Personalized Medicine in Cystic Fibrosis: The Newest Therapies

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DISCLOSURES

• I participate as a clinical research site for the Cystic Fibrosis Foundation’s Therapeutic Development Network

• I am a participating site on various Vertex Pharmaceuticals, Inc. clinical trials
Objectives

• Describe personalized and precise care
• Understand the genetics and pathophysiology of CF
• Become familiar with the newest treatments used in CF
• Recognize some of the techniques to personalize care
Why Should I Care?

• This approach is applicable to any disease—single gene or multifactorial

• The techniques described here are widely applicable

• The CF Foundation has invested in this approach and is leading the field in personalized and precise care
Personalized vs. Precise

Personal (Personalize)
To design or tailor to meet an individual's specifications, needs, or preferences

Precise (Precision)
- Accuracy
- exactness

• We currently practice medicine in a personalized way
• We now have information and emerging tools to do this in a precise fashion
Personalizing therapy – A common part of CF culture

- Culture-based treatment of pulmonary infections
- PERT, vitamins and nutritional supplements
- Insulin: growth, glucose intolerance and CFRD
- Choice of ACT, antibiotics, duration
New Ideas of Personalizing

Therapies based on mutation, responses or neither
- Genotype
- Theratype
- Genotype agnostic

Bringing personalized concepts to CF
- Personalized model systems
- Disease monitoring
- In the clinic and at home
Genetics

- Autosomal recessive inheritance
- Chromosome 7
- Codes for CFTR, a chloride channel
- Over 1700 known mutations of the gene
- F508del accounts for over 70% of the mutations
- Five classes of mutations: 1--protein production, 2--defective processing, 3--defective regulation, 4--defective conduction, 5--reduced CFTR production
Basic Defect

non-CF

Mucus Flow

(-)

Na⁺ Cl⁻ H₂O

CF

Mucostasis

Na⁺ H₂O Cl⁻
Pathophysiology

CFTR Gene Defect

Defective Ion Transport

Airway surface liquid depletion

Defective mucociliary clearance

Mucus obstruction

Inflammation

Infection
5 Classes of CFTR Mutations

I. Defective Production
II. Defective Processing
III. Defective Regulation
IV. Defective Conductance
V. Reduced Amounts
Summary of genotype groupings

- **F508del Homozygotes**: ~50% (12,944 in US)
- **F508del Heterozygotes**: ~40% (11,213 in US)
- **gating/R117H**: ~7%
- Other: ~5%
CFTR to CF – numerous targets

Loss of CFTR
- Cl-, HCO3-, Na+

CFTR modulators
Gene transfer
Gene/RNA editing

Hydrators
Mucolytics

Antimicrobials

Thick mucus
Airway infection
Persistent inflammation
Airway damage
Anti-inflammatories
Evidence-based medicine success

Median Predicted Survival Age, 1986–2014 (In 5-Year Increments)

- 1986-90
- 1987-91
- 1988-92
- 1989-93
- 1990-94
- 1991-95
- 1992-96
- 1993-97
- 1994-98
- 1995-99
- 1996-00
- 1997-01
- 1998-02
- 1999-03
- 2000-01
- 2001-02
- 2002-03
- 2003-04
- 2004-05
- 2005-06
- 2006-07
- 2007-08
- 2008-09
- 2009-10
- 2010-11
- 2011-12
- 2012-13
- 2013-14

- PERT
- dornase alpha
- IBU
- AZM
- Inhaled Abx
- 7% HS
- CFTR
Targeting the Genetic Defect

- Gene therapy
- CFTR modulation
  - Potentiator
  - Inhibitor of proteostasis
  - Corrector
  - Stop codon read-through drug
- Gene editing
- RNA repair
  - mRNA modulation
  - Correction of mRNA translation to protein

Gene Therapy Summary

| 1. | Only 1 year after the cloning of CFTR was published, Drumm et al. [8] established proof of principle that retrovirus-mediated gene transfer of CFTR can correct cAMP-mediated chloride conductance in vitro |
| 2. | 3 years after cloning of CFTR, Rosenfeld et al. [9] provided evidence of successful CFTR mRNA and protein expression after adenovirus-mediated CFTR cDNA transfer into cotton rats |
| 3. | 4 years after cloning of CFTR, Hyde et al. [10] showed that nonviral CFTR cDNA transfer was able to partially correct the chloride transport in tracheal epithelium of CF knockout mice |
| 4. | In the same year, Zabner et al. [11] performed the first, albeit small and not placebo-controlled, CF gene therapy trial in three patients. A first-generation adenoviral vector carrying the CFTR cDNA was administered to the nasal epithelium and shown to partially restore cAMP-mediated chloride transport |
| 5. | 5 years after cloning of CFTR, Crystal et al. [12] performed the first phase one dose-escalation CF gene therapy study. This was first and foremost a safety study and showed transient inflammatory responses at the highest dose (5 × 1e9 plaque forming units per patient) |
| 6. | 6 years after cloning of CFTR, Caplen et al. [13] provided first evidence that a nonviral gene transfer agent (DC-Chol:DOPE) complexed with CFTR cDNA could partially correct cAMP-mediated chloride transport in the nasal epithelium of CF patients |
| 7. | 10 years after cloning of CFTR, Alton et al. [14] demonstrated that a nonviral gene transfer agent (GL67A) complexed with a plasmid DNA carrying the CFTR cDNA could partially correct cAMP-mediated chloride transport in the lungs of CF patients |
| 8. | 26 years after cloning of CFTR, Alton et al. [15] demonstrated that repeated administration of GL67A complexed with a plasmid DNA carrying the CFTR cDNA significantly, albeit modestly, stabilized lung function in CF patients |

Griesenbach, Uta; Davies, Jane; Alton, Eric
DOI: 10.1097/MCP.0000000000000327

Table 1 Gene therapy milestone studies in the first decade after cloning the cystic fibrosis transmembrane conductance regulator gene

cAMP, cyclic AMP; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DC-Chol, 3beta-[N-(N’N’-dimethylaminoethane) carbamoyl] cholesterol; DOPE, dioleoylphosphatidylethanolamine.
Gene Therapy with Non-Viral Vector GL67A

Griesenbach, Uta; Davies, Jane; Alton, Eric
DOI: 10.1097/MCP.0000000000000327

FIGURE 1. Stabilization of lung function after repeated administration of the nonviral formulation pGM169/GL67A. Cystic fibrosis patients were treated monthly for 12 months with either active drug or the placebo. Lung function (FEV1) was measured at each treatment visit before administration of study drugs. Data are expressed as relative change from baseline in percentage predicted FEV1. Error bars show the SEM. (a) All patients. There was a significant, albeit modest, treatment effect in the pGM169/GL67A group versus placebo at 12-month follow-up (3.7%, P = 0.046). (b) Patients with more severe lung function at start of treatment (baseline FEV1 = 50-70%). (c) Patients with less severe lung function at start of treatment (baseline FEV1 = 70-90%). FEV1, forced expiratory volume in 1 s. Adapted with permission from [24] as part of a CCBY license.

Study parameters
- FEV1 = 50-90%
- N=62 placebo; n=78 drug
- Monthly treatment

Outcomes
- FEV1 (+3.7%, p=0.046)
- Other biomarkers
- PD s
FIGURE 2. Generation of F/HN-pseudotyped lentiviral vector. The gp120 protein on the lentivirus envelope glycoprotein was replaced with F and HN proteins from the Sendai virus. F, fusion; HN, hemagglutinin-neuraminidase. Adapted with permission from [17].
Lentiviral Vector Expression in Mice

FIGURE 3. Fusion/hemagglutinin-neuraminidase-pseudotyped lentivirus transduction leads to persistent gene expression in mouse airways. Mice were transduced with fusion/hemagglutinin-neuraminidase-pseudotyped lentivirus expressing a luciferase reporter gene by nasal sniffing (or received PBS (negative controls)). Luciferase expression was visualized using bioluminescence imaging, 2-22 months after transduction.
### CF Mutation Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Impact on CFTR</th>
<th>Mutation Example</th>
<th>Potential Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No functional CFTR created</td>
<td>G542X, W1282X</td>
<td>Gene therapy, RNA correction, Read-through drug</td>
</tr>
<tr>
<td>II</td>
<td>Processing defect</td>
<td>Phe508del</td>
<td>Corrector + Potentiator</td>
</tr>
<tr>
<td>III</td>
<td>Regulation defect</td>
<td>G551D</td>
<td>Potentiator</td>
</tr>
<tr>
<td>IV</td>
<td>Decreased conductance</td>
<td>R117H</td>
<td>Potentiator</td>
</tr>
<tr>
<td>V</td>
<td>Reduced synthesis of CFTR</td>
<td>3849+10kbC→T A455E</td>
<td>Corrector, Potentiator</td>
</tr>
<tr>
<td>VI</td>
<td>Altered channel stability</td>
<td>4326delTC</td>
<td>Potentiator, Proteostasis inhibitor</td>
</tr>
</tbody>
</table>

## CFTR Modulators

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Mechanism of Action</th>
<th>Phase III</th>
<th>Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor</td>
<td>Potentiator</td>
<td>Increases channel opening</td>
<td></td>
<td>★</td>
</tr>
<tr>
<td>Ataluren</td>
<td>Read-through</td>
<td>Enables the formation of a functioning protein</td>
<td></td>
<td>★</td>
</tr>
<tr>
<td>Lumacaftor</td>
<td>Corrector</td>
<td>Moves defective CFTR protein to proper place in cell membrane and improves its function as a chloride channel</td>
<td></td>
<td>Lumacaftor + Ivacaftor</td>
</tr>
<tr>
<td>VX 661</td>
<td>Corrector</td>
<td>-</td>
<td></td>
<td>VX 661 + Ivacaftor</td>
</tr>
</tbody>
</table>

Ivacaftor

• Mechanism of action
  – Increases the time that activated CFTR channels at the cell surface remain open, thereby restoring CFTR function

• Approved for use
Ivacaftor

• Study results ($P < 0.05$)
  – Improved pulmonary function and reduced rate of pulmonary exacerbations$^{1,2}$
  – Less frequent infection with *Pseudomonas*$^3$
  – Improved glucose tolerance, sustained weight gain, and better growth in children$^4$
  – Benefit is seen across age and disease severity groups and is sustained after prolonged use

Ivacaftor for gating mutations

Ivacaftor

G551D patients: STRIVE results: N=161 (>12 yr); FEV₁ = 63.6%; RDBPC

Additional ivacaftor successes

- KONNECTION
  - Non-G551D Gating Mutations (8)
  - Different study design, similar FEV1 results
- KIWI
  - Gating mutations in children 2-5 yrs (9)
  - Potential impact on pancreatic function
  - LFTs, cataracts monitoring
- KONDUCT
  - R117H CFTR
  - Variable efficacy based on age, T status

http://www.vrtx.com/releasesArchive.cfm
Modulating F508del CFTR

Correcting F508del

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


(Courtesy of CFF and M Mall)
Lumacaftor / Ivacaftor

• Mechanism of action
  – Lumacaftor (corrector) moves CFTR to the cell surface where ivacaftor (potentiator) can boost the protein’s function
  – In other words, a two-step process is employed: (1) correction of cellular misprocessing to increase the amount of functional CFTR, then (2) potentiation to further increase channel opening
Lumacaftor / Ivacaftor

• Approved for use
  – Patients ≥ 12 years old with two copies of Phe508del (46.4% of patients with CF are homozygous for this genetic mutation)

• Study results ($P < 0.05$)
  – Improved pulmonary function
  – Reduced rate of pulmonary exacerbations
  – Weight gain

TRAFFIC and TRANSPORT

- RDBPC trial (24 week) 1122 F508del/F508del randomized
- \( \text{FEV}_1 \) improvement \((p<0.001)\); APEx improvement \((p<0.001)\)

Development of Co-therapies

VX-661 phase 3 program (Vertex)

- F508/F508
- F508/gating
- F508/function
- F508/nonfunction

Ivacaftor/VX-661

Different designs, common co-therapy

www.clinicaltrials.gov
Modulator pipeline is diversified and very robust

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Drug Name</th>
<th>Class</th>
<th>R&amp;D Stage</th>
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<tbody>
<tr>
<td>Genzyme</td>
<td></td>
<td>2nd gen corrector</td>
<td>Discovery</td>
</tr>
<tr>
<td>Reata</td>
<td></td>
<td>2nd gen corrector</td>
<td>Discovery</td>
</tr>
<tr>
<td>Parion</td>
<td></td>
<td>2nd gen corrector</td>
<td>Discovery</td>
</tr>
<tr>
<td>Flatley</td>
<td>FDL176</td>
<td>potentiator</td>
<td>Pre-Clinical</td>
</tr>
<tr>
<td>Pfizer</td>
<td></td>
<td>potentiator</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Pfizer</td>
<td></td>
<td>corrector</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Proteostasis</td>
<td>PTI-428</td>
<td>amplifier</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Galapagos-Abbvie</td>
<td>GLPG2451</td>
<td>potentiator</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Galapagos-Abbvie</td>
<td>GLPG2222</td>
<td>corrector</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Galapagos-Abbvie</td>
<td>GLPG2665</td>
<td>corrector</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Novartis</td>
<td>QBW267 corrector</td>
<td>potentiator</td>
<td>Ph 1</td>
</tr>
<tr>
<td>Concert Pharma</td>
<td>CTP-656</td>
<td>potentiator</td>
<td>Ph 2</td>
</tr>
<tr>
<td>Bayer</td>
<td>BAY 63-2521</td>
<td>corrector</td>
<td>Ph 2</td>
</tr>
<tr>
<td>Flatley</td>
<td>FDL169</td>
<td>1st gen corrector</td>
<td>Ph 2</td>
</tr>
<tr>
<td>Nivalis</td>
<td>N91115</td>
<td>GSNOR inhibitor</td>
<td>Ph 2</td>
</tr>
<tr>
<td>Vertex</td>
<td>VX-152</td>
<td>2nd gen corrector</td>
<td>Ph 2</td>
</tr>
<tr>
<td>Galapagos-Abbvie</td>
<td>GLPG1837</td>
<td>corrector</td>
<td>Ph 2</td>
</tr>
<tr>
<td>Vertex</td>
<td>VX-440</td>
<td>2nd gen corrector</td>
<td>Ph 2</td>
</tr>
<tr>
<td>Vertex</td>
<td>VX-661</td>
<td>1st gen corrector</td>
<td>Ph 3</td>
</tr>
<tr>
<td>Vertex</td>
<td>ivacaftor (VX-770)</td>
<td>potentiator</td>
<td>Available to Patients</td>
</tr>
<tr>
<td>Vertex</td>
<td>lumacaftor (VX-809)</td>
<td>1st gen corrector</td>
<td>Available to Patients</td>
</tr>
</tbody>
</table>
Emerging (next-generation) F508del corrector molecules

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.
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
Ataluren

• Mechanism of action
  – Premature stop codon suppressor that enables the formation of a functioning protein in patients with nonsense genetic mutations

• Study results \((P < 0.05)\)
  – Improved pulmonary function in subpopulation of patients not taking TSI

• Ongoing research
  – Chronic use of TSI is not permitted by participants

Compounds under development that overcome premature truncation defects

lumacaftor + CFFT-573:
- DMSO
- G418 (50 μM)
- G418 (100 μM)
- gentamicin
- CFFT-017697

Nikole Jordan, Feng Liang/CFFT Laboratory
Current challenges

Does one size fit all?

- Modulators
- Azithromycin
- Vitamins
- Enzymes
- High-calorie meals and snacks
- School/work
- Sports/play
- Homework
- Social life/friends
- Family time
- Rest
- Chest PT
- Nebulized antibiotics
- Albuterol
- rhDNAse
- Hypertonic saline
- Does one size fit all?
What Else Can We Personalize?

• N of 1
• Model systems
• Personal monitoring
N of 1 trials

- Randomize subjects - on/off treatment
- Enabled by platforms to obtain and track data
- Support for new drug indications (new patients, rare mutations)
Selecting the right therapies

Lumacaftor + ivacaftor

Why does one patient respond and another patient not?

We need tools:
1. Predict responders
2. Understand variable responses
3. Guide clinical trial design

Require regulatory input

F508/F508 subjects, phase 2 study
Personalized model systems

- Organoids – GI tissue
- Airway cells – nasal cells
- Stem cells – patient cells coaxed into CF epithelia
Intestinal organoids

Non-CF and CF organoids

WT

+/+ WT cftr

10μM FSK

CF

-/- F508 del cftr

10μM FSK

Courtesy of AP Naren and CS Moon (CCHMC)
Examining nasal cell model systems

- Primary human lower airway cells – track record for validation of CFTR modulator (and other therapy) efficacy prior to studies in CF patients
- Can we obtain cells from patient nose and use this as a testing ground for CFTR-active (and other) drugs?
  - Rare mutations
  - More common mutations
  - How should we grow them?
  - Do nasal cells behave like lung cells?
  - Does nose cell response predict patient response?
Activating F508del CFTR in HNEs

Courtesy of Alicia Ostmann, John Brewington (CCHMC) and Cal Cotton (CWRU)
Nasal spheres to monitor CFTR activity

Baseline

CFTR Activation

Courtesy of Alicia Ostmann, CS Moon, AP Naren, John Brewington (CCHMC)
Disease monitoring

• Observational studies

• Functional imaging modalities
  – MRI
  – Perfusion
  – HP gases

• Disease monitoring at home
  – Apps/EMR
Observational studies to inform future treatments

- **GOAL, GOALe**
  - G551D, gating, R117H before/after ivacaftor

- **PROSPECT**
  - PROSPECT A – variable CFTR cohorts (3)
  - PROSPECT B – F508del/F508del – before/after ivacaftor/lumacaftor co-therapy

- Banking, nasal cells, new outcome measures
Biomarkers in PROSPECT (GOAL)

MBW/LCI

FENO

pH pill

MCC

Bank

Small bowel pH changes (1 min means)

Pre VX-770

Post VX-770

p < 0.05

Minutes from gastric emptying

pH

 Courtesy of Felix Ratjen, Drucy Borowitz, Scott Donaldson, Toni Moran
Sensitive monitoring of regional disease

- Imaging offers opportunity to monitor lung regions
- MRI provides capability to monitor structure and function (perfusion, ventilation) regionally
- Imaging can be a life long tool

Compliments of David Roach, Jason Woods (CCHMC)
Functional imaging

Wielpütz MÔ, Puderbach M., Mall MA. et al. *Am J Respir Crit Care Med.* 2014 Feb 24

Jason Woods
Zack Cleveland
Novel biomarkers for clinical trials and matching therapies

- CFTR biomarkers
  - Sweat Cl, NPD, ICM, pH, FENO - **bioactivity**
- Sensitive biomarkers
  - MCC, LCI – **early response**
- Lung remodeling biomarkers
  - Chest CT, UTE MRI
- Disease modification
- Peripheral biomarkers
  - CFTR, disease status
- Monitoring

- **Surrogates**
  - Predict

- **Clinical efficacy outcome measures**
  - Feel, function, survive
Use of novel home monitoring (personalizing therapeutic plans)

- Apps for tracking activities, symptoms, therapies
  - Goal to interface with EMR
  - Pre-visit planning
  - Care planning
  - Monitor interventions

- Orchestra platform

- Patient activation - impact on adherence?
Ivacaftor treatment ... still work to do

- 6 pediatric, 6 adult subjects
  - 11/12 self-report use = 100%
  - Pharmacy refill history (MPR) = 84%
  - Electronic monitoring = 61%
  - Dosing interval = 16.9 hr

Use of apps to drive engagement?

- **Mobile App**
- **Web App**
- **SMS**
- **Desktop**

**NEEDS:**

- Scalable, consumer grade
- Behavioral design
- Engagement & collaboration
- Symptom observation & monitoring
- Personalized learning & experimentation

Feasibility of a Mobile Medication Plan Application in CF Care

Courtesy of:
Heather Kaplan
Lisa Opipari-Arrigan
Michael Seid
Peter Margolis
Data used to determine treatment plan

14 day on/off inhaled antibiotic cycles to manage multi drug resistant bacteria

• “on” cycles keep cough to a baseline of no cough

• “off” cycles increased cough frequency

![Graph showing cough frequency and symptoms over time with on/off therapy cycles.](image)
Summary – from patient to therapy?

Undefined Mutation

Choosing among modulators

Patient-derived model system To assess therapeutic options

Model system

Novel personalized trial
Summary

• Personalization with precision is an exciting next step in CF care and general pediatric care
• Genotypes and theratypes are emerging ways to consider new therapies
• Patient-derived model systems may serve as a valuable platform to predict clinical benefit of new therapies
• Novel biomarkers will accelerate clinical trials, streamline therapies
• Addressing adherence on a personalized level is critical to improve outcomes
• Harnessing the data and experience of patients will help us to have a truly personalized healthcare system
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• Eric Sorscher, MD—Emory University
• CFF