Poster 56

Precision Medicine in Cystic Fibrosis

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BACKGROUND

- Cystic fibrosis (CF) is a rare, life-limiting genetic disease that affects ≈75,000 people worldwide[1,2]
- Although clinical manifestations occur throughout the body, today, ineluctable progressive lung disease is the main cause of death
- CF is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel that result from mutations in the *CFTR* gene[3]
  - Of the ≈2000 *CFTR* gene mutations identified to date, more than 250 are known to cause CF[4]
  - *F508del*, the most common mutation in CF, is present on 1 or both *CFTR* alleles in 90% of people with CF[5,6]
- Normally, CFTR is located at the epithelial cell surface, where it regulates chloride ion and fluid transport and pH balance
- *CFTR* gene mutations can reduce the function and/or amount of CFTR at the cell surface
- The first medicines developed to treat the underlying causes of CF are CFTR potentiators that work by improving CFTR channel function and correctors that work by increasing the number of CFTR channels[7,8]
  - Kalydeco™ (ivacaftor) was approved by the US FDA for the treatment of patients aged 2 years and older with select gating mutations
  - Orkambi™ (ivacaftor and lumacaftor) was approved by the US FDA for the treatment of patients aged 12 years and older homozygous for the *F508del* mutation

OBJECTIVE

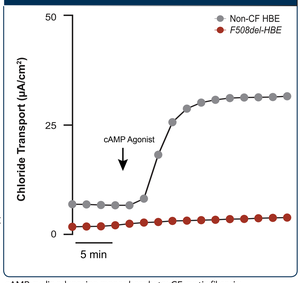
- The preclinical and clinical development of ivacaftor and lumacaftor/ivacaftor has significantly advanced the biology of disease modification in CF by targeting the underlying cause of CF in a significant proportion of patients, including those who are homozygous for the *F508del* mutation
- Here we discuss unmet needs in CF therapy and progress in the evolving field of precision medicine

METHODS

In Vitro Models Have Been Used to Identify Populations Likely to Respond to CFTR Potentiators and Correctors

- Human bronchial epithelial (HBE) cells derived from the bronchi of people with CF
  - Provide different genotypes
  - Allow for multiple donors to assess donor-to-donor variability
  - Provide in vitro efficacy targets based on natural history studies
- Fischer rat thyroid cell lines, each expressing a single mutant CFTR form
  - More than 100 mutant CFTR forms have been profiled, including those that cause defects in protein quantity and function
  - Allow characterization of single mutant CFTR forms, but, unlike primary cells, only 1 mutation is present
- Other potential sources of tissues include gut organoids from people with CF; these would facilitate greater access to rare genotypes
- Ussing chambers are used to measure chloride transport across HBE cell monolayers[9,10] (**Figure 1**)

Figure 1. Chloride Transport Over Time Measured in Ussing Chamber Assays



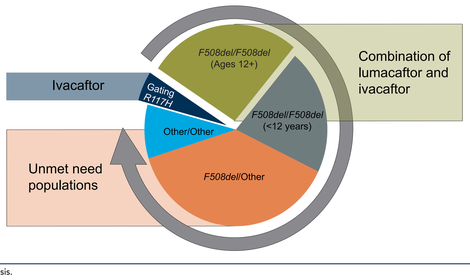
cAMP, cyclic adenosine monophosphate; CF, cystic fibrosis; HBE, human bronchial epithelial.

RESULTS

New Treatment Approaches Are Needed to Address the Variety of CF Mutations

- Clinical trials and real-world data have generated a body of evidence regarding the effects of CFTR potentiators and correctors on CF disease progression[11-13]
  - To date, the focus of these studies has been patients with CF and gating mutations, residual function mutations, and patients with CF homozygous for the *F508del* mutation
  - However, research efforts are being expanded to develop therapeutic approaches for all patients with CF (**Figure 2**)

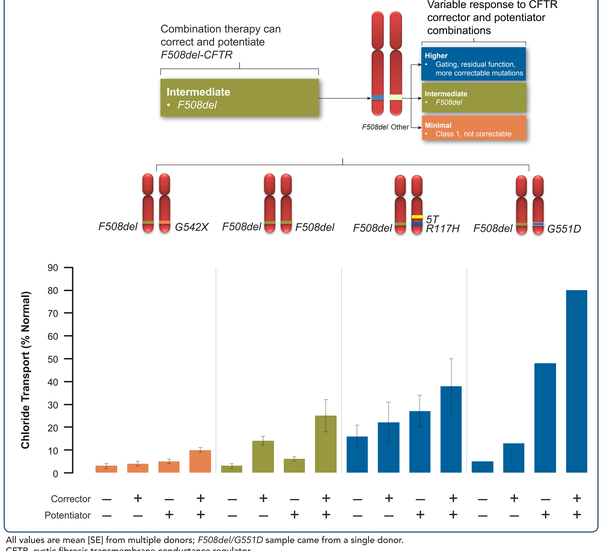
Figure 2. Treatment Options Available for Patients With CF Based on *CFTR* Mutation Type on Each Allele and Age



CF, cystic fibrosis.

CFTR Corrector and Potentiator Combinations Have the Potential to Address Both Mutant *CFTR* Alleles (Figures 3,4)

Figure 3. Corrector Plus Potentiator Combination Therapy Was Better at Increasing Chloride Transport When Compared With Either Alone in Multiple Genotypes



All values are mean [SE] from multiple donors; *F508del/G551D* sample came from a single donor.
CFTR, cystic fibrosis transmembrane conductance regulator.

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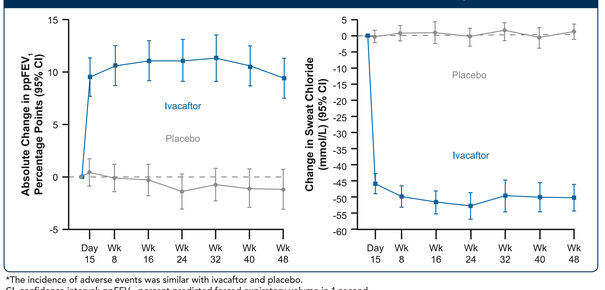
Figure 4. In Vitro Data Translate into Clinical Benefit: Efficacy With Ivacaftor Has Been Demonstrated in Clinical Trials – Improvements in Lung Function (FEV_1) and Sweat Chloride Levels in a Placebo-Controlled Phase 3 Study*

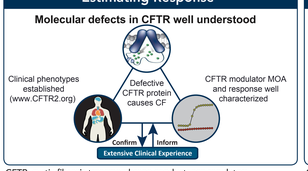


*The incidence of adverse events was similar with ivacaftor and placebo.
CI, confidence interval; $ppFEV_1$, percent predicted forced expiratory volume in 1 second.
Ramsey BW, et al. *N Engl J Med.* 2011;365:1663-72.

Research Needs to Move Beyond Treating Individual Molecular Defects Toward Identifying Responsive CF Genotypes

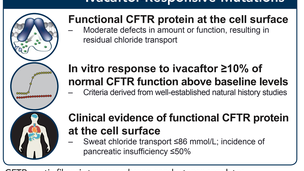
- Targeting a molecular defect alone worked well for ivacaftor and CFTR gating mutations due to
  - A single CFTR defect directly targeted by CFTR potentiator activity
  - A relatively homogeneous clinical phenotype and disease progression dynamic
- On the other hand, the heterogeneity of phenotypes across many mutant *CFTR* forms requires a framework for identifying responsive mutations
- Framework for precision medicine (**Figure 5**): evaluating the potential responsiveness of CFTR mutations based on extensive clinical knowledge of established phenotypes, associated molecular defects in CFTR, and response to available therapies, such as ivacaftor (**Figures 6,7**)

Figure 5. Framework for Precision Medicine: Multifactorial Approach to Estimating Response



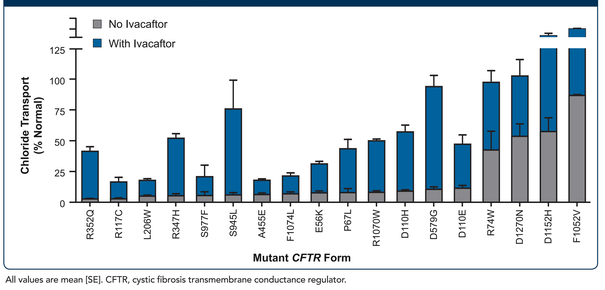
CFTR, cystic fibrosis transmembrane conductance regulator; MOA, mechanism of action.

Figure 6. Precision Medicine With Ivacaftor: Characteristics of Ivacaftor-Responsive Mutations



CFTR, cystic fibrosis transmembrane conductance regulator.

Figure 7. Chloride Transport in *CFTR* Mutations Associated With Residual CFTR Function Suggests Responsiveness to Ivacaftor In Vitro

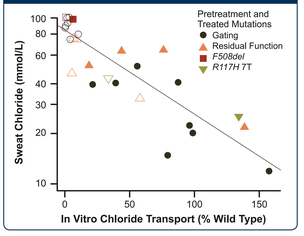


All values are mean [SE]. CFTR, cystic fibrosis transmembrane conductance regulator.

Research Is Needed to Understand the Complexity of Factors Contributing to Clinical Outcomes With Mixed Genotypes

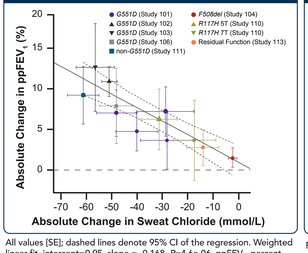
- The goal of CF treatment is to improve clinical symptoms, including but not limited to symptoms of lung disease, by modulating the function or amount of CFTR. Sweat chloride has become an established pharmacodynamic marker for measuring CFTR function with treatment (**Figure 8**)
- Percent predicted forced expiratory volume in 1 second ($ppFEV_1$) is a standard measure of lung function
- But the relationship between sweat chloride and $ppFEV_1$ appears to be complicated by multiple factors (**Figures 9,10**)
- A wide variety of factors play a role in lung function changes with treatment, including:
  - Variable type and severity of defect
  - Onset of disease in different organs
  - History of pulmonary disease
  - Time of intervention
  - Treatment durations
  - Modifier genes
  - Drug exposure (parent, active metabolites)

Figure 8. In Vitro Chloride Transport Correlates With In Vivo Sweat Chloride Levels



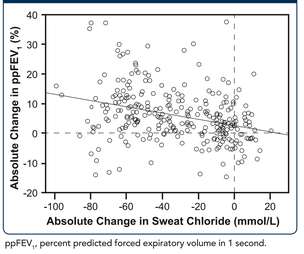
Open symbols denote pretreatment, filled symbols denote treated. Slope = -0.012, P=6.83e-06. CFTR, cystic fibrosis transmembrane conductance regulator.

Figure 9. Population-Based Analyses Across Genotypes Indicates a Relationship Between Improvements in Sweat Chloride and $ppFEV_1$ With Treatment



All values [SE]; dashed lines denote 95% CI of the regression. Weighted linear fit, intercept=0.95, slope = -0.168, P=4.6e-06. $ppFEV_1$, percent predicted forced expiratory volume in 1 second.

Figure 10. At the Individual Patient Level, On-Treatment Change in Sweat Chloride Is Poorly Predictive of Change in $ppFEV_1$



$ppFEV_1$, percent predicted forced expiratory volume in 1 second.

CONCLUSIONS

- There is a clear scientific framework for treating underlying causes of CF using a combination of CFTR correctors and potentiators that maximizes the function of CFTR from 1 or both alleles; to date this approach has led to successful development of new medicines for patients with *CFTR* gating mutations and who are homozygous for the *F508del* mutation
- A combination of molecular, clinical, and pharmacological approaches may be used to identify mutations responsive to CFTR potentiator and corrector combinations in people without the *F508del* mutation

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AUTHOR DISCLOSURES

FVG, **JS**, **AC**, and **JS** are employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in that company.

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