CF: Understanding the Biology – Curing the Disease

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Defining the path

- Drilling down on CF biology
- Measuring CFTR function \textit{in vitro, in vivo}
- Fixing CFTR!
Early, big picture view

- Infants dying from GI complications
- Earliest lung lesion = bland mucus obstruction
- = “Mucus problem”

Zuelzer and Newton, Pediatrics 1949
Abnormal Chloride Permeability

Table 3. Ductal Transport Rates for Electrolytes in Single Sweat Glands of Normal Controls and of Patients with Cystic Fibrosis.*

<table>
<thead>
<tr>
<th></th>
<th>Sodium Reabsorption</th>
<th>Chloride Reabsorption</th>
<th>Potassium Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>252±64</td>
<td>208±47</td>
<td>10.9±3.7</td>
</tr>
<tr>
<td>Patients</td>
<td>101±18†</td>
<td>41±15‡</td>
<td>14.4±2.3</td>
</tr>
</tbody>
</table>

* pmol/min/gland

Focus on CFTR!
CF sequence of events

Abnormal CFTR gene/protein

Abnormal ion (salt) transport

Mucus retention

Chronic lung disease
CFTR Biology
Which CFTR functions are essential – and must be corrected to restore health?
- Pancreas
- Intestine
- Lung

Pick endpoints that reflect these functions
The CF pancreas

Courtesy of Dr. Michael Gray, Newcastle University
Essential CFTR Functions

Exocrine Pancreas

140 mM bicarb
20 mM chloride
2.5 l/day

DUCTS < 10 % by volume

ACINI - digestive enzymes

DUCTS - bicarb & H₂O

140 mM bicarb
20 mM chloride
2.5 l/day

DUCTS < 10 % by volume

Courtesy of Dr. Michael Gray, Newcastle University
Enzyme secretion

Acini

Duct

Bicarb-rich alkaline fluid secretion

Normal

HCO₃⁻

Cl⁻

CF

NaCl-rich fluid secretion

Blockage

Destroyed!

 Courtesy of Dr. Michael Gray, Newcastle University
CFTR critical to bicarbonate secretion by ducts

Clinical implications of CFTR restoration
- Early restoration required to preserve exocrine function
- Could pancreatic sufficient patients
- Other benefits from bicarbonate secretion even after “insufficient”?

Possible beneficial effect on insulin secretion

Bellin MD et al. Pediatr Diabetes 2013
CFTR Essential Functions
Intestine

- CFTR = bicarbonate and chloride secretion
- Abundant CFTR expression in small intestinal enterocytes
Human CF Intestine

**CLINICAL MANIFESTATIONS**

- Altered ion/bicarbonate transport
- Mucus retention
- Small Intestinal Bacterial Overgrowth
- Inflammation, Mucosal Injury

**CLINICAL MANIFESTATIONS**
Insights: CF mouse

- Severe intestinal disease and growth failure
- No pancreatic insufficiency or lung disease

Intestine: Summary

- CFTR is required for bicarbonate and chloride secretion
- Sticky mucus ("Mucoviscidosis") results\(^1\) - reminiscent of airways pathogenesis
- **Restoration of CFTR function in the intestine yields meaningful benefits in animal models**
  - Pig and mouse gut-corrected animals\(^2,3\)

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\(^1\)Garcia MA et al. *J Clin Invest* 209, 119(9):2613-22
\(^3\)Stoltz DA et al. *J Clin Invest* 2013, 123(6):2685-93
CFTR and Lung Disease

Mucus plugging – CF Human and Pig

Stoltz D A et al. Sci Transl Med 2010;2:29ra31-29ra31
Mucociliary clearance and obstruction

- Thick Mucus
- Periciliary Liquid (PCL)
- CFTR
- Normal
- CF
Lung Defense: Bacterial killing

In vivo
(newborn trachea)

AA Pezzulo et al. Nature 2012 487, 109-113
CFTR and pH dependent lung defense

*In vivo* trachea

AA Pezzulo *et al.* *Nature* 2012 487, 109-113
How do we fix mutant CFTR?
## CFTR Mutation Classes

<table>
<thead>
<tr>
<th>Normal</th>
<th>I synthesis</th>
<th>II maturation</th>
<th>III regulation</th>
<th>IV conductance</th>
<th>V quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example: R1162X</td>
<td>ΔF508</td>
<td>G551D</td>
<td>R117H</td>
<td>2789+5G&gt;A</td>
<td></td>
</tr>
</tbody>
</table>

Two approaches to increase CFTR function

Potentiators:
Increase the flow of ions through activated CFTR present at the cell surface

Correctors:
Increase the cellular processing and delivery of CFTR proteins, such as F508del-CFTR, to the cell surface
Ivacaftor has a profound impact in G551D on lung function

Effect of ivacaftor on hospitalization rate in G551D patients

![Diagram showing hospitalization rates before and after Ivacaftor treatment.](image-url)
Moving beyond one drug and one mutation!

What about me?
Are there other patients with CF who may benefit from ivacaftor monotherapy?

- ΔF508? – No!
- Milder/younger patients with G551D?
  - Probably. *KIWI Study*: in 2-5 yr olds; pending
- Severely diseased patients with G551D?
  - Yes! Hebestreit et al. JCF 2013; Barry et al. CHEST 2014
- Other gating mutations?
  - Yes! *KONNECTION Study*. FDA approval pending
- R117H? (Class IV, residual function; pancreatic sufficient)
  - Maybe – *KONDUCT Study*: benefits only in older (>18 yrs) and sicker patients
ΔF508 – Our Major Target

- ΔF508del Homozygotes (48.0%)
- ΔF508del Heterozygotes (40.1%)
- Class III/IV (6.8%)
- Others (9.9%)
VX-809 (lumacaftor) increases the amount of ΔF508-CFTR at cell surface

But…VX-809 not effective in clinical trials

1Van Goor et al., PNAS 2011; 2Clancy et al., Thorax 2012
Increased effectiveness through combination of VX-809 + ivacaftor

ΔF508 homozygous cells

Chloride transport (% Normal CFTR)

Baseline  Lumacaftor  Lumacaftor + Ivacaftor

Van Goor et al., PNAS 2011
Phase 2: VX-809 +/- ivacaftor in F508del homozygotes

Boyle et al. NACFC 2012
Phase 2: VX661 + ivacaftor in F508del homozygotes

Combination

Washout

Mean Relative Change from Baseline in % Predicted FEV₁ (% SE)

Visit

Baseline Day 7 Day 14 Day 21 Day 28

Day 28 Day 35 Day 42 Day 56

Modeled Results

Summary Statistics

Donaldson et al. ECFS 2013
**VX-809+ ivacaftor Phase 3 studies:**

“TRAFFIC” & “TRANSPORT”

- **Primary Endpoint:**
  - Relative change in FEV$_1$ %

- **Key Secondary Endpoints:**
  - BMI, exacerbations, safety and tolerability

**Study Status:** Fully enrolled and data anticipated mid 2014
How do we rapidly get where we need to go?

- Continue to improve treatment approaches
- Develop best tests of CFTR function
Improving ΔF508 Correction: Understanding all the issues

Class I
• VX-809
• VX-661
• C3, C18

Class II
• core-corr II
• C4, C13

Class III
• Glycerol
• Myo-insolitol

Adapted from: T. Okiyoneda et al. Nat. Chem Biol 2013
Novel *in vitro* assays of CFTR function

Intestinal organoids

Intestinal organoids: Quantitatively reflect *in vivo* CFTR function

Dekkers JF et al. Nat Med 2013, 19(7):939-47; data courtesy Dr. Jeff Beekman, UMC Utrecht
Organoids: Report on ΔF508-CFTR correctors

Adapted from: T. Okiyoneda et al. Nat. Chem Biol 2013
Personalized Medicine

- Characterize rare mutations and pursue personalized medicine
- Test multiple drugs, doses, drug combinations – hope of predicting clinical benefit

Fraction of all variants reported in CFTR

- 23 ACMG mutations: 1.2% of variants (85% of patients)
- 160 CFTR2 mutations: 8.4% of variants (97% of patients)

Courtesy of Dr. Garry Cutting
Measuring CFTR functions *in vivo*

- Study intact, physiologic systems impacted by CFTR function
- Observe reversal of functional defects that are pathophysiologically important in cystic fibrosis
Measuring CFTR *in vivo*: Future state

- **G551D Observational Study – GOAL**

  *Hypothesis*: Restoration of CFTR activity by Ivacaftor in G551D patients may allow identification of outcome measures closely tied to CFTR function
CFTR Essential functions

Essential Function/Effects

- Pancreas
  - Bicarbonate flow/pH
  - Enzyme function
- Intestine
  - Mucus layer formation
  - Nutrient Absorption
  - Gut inflammation
- Lung
  - Mucus hydration/clearance
  - ASL pH/antimicrobial function

What we measured

- Intestinal pH
- Mucociliary Clearance
- Bacterial infection
- Inflammation
GOAL Study Design

Visit 1 → Decision made to start ivacaftor? (before end of study enrollment)

Yes: Visit 2 → Day 1 → Visit 3 → Visit 4 → Visit 5

No: Visit 1b

Visit 2 → Pre-Dose
Visit 3 → First dose of ivacaftor 1 month after Day 1
Visit 4 → 3 months after Day 1
Visit 5 → 6 months after Day 1

Core Study Measures
- Clinical outcome
- Sweat chloride
- Quality of life
  - CFQ-R
  - SNOT-20
- Biomarker collection
  - Serum
  - Plasma
  - DNA
  - Urine
  - Sputum

Additional Sub-Study Measures

MCC/Rheology
- Radionuclear mucociliary clearance
- Rheology

Sputum Inflammation & Microbiome
- Induced sputum
- Inflammatory mediators

Intestinal pH
- Intestinal pH by radiofrequency transmitter

Sweat Rate
- Sweat evaporimetry
- Exploratory sweat outcomes
Intestinal pH Measurement

Wireless Motility Capsule

- Measures luminal
  - pH
  - Motility
  - Temperature

Study Hypothesis: Intestinal pH is low in CF and can be corrected with Ivacaftor in G551D patients
CF Intestinal pH is Abnormal

Mean pH starting with duodenal entrance (1 minute interval)

A
B

pH optima for enzymes

Effect of Ivacaftor on Small Bowel pH

Clinical Implications:
• Improved exogenous pancreatic enzyme efficacy
• Reduced GI symptoms and improved nutrition
• Early use: preserve endogenous exocrine function?

Data courtesy of Dr. Daniel Gelfond and the GOAL pH Pill Sub-study Team
CFTR and Mucociliary Clearance

Study Hypothesis: If CFTR activity supports mucus clearance, Ivacaftor treatment of G551D patients should yield significant improvements in MCC.

Study Design: N=22 treated; 4 study sites MCC at baseline, 1 month, 3 months.

Defective CFTR

- Infection
- Reduced MCC
- Bronchiectasis

Reduced MCC

- Infection
- Bronchiectasis
Measurement of MCC by $\gamma$-scintigraphy

Define lung boundaries:

Tc99m-SC particle inhalation:

Serial images track particle retention/clearance:
Mucociliary Clearance: *The movie*

Baseline

Ivacaftor - 3 months

Courtesy of Dr. Tim Corcoran, U. Pittsburgh
Whole Lung MCC

Data courtesy of the GOAL MCC Sub-study Team
Change in *P. aeruginosa* Culture Rate

<table>
<thead>
<tr>
<th>Number of months pre/post Ivacaftor start date</th>
<th>Percent with <em>Pseudomonas Aeruginosa</em> &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>[-12, -6)</td>
<td>55%</td>
</tr>
<tr>
<td>[-6, 0)</td>
<td>52%</td>
</tr>
<tr>
<td>[0, 6)</td>
<td>34%</td>
</tr>
<tr>
<td>[6, 12)</td>
<td>35%</td>
</tr>
</tbody>
</table>

Data courtesy of Dr. Steve Rowe and the GOAL Study Team

* p < 0.01  ** p < 0.001 Wilcoxon sign test
Moving the Bar
The Ivacaftor-G551D Benchmark

~30% CFTR Function

- persistent disease
- borderline sweat and NPD

Ivacaftor: 2-5 yr olds with gating mutations

VX661 +/- Ivacaftor: ΔF508/G551D
ΔF508/partial function

CFF and NIH working with academic and industry groups
Moving Forward

- **Challenges**
  - Refine and expand CFTR endpoints at all stages of development
  - Use these tools to identify new therapeutics that will take us further toward “There”!

- We’ve made tremendous progress on what to measure in vitro and in vivo
- CFTR therapies will continue to improve along a clear development pathway

*A CF cure is in sight!*
Thank you!