Michael P. Boyle, MD
Senior Vice President of Therapeutics Development
Cystic Fibrosis Foundation
Cystic Fibrosis Foundation
Meetings Team

- Cynthia Adams, HMCC, Senior Director of Meetings
- Kristin Piasecki, Manager, Meetings Logistics
- Christie Riley, Specialist, Meetings Logistics
- Brandi Barnum, Manager, Meetings Program Resources
- Rebekah Kim, Senior Coordinator, Meetings
- Shawna Gordon, Senior Coordinator, Meetings
- William Ballou, Project Coordinator, Program Resources
- Susan Nich, Administrative Specialist, Meetings
- Cristina Castro-Rivera, Project Coordinator, Meetings Education Resources
Quality Care Awards

Ann and Robert H. Lurie Children's Hospital of Chicago Pediatric Program

Augusta University Adult Program

Children's Hospital Colorado Pediatric Program

Cook Children's Medical Center Pediatric Program

Helen DeVos Children's Hospital Pediatric Program

National Jewish Health Adult Program

Northwestern University Adult Program

The Cystic Fibrosis Center of Western New York, Buffalo Pediatric and Adult Programs

The Marie and Raymond Beauregard Adult CF Center at Hartford Hospital Adult Program

The Nemours Children's Clinic – Orlando Pediatric Program

University of Virginia Pediatric and Adult Programs

University of California, San Francisco Adult and Pediatric Program

University of Arkansas Adult Program

University of Miami Adult Program

Kaiser Permanente Northwest Region Pediatric and Adult Programs

University of Texas Southwestern Adult Program

University of Texas Southwestern/Children's Health Pediatric Program

Vanderbilt Children's Hospital Pediatric Program

Vanderbilt University Medical Center Adult Program

Virginia Commonwealth University Pediatric Program
Outstanding Partnerships Between Care Centers and CF Foundation Chapters Awards

- Brown University Medical School at Rhode Island Hospital
  Pediatric and Adult Programs
- Children’s Hospitals and Clinics of Minnesota
  Pediatric Program
- Emory University
  Pediatric and Adult Program
- Greenville Health System
  Pediatric Program
- Helen DeVos Children's Hospital
  Pediatric Program
- Joe DiMaggio Children's Hospital
  Pediatric and Adult Program
- Oregon Health Sciences University
  Pediatric Program
- Seattle Children's Hospital
  Pediatric Program
- St. Mary’s Medical Center
  Pediatric and Adult Program
- SUNY Upstate Medical University
  Pediatric and Adult Program
- University of Louisville
  Adult Program
- University of Nebraska Medical Center
  Pediatric Program
- University of North Carolina at Chapel Hill
  Pediatric and Adult Program
- Virginia Commonwealth University
  Pediatric Program

#NACFC
Richard C. Talamo Distinguished Clinical Achievement Award

In recognition of those who have spent their careers researching and caring for individuals with CF and whose contributions have altered the course of this disease
Richard C. Talamo Distinguished Clinical Achievement Award

George Z. Retsch-Bogart, MD
Professor, Division of Pediatric Pulmonology
University of North Carolina, Chapel Hill
Co-Director, UNC Therapeutics Development Center
Medical Director, Clinical and Translational Research Center
of the North Carolina Translational and Clinical Sciences Institute

#NACFC
Felix Ratjen, MD, PhD, FRCP(C) FERS

Sellers Chair in Cystic Fibrosis
Head, Division of Respiratory Medicine
Program Head, Translational Medicine
The Hospital for Sick Children
Professor of Pediatrics
University of Toronto

#NACFC
Anti-Inflammatories and Mucociliary Clearance Therapies in the Age of CFTR Modulators

Felix Ratjen, MD, PhD, FRCP(C), FERS
Felix Ratjen, MD

The following relationships exist related to this presentation:

• Research funding:
  – CFF, CF Canada, CIHR, Genome Canada, NHLBI, Vertex

• Advisory:
  – Bayer, Boehringer Ingelheim, Genentech, Novartis, Proteostasis, Spyryx, Vertex
In memoriam: Peter Durie, MD
What type of research are adult people with CF interested in participating in? (n=129)
What defines inflammation?

Latin: inflamma; meaning fire
Acute Inflammation: first-line defense

Neutrophils act as border control
What causes airway inflammation in CF?

Dysfunctional CFTR

Infection

Mucostasis

Neutrophilic airway inflammation

Airway and lung tissue damage
Multiplicity of triggers and pathways

**Neutrophil Activators**
- Cytokines
  - TNF-α
  - IL-1β
  - GM-CSF
- Serine Proteinases
  - Cathepsin G
  - Neutrophil elastase
- Arachidonic Acid Metabolites
  - LTB₄
- Complement Components
  - C5α
  - C5α-des-Arg
- ECM Products
  - PGP
  - N-acetyl PGP
- Bacterial Products
  - f-Met-Leu-Phe
- flagellin

**Neutrophil Chemoattractants present in the CF airway**
- Cytokines
  - IL-8
  - IL-17
  - HMGB1
- Arachidonic Acid Metabolites
  - LTB₄
- Complement Components
  - C5α
  - C5α-des-Arg
- ECM Products
  - PGP
  - N-acetyl PGP
- Bacterial Products
  - f-Met-Leu-Phe
  - flagellin

**Macrophage**
- Decreased Apoptosis and Decreased Efferocytosis

**Impaired Cough Clearance**

**AIRWAY PLUGGING: STRUCTURAL LUNG DAMAGE**

**Activators and Chemoattractants**
- Decreased Clearance of Neutrophils

**Pro-Inflammatory Products**
- Consequences

Nichols & Chmiel. *Pediatr Pulmonol* 2017
Dysregulated airway inflammation in CF

“Flare ups” (Exacerbations)

Increased inflammatory response

Defective downregulation of inflammation

CF Basal Inflammation

Baseline in Health
Is the inflammatory process specific for CF?

PCD = primary ciliary dyskinesia

Ratjen F et al. Eur Respir J 2015
## Neutrophil elastase predicts bronchiectasis

<table>
<thead>
<tr>
<th>Multivariate analysis</th>
<th>Odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meconium ileus</td>
<td>3.17 (1.51-6.66)</td>
<td>0.002</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>2.27 (1.24-4.14)</td>
<td>0.008</td>
</tr>
<tr>
<td>+ Neutrophil elastase activity</td>
<td>3.02 (1.70-35.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


## Sputum neutrophil elastase predicts FEV₁ decline

Sagel S et al., *Am J Respir Crit Care Med* 2012
Do CFTR modulators improve inflammation?

IL-6 (log10 pg/ml)

Baseline | 6 months

IL-8 (pg/ml)

Days

Neutrophil Elastase (mcg/ml)

Days

Rowe S et al., AJRCCM 2014

Hisert K et al., AJRCCM 2017
Lung function decline in bronchiectasis: The future for CFTR modulator-treated patients?

Twiss et al., Thorax 2006

Sawicki G et al., Am J Respir Crit Care Med 2014
Targeting inflammation: a balancing act
Therapy of airway inflammation

$LTB_4$ receptor antagonist ($BIL285S$)

• Large phase II study (600 patients)

• Early termination due to higher rate of pulmonary exacerbations in the $BIL285S$ treatment group

• Negative impact on host defense of bacterial or viral pathogens?

Konstan MW et al. J Cyst Fibros 2014
Ibuprofen therapy and subsequent survival

Konstan MW et al., Ann Am Thorac Soc 2018
CFF Inflammation Strategic Plan

• What are the exciting pathways or targets warranting investigation and evaluation?

• Is there a target population group most amenable to anti-inflammatory therapy?

• What have we learned from past successes and failures?

• How will clinical trials be designed to both predict long-term outcomes and facilitate comparison of different agents?
Recent anti-inflammatory treatment studies
CFF anti-inflammatory pipeline

<table>
<thead>
<tr>
<th>Pre-Clinical</th>
<th>Phase One</th>
<th>Phase Two</th>
<th>Phase Three</th>
<th>To Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td></td>
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<tr>
<td>Lenabasum (JBT-101)</td>
<td></td>
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<tr>
<td>Acebilustat (CTX-4430)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAU-7b</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>POL6014</td>
<td></td>
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</tr>
</tbody>
</table>
Acebilustat addresses excessive inflammatory response

Excessive neutrophilic inflammation

Resolution of neutrophilic inflammation

LTB4

LTA4

LXA4

ACEBILUSTAT

Rao NL et al., AJRCCM 2010

Tobin DM et al., Cell 2010
Acebilustat EMPIRE-CF Phase 2B Program

**Patient Entry Criteria:**
- All genotypes
- Aged 18-30 years
- Baseline FEV$_{1}$pp≥50
- >1 PEx in prior year

**48 Week Treatment:**
- Randomized 1:1:1
- Acebilustat 50mg, 100mg or Placebo
- On top of standard of care

**Primary Endpoints:**
- FEV$_{1}$pp
- Safety

**Secondary Endpoint:**
- PEx

**Stratification Criteria:**
- FEV$_{1}$pp: 50-75 versus >75
- +/- CFTR Therapy
- >2 PEx v. 1 PEx in prior year

Stuart Elborn, MD, FRCP (EU PI)
Steven M. Rowe, MD, MSPH (North American PI)
Acebilustat primary endpoint: \( \text{ppFEV}_1 \) change from baseline v. placebo

### Acebilustat doses
- 100 mg
- 50 mg
- Combined

**FAP**
- 100 mg: \( P=0.5 \) (N=66)
- 50 mg: \( P=0.45 \) (N=67)
- Combined: \( P=0.6 \) (N=133)

**Per Protocol**
- 100 mg: \( P=0.9 \) (N=54)
- 50 mg: \( P=0.43 \) (N=108)

Courtesy of Celtaxsys
Freedom from protocol-defined exacerbation for patients with FEV₁ >75% predicted

Exacerbation-Free Patients over 48 Weeks

All Subjects

- Acebilustat (N=47): 48.9%
- Placebo (N=24): 25.0%

Subjects on CFTR Modulators

- Acebilustat (N=17): 58.8%
- Placebo (N=9): 22.0%

Subjects not on CFTR Modulators

- Acebilustat (N=30): 43.3%
- Placebo (N=15): 26.6%

Courtesy of Celtaxsys
Lenabasum triggers inflammation resolution without immunosuppression

- Tissue infiltration with neutrophils and other inflammatory cells
- Pro-inflammatory cytokines
- Pro-inflammatory lipids
- Vasodilation/edema
- Chemokines

Resolution of Inflammation

- Resolution of tissue infiltration with inflammatory cells
- Clearance of bacteria
- Pro-resolving lipid mediators

Time

Inflammation/Fibrosis

Resolution

CB2

Activation

Decreases

Increases
Phase 2 study of lenabasumum in persons with CF

**First-in CF Patient Study**

**Design**
- Double-blind, randomized, placebo-controlled study
- 21 sites in U.S. and EU
- 85 subjects ≥ 18 to < 65 years old
- 5:2 overall ratio of lenabasum: placebo
- 12 weeks of active dosing

**Primary Objective**
- Evaluate safety and tolerability. Pulmonary exacerbations were an event of special interest.

**Biomarker Objective**
- Evaluate sputum and blood biomarkers of inflammation.
Pulmonary exacerbation event rates

Rates of Pulmonary Exacerbations Requiring:

- Any New Antibiotic
- IV Antibiotics

Events per subject per 12 weeks

- Placebo: 0.46
- 20 mg lenabasum: 0.25
- 20 mg lenabasum BID: 0.21
- Placebo: 0.26
- 20 mg lenabasum: 0.10
- 20 mg lenabasum BID: 0.05

Courtesy of Corbus
Lenabasum Phase 2b study design

• Double-blind, randomized, placebo-controlled
• Sites in North America and Europe
• Patients ≥ 12 years of age
• 28 weeks of active dosing
Future outlook for anti-inflammatory therapy

- What is the best target for treatment?

- What is the right population?
  - All patients regardless of genotype, disease state, and CFTR modulator therapy?
  - Early when the inflammatory burden is still limited?
Mucociliary clearance

Cough clearance

mucus

epithelial cells
Mucus clearance abnormalities in CF

Ratjen F et al, Nat Rev Dis Prim 2015
Drugs to improve mucus clearance

- **Dornase alfa**
- **Hypertonic saline and Mannitol**
- **CFTR modulators**
- **Sodium channel blocker**

Ionocytes versus airway epithelial cells?
CFTR modulation and mucus clearance

Baseline

Ivacaftor treatment

After stopping treatment

Altes TA et al., J Cyst Fibros 2017
Dornase alfa in bronchiectasis: Implications for modulator-treated patients?

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Dornase alfa</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-defined exacerbations</td>
<td>0.56</td>
<td>0.66</td>
<td>1.17</td>
<td>0.85, 1.65</td>
</tr>
<tr>
<td>Non-protocol-defined exacerbations</td>
<td>0.14</td>
<td>0.29</td>
<td>2.01</td>
<td>1.15, 3.50</td>
</tr>
<tr>
<td>Combined</td>
<td>0.71</td>
<td>0.95</td>
<td>1.35</td>
<td>1.01, 1.79</td>
</tr>
</tbody>
</table>

FEV₁ decline:

-1.7% in the placebo group (n=176)
-3.6% in the dornase alfa group (n=172)
How hypertonic agents work

Ratjen F. *NEJM* 2006
Saline Hypertonic in Preschoolers

- 150 preschool CF patients from centers in North America
- Randomized to isotonic or hypertonic saline (7%) for 48 weeks
- Primary outcome measure:
  - Change in the lung clearance index (LCI) measured by nitrogen multiple breath washout from baseline to 48 weeks

Also presented in workshop 24
Multiple Breath Nitrogen Washout

Medical air
100% O₂

Washout Phase

Flow Analyzer

Gas analyzer

LCI = How many turnovers (FRCs) it takes to reduce the tracer gas to \(1/40^{th}\) of the starting concentration

Higher LCI = Greater Inhomogeneity = More Disease
## SHIP baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Hypertonic Saline (N=76)</th>
<th>Isotonic Saline (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs</strong></td>
<td>4.48 ± 0.95</td>
<td>4.42 ± 0.89</td>
</tr>
<tr>
<td><strong>Age category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young (36-54 months)</td>
<td>44 (57.9%)</td>
<td>43 (58.1%)</td>
</tr>
<tr>
<td>Old (&gt;54 months)</td>
<td>32 (42.1%)</td>
<td>31 (41.9%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>36 (47.4%)</td>
<td>33 (44.6%)</td>
</tr>
<tr>
<td><strong>CFTR Genotype</strong></td>
<td></td>
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<tr>
<td>Homozygous F508del</td>
<td>38 (50.0%)</td>
<td>40 (54.1%)</td>
</tr>
<tr>
<td>Compound Heterozygote F508del</td>
<td>33 (43.4%)</td>
<td>28 (37.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (6.6%)</td>
<td>6 (8.1%)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
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</tr>
<tr>
<td>Caucasian</td>
<td>72 (94.7%)</td>
<td>73 (98.6%)</td>
</tr>
<tr>
<td>African American</td>
<td>2 (2.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.6%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>17.44 ± 3.15</td>
<td>17.69 ± 2.66</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>104.46 ± 8.16</td>
<td>105.34 ± 6.91</td>
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</tbody>
</table>
Primary Endpoint: Change in LCI

Treatment effect at 48 weeks:
-0.63; -1.10, -0.15 p=0.01
# Mucociliary clearance pipeline

<table>
<thead>
<tr>
<th>Pre-Clinical</th>
<th>Phase One</th>
<th>Phase Two</th>
<th>Phase Three</th>
<th>To Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dornase Alfa (Pulmozyme®)</td>
<td></td>
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<tr>
<td>Hypertonic Saline</td>
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<tr>
<td>OligoG</td>
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<tr>
<td>QBW276</td>
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<tr>
<td>SPX-101</td>
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<tr>
<td>AZD5634</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ionis</td>
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</tbody>
</table>
SPX-101: Channel internalization restores airway hydration and promotes mucociliary clearance

1. Peptide binds to epithelial sodium channel

2. Removal of channels from airway surface

3. Reduction in Na+ absorption
   - Reduces ENaC levels agnostic of CFTR
   - Increases ASL volume
   - Hydrates mucus
   - Improves mucociliary clearance

Garland et al, PNAS 2013; 110: 15973-8; Scott et al, AJRCCM 2017; 196:734-44
SPX-101: 28 days ppFEV$_1$ change

**Baseline ppFEV$_1$ > 55%**
(n = 20)

- Placebo 60 mg BID
- 120 mg BID

**Baseline ppFEV$_1$ < 55%**
(n = 20)

- Placebo 60 mg BID
- 120 mg BID

P = 0.048

Courtesy of Spyryx
TMEM16A: a novel genotype-independent approach

Potentiators increase fluid secretion in primary CF bronchial epithelial cells

TMEM16A: a novel genotype-independent approach

Potentiators increase fluid secretion in primary CF bronchial epithelial cells

TMEM16A: a novel genotype-independent approach

Potentiators increase fluid secretion in primary CF bronchial epithelial cells

TMEM16A: a novel genotype-independent approach
Future treatment scenarios

- Patients without effective CFTR modulator therapies need progress on all fronts
  - Search for effective CFTR-directed therapies
  - Improved mucus clearance agents
  - Effective anti-infective and anti-inflammatory therapies
Future treatment scenarios

- Patients with effective CFTR modulator therapies but established lung disease
  - Search for more effective CFTR directed therapies
  - Improved mucus clearance agents
  - Effective anti-infective and anti-inflammatory therapies
Future treatment scenarios

• Patients on effective CFTR modulators initiated before lungs are damaged

  *Does CFTR modulation halt the progression of disease?*

• If yes:
  – No other airway therapies may be needed

• If improved, but not halted:
  – Search for more effective CFTR-directed therapies
  – Improved mucus clearance agents
  – Effective anti-infective and anti-inflammatory therapies
Progress for CF happens on all fronts

“It always seems impossible until it is done.” - Nelson Mandela
Presented at the Cystic Fibrosis Foundation’s NACFC 2018