A Cure for All: Leaving No One Behind

Assuring Effective Therapies for All Patients with Cystic Fibrosis
Topics for Today’s Presentation

• Demographics of the CF patient population in the modulator era

• Symptomatic therapy as a priority for the near and long-term

• Gene editing and other approaches to a “one-time” cystic fibrosis cure
Current US CF genotypes with approved CFTR modulators

- Lumacaftor + Ivacaftor (46.5%)
  - F508del/F508del
- Ivacaftor (12.3%)
  - R117H
  - Other gating
  - G551D
  - More genotypes
- Single F508del allele (36.2%)
- Untreated Genotypes (5.0%)
- 13,000 patients

Cystic Fibrosis Foundation Patient Registry, 2014
Today, the available corrector for F508del variants (lumacaftor + ivacaftor) is not as effective at restoring CFTR activity as ivacaftor is for gating mutations. Next-generation F508del correctors promise to be more effective.
# Modulator pipeline is diversified and very robust

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<th>R&amp;D Stage</th>
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<td>lumacaftor (VX-809)</td>
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<td>Available to Patients</td>
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Several programs specifically targeting premature truncation or “X” mutations

Developing drugs that read through the nonsense mutation to generate functional CFTR protein

- PTC Therapeutics - Ataluren - Primarily a read-through agent
  - Initial trial indicated interference with tobramycin
  - Second trial now concluding, data expected early 2017
- Southern Research Institute/University of Alabama, Birmingham
  - Pilot program 2014 identified several promising compounds
  - Initiated new high throughput screening program in 2015
- CFFT laboratory (Lexington, MA)
  - Major expansion in 2015 to accommodate new initiatives
  - Nonsense mutations, gene editing, stem cell biology are priorities
  - Approximately 50% of effort is directed towards X-variant therapy
- Numerous other pharmaceutical and academic groups
Compounds under development that overcome premature truncation defects

lumacaftor + CFFT-573:

DMSO  G418 (50 μM)  G418 (100 μM)  gentamicin  CFFT-017697

Y122X  150 kD

Na/K-ATPase

Nikole Jordan, Feng Liang/CFFT Laboratory
Achieving modulator-type treatments for every patient with CF

• Over 1,700 variants are associated with disease – the complexity and challenge of theratyping is significant
• Features of the challenge that work to our advantage:
  – Laser focus on getting an effective therapy to every patient
  – International consortia with personalized therapeutics as a mission priority
  – Approved modulators with activity against numerous distinct variants that otherwise would not be expected
  – Variants that share common features with each other – so that a single drug may have broad impact
  – New endpoints being developed that may indicate benefit for ultra-rare gene defects
Changing demographics of our CF patient population

• As *more* CF genotypes are treated...
  with *better* modulators...
  at *younger* ages...

  ...the health of the CF population will shift dramatically

• A smaller proportion of *individuals* will have need for ‘downstream’ therapies
  – But there will still be a need for these therapies
Anticipated changes in population size, health, and treatments
(Respiratory therapies will still be imperative in the future)

**Today**
- Symptomatic therapies: 96%
- Modulators: 52%
- 48% symptomatic therapies
- 48% modulators
- 4%

**5 Years**
- Symptomatic therapies: 52%
- Modulators: 30%
- 40% symptomatic therapies
- 30% modulators
- 5%

**10 Years**
- Symptomatic therapies: 46%
- Modulators: 49%
- 46% symptomatic therapies
- 49% modulators

*US population projection, 85% followed in CFFPR; CFF Patient Registry Team*
There is a vital need to develop additional respiratory treatments that help CF patients irrespective of genotype – both now and in the future.
Topics for Today’s Presentation

• Demographics of the CF patient population in the modulator era

• Symptomatic therapy as a priority for the near- and long-term

• Gene editing and other approaches to a “one-time” cystic fibrosis cure
CF respiratory disease pathways

- Mutant CFTR
  - Abnormal secretion
  - Defective mucociliary clearance
  - Infection
  - Obstruction
  - Inflammation
  - Altered inflammatory response
Therapies that treat the primary defect

- CFTR<sup>mut</sup> modulation
- gene repair

mutant CFTR

- abnormal secretion
- defective mucociliary clearance
- infection
- obstruction
- inflammation
- altered inflammatory response
Therapies that treat downstream effects

- CFTR\textsuperscript{mut} modulation
- gene repair

mutant CFTR

- abnormal secretion
- defective mucociliary clearance

- infection
- obstruction

- inflammation
- altered inflammatory response
Targeting mucociliary clearance

- Mutant CFTR
- Altered inflammatory response
- Inflammation
- Obstruction
- Infection
- Defective mucociliary clearance
- Abnormal secretion

- Mucolytics
- Hydrators
- ENaC inhibitors
Mucus fails to clear from the trachea in newborn CF pigs

David Stoltz, Mark Hoegger, Mike Welsh
Mucin profiling of airway epithelial secretion

Mucin composition analysis

MUC5AC (green)
MUC5B (red)

Surface epithelium
SMG duct
Submucosal gland
Nuclei (blue)

Lynda Ostedgaard, James McMenimen, Mike Welsh
Lynda Ostedgaard, James McMenimen, Mike Welsh
Mucociliary Clearance- and Airway Surface Liquid-focused programs
A Robust Pipeline with Available Agents and New Compounds under Clinical Development

Clinical
- Hypertonic saline – available to patients
- Pulmozyme – available to patients
- Algipharma (OligoG) – Phase 2
- Novartis (ENaC inhibition) – Phase 2
- Parion/Vertex (VX-371) – Phase 2
- Pharmaxis (mannitol) – Phase 3
- Protalix (DNase) – Phase 1
- Spyryx (SPX-101) – Phase 1

Preclinical
- University of Iowa (THAM)
- Ionis (ENaC inhibition)
- OrPro (recombinant thioredoxin)
- Silurian (brevenal)
- Synedgen (SYGN113)
Targeting infection

- mutant CFTR
- antimicrobials
- infection
- altered inflammatory response
- inflammation
- obstruction
- defective mucociliary clearance
- abnormal secretion
Expanding the CF antimicrobial armamentarium

• Additional inhaled antimicrobials
  – Inhaled fosfomycin/tobramycin (FTI)
    • Preparing for Phase 3 (CURx)
  – Dry-powder vancomycin for chronic MRSA
    • Preparing for Phase 3 (Savara)
  – Inhaled levofloxacin (approved in Canada and EU)
    • Preparing NDA (Raptor)
  – Alaxia (nebulized OSCN/lactoferrin)
    • For *Burkholderia* spp. Eradication (Alaxia)

• Systemic antimicrobials
  – Gallium (IGNITE study)
    • Phase 2 IV trial is now enrolling

Also includes other programs targeting multi-drug resistant *Pseudomonas*, non-tuberculous mycobacteria, *B. cepacia* complex and MRSA.
Ivacaftor markedly reduces sputum *P. aeruginosa* count
- Patients remain infected; bacterial burden may increase after 12 months of treatment

Further emphasizes that a robust pipeline to address infection and inflammation will be needed in the post-corrector/potentiator era

P. Singh, K. Hisert, E. McKone
Could Ga be effective against *P. aeruginosa* infections?

A Trojan Horse strategy

- Iron (Fe) is essential for bacterial growth and biofilm formation
- Gallium (Ga) is iron-like but non-functional:
  - Ionic radius similar to Fe
  - Cannot undergo oxidation-reduction reactions vital to Fe biological activity
- Ga is FDA approved, already used clinically
Gallium treatment of *P. aeruginosa* infection

Single dose IP Ga also prevented death, even given 12 h after infection

10^6 bacteria, followed by Ga in lung

Mice surviving

0% 20% 40% 60% 80% 100%

0 12 24 36 48 60 72

Time after infection (hours)

Vehicle (no gallium)

Ga was safe and showed an efficacy signal in CF patients

Mean FEV_1 Change from Baseline (liters with 95% CI)

0 0.1 0.2 0.3

0 7 14 21 28

Study Day

100 mg/m^2 gallium per day (N = 9)

200 mg/m^2 gallium per day (N = 11)

P. Singh

C. Goss, D. Hornick, N. Lechtzin, P. Singh
Targeting inflammation

mutant CFTR

- altered inflammatory response
- infection
- obstruction
- inflammation

- abnormal secretion
- defective mucociliary clearance

anti-inflammatories
A simplified map of CF airway inflammation

Mike Boyle
Emerging CF anti-inflammatory treatments

• Celtaxsys CTX-4430
  – Oral inhibitor of Leukotriene A4 Hydrolase (LTA4H)
  – Reduces neutrophil infiltration and neutrophil elastase

• Corbus JBT-101
  – Novel mechanism: cannabinoid type 2 receptor (CB2) agonist
  – Reduces pro-inflammatory mediators and induces anti-inflammatory cytokines

• Laurent LAU-7B
  – Oral corrector of AA/DHA imbalance
  – Reduces inflammatory fatty acid imbalance described for CF

• Gilead GS-5745
  – MMP-9 antibody
  – Binds pro-inflammatory mediator present in CF sputum and lung

• Polyphor POL-6014
  – Potent inhaled human neutrophil elastase (HNE) inhibitor
Development of new CF anti-inflammatory therapies may require a different clinical trial paradigm

• Agents that arrest lung function decline may not cause immediate sustained *improvement* in FEV$_1$ or exacerbation rate
  – Prior experience suggests longer (6-12 month) studies may be needed to observe clinical benefit
    – Torphy 2015, Chmiel 2015
  – A better understanding of the predictive relationships among inflammatory biomarkers (such as sputum elastase) to clinical outcomes (such as FEV$_1$) may be essential

• The threshold for anti-inflammatory intervention should be approached carefully, since excessive blunting of inflammation could also impair clearance of bacteria

Leading-edge drug development resources produce results

- Increasingly representative animal models
- Research consortia
- Modulators that overcome the basic defect
- Therapeutic Development Network
- CF Patient Registry
- CFTR2 database
- Many others

Gastroenterology & Hepatology Workshop Session I (this morning)
- Improved pulmonary outcomes

CF Gastroenterology Comes of Age: Best Practices & DIGEST Symposium Session II (10:30-11:55 tomorrow)

Nutrition-focused Physical Assessment Brown Bag Luncheon (12:15-1:35 tomorrow)

Endocrine Workshop Session II (2:00-3:20 tomorrow)

Nutrition Research Workshop Session II (2:00-3:20 tomorrow)

Update on Enteral Feeding & Colorectal Cancer Screening Guidelines Symposium Session II (2:30-3:55 Saturday)

- CF related diabetes
- CF liver disease
- Pancreatic insufficiency
- Nutritional interventions
- Etc.
The Future
NEXT EXIT
What the future holds

mutant CFTR

- CFTR\textsuperscript{mut} modulation
- gene repair

- ASL depletion
- defective mucociliary clearance
- altered inflammatory response
- infection
- obstruction
- inflammation
Wrigley Field
Home of
Chicago Cubs

Cubs Win!!!