Plenary I: CF Research and Care in the 21st Century — It’s Time to Get Personal
21st Century Medicine for CF: It’s time to get personal (...or personnel 😊)

JP Clancy, MD – Cincinnati Children’s Hospital Medical Center
Disclosures

Clinical trial contracts
- Vertex
- Novalis
- Bayer
- Parion
- Gilead
- CFFT

Educational presentations
- Vertex
- Genentech
- Novalis

Consulting
- Vertex
- Spyryx
- Novalis
- AIT
- Insmed
- ProQR
- Abbvie

Grant funding, grant reviews
- NIH,
- CFFT, US CFF, Canadian CFF
- Gilead

No off label medication use discussed
Reflection from my last Plenary invitation (Denver, 2006)

- Where were we then, where are we today?
- New standard therapies (PERT, antibiotics, mucolytics)
- Genotype-directed therapies (modulators, others)
- Mutation agnostic studies (gene transfer, ion transport)
- Patient-derived model systems, biomarkers
- Novel study designs and monitoring tools (N of 1, adaptive trial designs, LCI, pH, MCC, OCT, MRI)
Overview

Personalized medicine – what is it?
• Thinking personal on the national stage and in the CF community

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
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. So tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases, and to give all of us access to the personalized information we need to keep ourselves and our families healthier..."
A new initiative on Precision Medicine

• ‘The initiative will encourage and support the next generation of scientists to develop creative new approaches for detecting, measuring, and analyzing a wide range of biomedical information, - including molecular, genomic, cellular, clinical, behavioral, physiological, and environmental parameters’

• ‘It will also pioneer new models for doing science that emphasize engaged participants and open and responsible data sharing…’

Francis Collins and Harold Varmus, Feb 26, 2015, New England Journal of Medicine
Personalize or 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
From their perspective, it’s personal
Evidence-based medicine success

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

- PERT
- dornase alpha
- IBU AZM
- Inhaled Atbx
- 7% HS
- CFTR

(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
- Does one size fit all?
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

Airway infection

Persistent inflammation

Airway damage

Thick mucus
The CFF pipeline

Drug Pipeline

- CFTR Modulation
  - Kalydeco™ (also known as ivacaftor)
  - Ataluren (formerly known as PTCT24)
  - Lumacaftor + Ivacaftor
  - VX-600 + Ivacaftor
  - QR-010
  - Riociguat
  - QBW251
  - N91115

- Restore Airway Surface Liquid
  - Hypertonic Saline
  - Bronchitol
  - P-1037

- Nutrition
  - AquADEKs
  - Pancrelipase Enzyme Products
  - Licotramase
  - Bulinipase

Mucus Alteration
- Pulmozyme®

Anti-Inflammatory
- Ibuprofen
- Alpha 1 Anti-Trypsin

Anti-Infective
- Inhaled Tobramycin
- Azithromycin
- Casablanca
- TIP (TOBI Inhaled Powder)
- Levofloxacin (Inhaled)
- Aikace™
- AeroVanc™

The CFF pipeline includes treatments for mucus, inflammation, infection, and nutrition.
Part 2

New therapies based on mutation, drug response or neither

- Genotype
- Theratype
- Genotype agnostic
Breakdown of CFTR mutations (>2000…)

Gene transfer DNA/RNA editing

Gene transfer DNA/RNA editing

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Gene transfer DNA/RNA editing

Gene transfer DNA/RNA editing

Gene transfer DNA/RNA editing
Summary of genotype groupings

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

PTCs

Ivacaftor for gating mutations

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

Class 3 gating

A new ‘benchmark’

Additional potentiator 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 – it’s complicated...

- 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)
TRAFFIC and TRANSPORT

- RDBPC trial (24 week) 1122 F508del/F508del randomized
- 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
Summary of genotype-based coverage

- F508del Homozygotes: ~50.0%
- Heterozygotes: ~40%
- Remaining: ~5%
- gating/R117H: 7%
- PTCs: ~5%
Therapies based on drug response – ‘theratype’

Consider mutations differently

- Class 1: biosynthesis
- Class 2: folding
- Class 3: gating
- Class 4: conductance
- Class 5: reduced

Less defined mutation

Drug response?
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)?
Mutation agnostic therapies (targeting any CFTR deficits)

**Phase 2B gene therapy trial**

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

**Outcomes**
- FEV1 (+3.7%, p=0.046)
- Other biomarkers
- PD s

Part 3

Bringing personalized concepts to CF

• *Personalized model systems*
• *Disease monitoring - In the clinic and at home*
The ion transport matrix:
In a world not too far away...

Getting the right therapies to the right patients in a world with numerous options

• …and so forth
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 in their own tissue

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, GOALe²

- 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

Pre VX-770

Post VX-770

p< 0.05

Small bowel pH changes (1min means)

Minutes from gastric emptying

pH pill

Bank

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

Structure and perfusion

UTE MRI

Structure

129Xe MRI

Function

Overlay UTE/129Xe

Structure-Function

Wielpütz MO, 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

Success with Therapies Research Consortium
- CFF-supported workgroup
- Adherence, self management
- Optimize outcomes, QOL

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

Courtesy of:
Heather Kaplan
Lisa Opipari-Arrigan
Michael Seid
Peter Margolles
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
Summary – from patient to therapy?

Undefined Mutation

Choosing among modulators

Patient-derived model system
To assess therapeutic options

Model system

Novel personalized trial
Personalization with precision is an exciting next step in CF 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 CF healthcare system.
Thank you!

And,

It’s time to Get Happy!