Obama State of the Union Address (January 20, 2015):

“I want the country that eliminated polio and mapped the human genome to lead a new era of medicine: **one that delivers the right treatment at the right time.**”

“In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable.
• 85% CF patients have one copy
• 50% have two

Correcting F508del CFTR – it’s complicated

- Two problems identified that contribute to folding defect
  - Co-translational folding of NBD-1
  - Domain assembly (NBD-1 and ICL4 interactions)

...And gating defect when at the plasma membrane
Correcting F508del CFTR (AECs) with VX-809

• **Strategy**
  – Increase N

• **TOP (VX-809):**
  – Dose/response of F508 correction
    • (C Band, current)
  – ~15% of non-CF

• **BOTTOM:**
  – VX-809 c/w other correctors

Correcting AND Potentiating F508del CFTR

- Lumacaftor + Ivacaftor

- Complex problems
  - N AND Po

- Two Phase II studies
  - Safety, dose-ranging, PK and PD

- RDBPC trial (24 week) 1122 F508del/F508del randomized
- Lumacaftor (2 doses) + ivacaftor vs placebo
- FEV\textsubscript{1} improvement (p<0.001); APEx improvement (p<0.001)
Summary: genotype-based coverage

- F508del Homozygotes ~50.0%
- F508del Heterozygotes ~40%
- Gating/R117H 7%
- Remaining ~5%
• Evidence based medicine has steadily advanced CF outcomes
  – Escalating burden of care

• HTS can successfully identify CFTR modulators

• CFTR is a valid target
  – Gating mutations
  – F508del CFTR

• Emergence of CFTR modulators offers potential to transform CF care and outcomes
Thanks to:

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