New Cystic Fibrosis Therapies

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Cystic Fibrosis

• Genetic condition – 1/3,500 births; 35,000 individuals in US
• Progressive lung disease

Median FEV$_1$ Percent Predicted vs. Age by Birth Cohort

Figure 49

FEV$_1$ is steadily improving and stays above 90 percent predicted into adolescence.

*Patient Registry, Cystic Fibrosis Foundation, Bethesda MD*
Cystic Fibrosis: Survival

- Median Predicted Survival – 37 years
- Median Age at Death – 26 years

*Patient Registry, Cystic Fibrosis Foundation, Bethesda MD*
CFTR

• CF gene encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein
  – CFTR functions as an ion channel and controls the movement of salt and water into and out of cells
  – Mutations in the CF gene impairs this movement, critically altering host defense in the lung
Molecular Consequences of CFTR Mutations

Cystic Fibrosis Mutation Database (Tsui, Zielenski)
http://www.genet.sickkids.on.ca/cftr/
Healthy Cell

Animation courtesy of the U.S. Cystic Fibrosis Foundation
Cell with CF

Animation courtesy of the U.S. Cystic Fibrosis Foundation
Summary: 663delT is seen in 9 patients in our worldwide CF database. Based on the combination of clinical and functional evaluation, this is a mutation that would cause CF. Based on the patients we have reviewed we would expect this mutation would be associated with pancreatic insufficient CF.

The information displayed below shows how we came to this decision.

- Clinical Characteristics
- Mutation Characteristics
- Functional Testing
- Literature Review
- Population Screening
- Bioinformatics Assessment

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A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation

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ABSTRACT

BACKGROUND
Increasing the activity of defective cystic fibrosis transmembrane conductance regulator (CFTR) protein is a potential treatment for cystic fibrosis.

METHODS
We conducted a randomized, double-blind, placebo-controlled trial to evaluate ivacaftor (VX-770), a CFTR potentiator, in subjects 12 years of age or older with cystic fibrosis and at least one G551D-CFTR mutation. Subjects were randomly assigned to receive 150 mg of ivacaftor every 12 hours (84 subjects, of whom 83 received at least one dose) or placebo (83, of whom 78 received at least one dose) for 48 weeks. The primary end point was the estimated mean change from baseline through week 24 in the percent of predicted forced expiratory volume in 1 second (FEV₁).

RESULTS
The change from baseline through week 24 in the percent of predicted FEV₁ was greater in the ivacaftor group than in the placebo group (P = 0.006).

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Potentiator

- Some CFTR proteins make it to the cell surface but do not allow chloride to pass through properly – Gating Mutations
- Potentiators bind to the CFTR located at the cell surface and allows chloride to move out of the cell.
Change from Baseline in Sweat Chloride

Phase 3 Trial  (Ramsey et al, NEJM, 2011)
Absolute Change in FEV₁ % Predicted

- Placebo
- VX-770

Treatment effect through Week 24:
+ 10.6 %
P < 0.0001

Treatment effect through Week 48:
+ 10.5 %
P < 0.0001

Phase 3 Trial (Ramsey et al, NEJM,

Slide courtesy of F. Accurso
Ivacaftor Potentiation in Gating Mutations

(Yu et al., 2012)
Ivacaftor (FDA approval 1/31/2012)

- First in Class (CFTR Modulators)
- No animal studies except toxicity
- CFTR Mutations
  - Only G551D (4%)… for now
  - Ultimately, 20% CFTR 2 program
- Treat “cellular phenotype” not by targeting biochemical abnormality (Swinney et al 2011)
- Molecular Mechanism of Action is incompletely understood
- Infection not considered as an outcome measure
- Currently approximately 1,000 patients under treatment
Corrector

- Normal CFTR proteins make their way to the cell surface and transport chloride ions. In most people with CF, the CFTR protein never makes it to the cell membrane.
- Correctors - drug that binds to the CFTR protein, allowing the protein to reach the cell surface.

Animation courtesy of the U.S. Cystic Fibrosis Foundation
STICKER SHOCK
Insurers, providers push back on high-priced specialty drugs
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Ivacaftor Cost –
Rare Disease Drug Development

• $294,000 per year.
• Comparable to some other drugs
• Resources for families
  • CFF patient assistance
  • Vertex patient assistance fund
  • No insurance – no cost to family
  • Insurance – help with copay
  • CFF legal assistance
New Cystic Fibrosis Therapies May Change the Trajectory

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Figure 49

FEV$_1$ is steadily improving and stays above 90 percent predicted into adolescence.
Conclusion

• Ivacaftor is changing the course of cystic fibrosis in a portion of CF patients

• Other compounds are being tested that are targeted at more common mutations (F508) that may cover >90% of CF patients

• Early introduction of potentiators and correctors following newborn screening may prevent early lung disease and could make CF a chronic disease controlled by a pill
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