Preston W. Campbell, III, MD
President and Chief Executive Officer
Cystic Fibrosis Foundation
The following relationship(s) exist(s) related to this presentation

To advance drug development and a search for a cure, the CF Foundation has contractual agreements with several companies to receive royalties related to drugs that are developed as a result of CFF funding. Any royalties we receive are used in support of our mission. More information about our model is available at cff.org/industry.
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Manager, Cystic Fibrosis Clinical Research Unit
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Professor of Pediatrics
Perelman School of Medicine at the University of Pennsylvania
Richard B. Johnston, Jr. Endowed Chair in Pediatrics
Director, Cystic Fibrosis Center
The Children’s Hospital of Philadelphia
<table>
<thead>
<tr>
<th>Company Name</th>
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<tr>
<td>AbbVie</td>
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<td>Fairview Specialty Pharmacy</td>
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</table>
William R. Skach, MD
Senior Vice President of Research Affairs
Cystic Fibrosis Foundation
Improving outcomes of infections in the age of CFTR modulators
Presenter Disclosure

William R. Skach, MD

- Dr. Skach has no relationships to disclose but is an employee of the CF Foundation and participates in programmatic funding decisions.

- To advance drug development and a search for a cure, the CF Foundation has contractual agreements with several companies to receive royalties related to drugs that are developed as a result of CFF funding. Any royalties we receive are used in support of our mission. More information about our model is available at cff.org/industry.

- Special thanks to Genevieve Maul, Jenna Vince, and Stephanie McDermott.

#NACFC
CF advances through the ages

Early Days
- 1955
  Median Survival <5 yrs

Care and Discovery
- 1989
  ~30 yrs

CFTR Gene
- 2012
  ~40 yrs

CFTR Modulators
- Ivacaftor (2012)
- Luma/Iva (2015)
- Tez/Iva (2018)

Cure
- 60, 70, 80 yrs
Triple combination therapy is highly effective in people with a single copy of ΔF508

February 2018
Phase II results:

VX-659 + Tez/Iva with one ΔF508 (n=63)
- 13% absolute improvement in FEV₁
- 51 mmol/L drop in sweat chloride
- Improved quality of life (+19.8 CFQ-R)

VX-445 + Tez/Iva achieved similar results
Vertex triple combinations move into phase III trials

**AURORA & ECLIPSE:**
- VX-659 + Tez/Iva
- VX-445 + Tez/Iva

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Study(s)</th>
<th>Status</th>
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<tr>
<td>ΔF / ΔF</td>
<td>659-103</td>
<td>4 Week vs. TEZ/IVA Enrollment completed</td>
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<tr>
<td></td>
<td>445-103</td>
<td>First Subject First Dose Q3 2018</td>
</tr>
<tr>
<td>ΔF / ?</td>
<td>659-102</td>
<td>24 week placebo-controlled Enrollment completed</td>
</tr>
<tr>
<td></td>
<td>445-102</td>
<td>Study conduct ongoing</td>
</tr>
</tbody>
</table>

open-label studies ongoing

Data Availability: VX-659 in late 2018, VX-445 in Q1 2019
Submission Plan: no later than mid-2019

Provided courtesy of Vertex Pharmaceuticals
Additional triple combinations are also advancing

Proteostasis Therapeutics:
Amplifier + Potentiator + Corrector
PTI-428  PTI-808  PTI-801

Multiple trials ongoing in ΔF/ΔF
• Dual Combination (801/808)
• Triple Combination (428/801/808)

Galapagos:
Potentiator + Corrector + Corrector
GLPG2451  GLPG2222  GLPG2737

FALCON trial now registered for subjects with 1 or 2 ΔF mutations (Europe)
Effect of CFTR modulators on lung function decline

See: Sawicki et al. AJRCCM 2015
Konstan et al. Lancet Resp Med 2017
Effect of CFTR modulators on population health

- Healthy
- Some decline in lung function
- Advanced disease/lung transplant

End of 2016

52% Adults

Note: Healthy = FEV1 >90%, Moderate = FEV1 40-90%, and Advanced disease = FEV1 <40%
Source: Revised Model for July 2018 CFF Medical Strategy Retreat
Future challenges

- Not everyone will respond to modulators
- Some people have existing lung disease
- Infections may not be eradicated
- Lung function may still decline

- Preventing CF complications to maintain health remains a top priority
  - Respiratory infections are the greatest concern
  - Inflammation remains a major cause of lung damage
Introducing the INFECTION RESEARCH INITIATIVE

- CFF is committing $100M over the next 5 years

- To improve detection, diagnosis, treatment, and outcomes of infections for people with CF
Improving outcomes of infections in the age of CFTR modulators

Lisa Saiman, MD MPH

Professor of Pediatrics, Department of Pediatrics, Columbia University Irving Medical Center, New York, NY
Hospital Epidemiologist, Department of Infection Prevention and Control, NewYork-Presbyterian Hospital, New York, NY

#NACFC
Lisa Saiman, MD, MPH

The following relationships exist related to this presentation:

- CF Foundation, Grant funding
- CF Foundation, Data Safety Monitoring Board
- Teva Pharmaceuticals, Advisory Board
- Gilead, Advisory Board
- ABComm, Inc., Honorarium

Today, I have the privilege and responsibility of presenting the research and insights of countless individuals from the CF community.
Objectives for Today’s Plenary

• Identify ongoing challenges in the treatment of infections in people with CF and discuss the potential impact of CFTR modulators on infections

• Update you on the results of ongoing work to improve our understanding of CF microorganisms including detection, diagnosis, and optimal treatment

• Discuss current strategies that will result in the new anti-infective therapies of tomorrow
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CF Microbial Burden and Treatment Challenges

Prevalence of Respiratory Microorganisms, 1991–2017

- MSSA
- *P. aeruginosa*
- MRSA
- *H. influenzae*
- *S. maltophilia*
- NTM
- MDR-PA
- Achromobacter
- *B. cepacia complex*
Nontuberculous mycobacteria (NTM) is increasing.
Different microorganisms are problematic in different age groups.

Prevalence of Respiratory Microorganisms by Age Cohort, 2017

- *P. aeruginosa*
- *H. influenzae*
- *B. cepacia complex*
- *MRSA*
- *MSSA*
- *Achromobacter*
- *S. maltophilia*
- *MDR-PA*
M. abscessus as common as M. avium through young adulthood
What questions are emerging for treating infections in the era of CFTR modulators?

• What will happen to microbiology among individuals with:
  – established lung disease already infected
  – less severe lung disease and positive cultures
  – without documented infections
• Some individuals may not tolerate or respond to existing modulators.
• Some may not have effective modulators available.
• All need monitoring of microbiology to guide treatment.
• We still need antimicrobials!!!
What have we learned so far about the impact of CFTR modulators on CF microbiology?
Restoring CFTR function associated with decreased *P. aeruginosa*

- Participants ≥ 6 years old
- G551D mutation
- Decreased *P. aeruginosa*
  - 6 months
  - 12 months

Rowe SM et al. Am J Respir Crit Care Med. 2014;190(2):175-84
Restoring CFTR function associated with other microbiology changes

- Decreased *P. aeruginosa*, mucoid *P. aeruginosa*, and *Aspergillus*
- Decreased frequency of isolation of *P. aeruginosa*

Restoring CFTR function associated with decreased density of *P. aeruginosa* -> rebounded within 2 years

- Adult participants
- G551D
- 8/12 chronic *P. aeruginosa*
- Initially density decreased
- Rebounded within 2 years

Video 1: Chronic Infection
<table>
<thead>
<tr>
<th>Topic</th>
<th>Community members (n=39-107)</th>
<th>Clinicians (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory microorganism detection and treatment</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>Mental health</td>
<td>45%</td>
<td>56%</td>
</tr>
<tr>
<td>Reducing treatment burden</td>
<td>57%</td>
<td>53%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>CF-related diabetes</td>
<td>18%</td>
<td>42%</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>CF-related liver disease</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Diet and nutrition</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Sinus disease</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Pain management</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Exercise</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Alternative/Holistic treatments and therapies</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>
Infection Research Initiative

- The Future of CF Infection
- Improving Detection and Diagnosis
- Developing New Treatments
- Optimizing Current Treatments
- Evaluating Long-Term Antimicrobial Use
- Understanding CF Microorganisms
Objectives for Today’s Plenary

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• Discuss current strategies that will result in the new anti-infective therapies of tomorrow
A decade ago...
Inflammation and Infection: Update on the CF Pipeline
NACFC 2009

Michael W. Konstan, MD and James Chmiel, MD MPH
Case Western Reserve University
Rainbow Babies and Children’s Hospital

Lisa Saiman, MD MPH
Columbia University
NewYork-Presbyterian Hospital

NACFC 2009; Plenary Session II
Natural History of Acquisition of *Pseudomonas aeruginosa*

**Birth**
- 1st *Pa* culture
- *Pa* negative culture

**2nd *Pa* + culture**
- Persistently *Pa* + cultures

**Intermittent infection**
- Eradication
- Pulmonary Exacerbations

**Chronic infection**
- Chronic Suppressive Therapy

**Mucoid *P. aeruginosa***
CF lung is a complex microbial ecology

- Unique growth conditions, available nutrition, metabolism
  - Can affect activity of antibiotics
  - Can affect mode of growth
    o Biofilms
    o *S. aureus* small colony variants
- Microorganisms interact, and microbial community may be ‘pathogenic unit’
- These interactions may impact progression of CF, response to therapy, and clinical outcomes

Microbial and host interactions that could impact CF progression

*P. aeruginosa* biofilm enhanced by RSV co-infection

What is the proposed mechanism?

- Dysregulation of host nutritional immunity
- Normally, host sequesters iron
- RSV infection: induces release of iron-bound transferrin by airway epithelial cells mediated by interferon (IFN)
- More iron -> increased biofilm growth

**W26.2: Abstract 326**

Hendricks MR et al. Prot Nat Acad Sci 2016;113:1642-7
Improving Detection and Diagnosis

• Conventional microbiology identifies single organisms
• New molecular, rapid diagnostic methodologies could:
  – Identify microorganisms directly from specimens
  – Improve eradication by earlier identification of lower airway infections
  – More rapid turnaround time for management of exacerbations
  – Could decrease the treatment burden
New methodologies have revealed potentially more complex polymicrobial community

- Must sort out role of community members

- Correlate structure (microbiome) and activity (metabolome/ transcriptome/ proteome) and clinical course

- Use translational science to study altering these parameters to improve outcomes

Improving detection of microorganisms in non-sputum producers

Induced sputum

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Throat swab</th>
<th>Induced sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher yield in IS samples</td>
<td>Negative</td>
<td>S aureus</td>
</tr>
<tr>
<td>1</td>
<td>Negative</td>
<td>S aureus</td>
</tr>
<tr>
<td>1</td>
<td>S aureus</td>
<td>S aureus</td>
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<tr>
<td>1</td>
<td>S malophilia</td>
<td>S malophilia</td>
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<tr>
<td>1</td>
<td>S aureus</td>
<td>S aureus</td>
</tr>
<tr>
<td>Higher yield in TS samples</td>
<td>H influenzae</td>
<td>H influenzae</td>
</tr>
</tbody>
</table>

2-D gas chromatography time-of-flight mass spectroscopy

- Can detect volatile metabolites
- Biomarkers to identify CF microorganisms


Nasir M et al. Science Rep 2018;8:82.
Imagine with me: Precision Medicine for CF Infections

• Abandoning conventional microbiology in favor of rapid molecular detection using point of care devices
• Integrating information about polymicrobial community to guide therapy
A decade ago...
Early Eradication Clinical Trials

• ELITE – Early Intervention TOBI Eradication

• EPIC – Eradication of *Pseudomonas* Infection Control

For more information:
Plenary III – Early Airway Infection in Young Children with CF – What is the Optimal Therapy?
Optimizing Current Treatments: The OPTIMIZE Trial

- Reduce exacerbations in children undergoing eradication of *P. aeruginosa*
- **Add azithromycin to inhaled tobramycin**
- Azithromycin group
  - 44% reduction in exacerbations
  - 1.27 kg weight gain
  - No impact on microbiology

STOP 2 Underway: Compares Antibiotic Treatment Duration for Exacerbations

Safety and effectiveness of different treatment durations based on response to therapy

- Regimen 1 & 2: early robust responders (ERR)*
  - treat 10 vs. 14 days
- Regimen 3 & 4: non-early robust responders (NERR)
  - treat 14 days vs. 21 days

* FEV$_1$ 5-10% and CRISS improved >11 units

---

<table>
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<tr>
<th>Rank</th>
<th>Clinician responses</th>
<th>Higher Priority</th>
<th>Patient/family responses</th>
<th>Higher Priority</th>
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<td>Antibiotic treatment duration</td>
<td>73%</td>
<td>Site of treatment (home, hospital)</td>
<td>51%</td>
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<tr>
<td>2</td>
<td>1 vs. 2 antibiotics for Pa$_1$</td>
<td>48%</td>
<td>When to start antibiotics</td>
<td>51%</td>
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<tr>
<td>3</td>
<td>Continuous infusion of β-lactam</td>
<td>38%</td>
<td>Antibiotic route(s)</td>
<td>43%</td>
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<tr>
<td>4</td>
<td>Site of treatment (home, hospital)</td>
<td>35%</td>
<td>Antibiotic treatment duration</td>
<td>40%</td>
</tr>
<tr>
<td>5</td>
<td>Use of corticosteroids</td>
<td>32%</td>
<td>Use of corticosteroids</td>
<td>20%</td>
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</table>

* Proportions of respondents indentifying topic as 1st or 2nd highest priority to study.
* Pseudomonas aeruginosa airway infection.
STOP 2 Current Enrollment: 10/1/18

- 58 sites
- 701 randomized: 501 NERR and 200 ERR (2.5:1 ratio)

880 Sample Size:
- 570 NERR
- 310 ERR

NCT02781610
Improving the Management of NTM

• Clinical observations
  – NTM can be transient
  – Remain indolent
  – Accelerate progression of lung disease

• International effort to write and disseminate diagnostic and treatment consensus guidelines

Prospective Evaluation of NTM Disease in Cystic Fibrosis (PREDICT Study)

- Prospective, observational study at Pediatric and Adult Colorado CF Care Center
- Use algorithm in consensus guideline to diagnose NTM disease
- Address NTM cultures, radiology, disease course, other microorganisms, and comorbidities

NCT02073409
PREDICT Preliminary Conclusions

• 42% of PREDICT subjects met criteria for NTM disease after median of 5 months

• Participants diagnosed with NTM disease had:
  – Significantly lower FEV$_1$ at enrollment
  – Significant and rapid decline in FEV$_1$
  – More frequent constitutional symptoms, severe exacerbations, and acute decline in BMI
Prospective Algorithm for Treatment of NTM in Cystic Fibrosis (PATIENCE)

- Open-label, treatment study at Colorado Pediatric and Adult CF Care Center
- Use single NTM treatment algorithm from consensus guideline
- Algorithm guides selection of therapy, obtaining NTM cultures, monitoring, and managing toxicity and intolerance

Inclusion:
- Age $\geq$ 7 years
- MAC or M. abscessus
- Judgment of CF physician that person with CF may benefit
- Person with CF and/or parent agrees with proposed treatment

NCT02419989
PATIENCE Preliminary Conclusions

Improved culture conversion rates (compared to historic rates) may in part be due to optimizing CF care first (PREDICT).
Expanding PREDICT and PATIENCE to Other CF Centers

- Increase enrollment, improve “power” to support findings
- Test and refine protocols
- Greater geographic diversity and distribution
- Benefits more individuals with CF
- Test feasibility and build “infrastructure” for future studies
IMAGINE with me…

These studies provide framework for future investigations.

- Standardize approach to diagnosing different disease-causing microorganisms
- Serve as comparator arm for investigating new treatment approaches
- Support biomarker discovery
Evaluating Long-Term Antimicrobial Use

- Important to revisit long term impact of drugs we use chronically
- Inadvertent drug interactions, intolerance, toxicity
- Only target single microorganisms, but may impact other microorganisms
- Could improve care through improving personalized medicine
Is there antagonism between azithromycin and tobramycin?

Secondary analysis of clinical trial
- Participants on tobramycin + azithromycin had less improvement in lung function than those on inhaled aztreonam + azithromycin

Biologic plausibility for antagonism
- Azithromycin upregulated MexXY efflux pump

Need for clinical trial

Testing the Effect of Adding Chronic Azithromycin to Inhaled Tobramycin: TEACH Enrollment: 10/1/18
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Video 2: Clinical Trial Experience
A decade ago…
# Cystic Fibrosis Foundation Anti-Infective Therapeutics Pipeline, 2009

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<th>Drug</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td>AZITHROMYCIN</td>
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<td>✔️</td>
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<tr>
<td>CAYSTON</td>
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<td>✔️</td>
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<tr>
<td>TIP (TOBRAMYCIN INHALED POWDER)</td>
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Cystic Fibrosis Foundation Anti-Infective Therapeutics Pipeline, 2009

#NACFC
Funded ID Therapeutic Portfolio

Discovery
- Diagnostic tool VITI

Preclinical
- Encocchelated Amikacin Matinas
- QRM-003 Qrumpharma
- Bismuth-thiols Microbion

Phase 1
- Itraconazole inhalation Pulmatrix
- SPI-3005 ebselen Sound Pharma
- Lactoferrin + OSCN Alaxia
- Gallium Citrate Aridis
- SNSP113 Synspira

Phase 2
- Nitric Oxide (inhaled) Novoteris
- Intravenous Gallium CFF

Phase 3
- Aerovanc Savara

Key:
- Pseudomonas
- MRSA
- NTM
- Fungal
- Ototoxicity
- Other (multi-pathogen)

In discussions with an additional 17 companies on potential therapeutics.

Last Updated: 3 Oct 2018
What are some approaches to developing new therapies?

- **Borrow agents from other infectious diseases**
  - MDR-TB agent Bedaquiline for NTM
- **Alter existing agents to become inhaled agents**
  - Inhaled itraconazole for ABPA
  - Inhaled vancomycin for MRSA
- **Repurpose drugs used for non-infectious conditions with unique mechanisms of action**
  - Gallium for *Pseudomonas* and others
  - Ca-EDTA for several pathogens
  - Inhaled NO for *Pseudomonas* and NTM
  - GM-CSF for NTM
Mechanism of Action for Gallium

• Bacteria use iron for DNA synthesis, oxidative stress response, other metabolic functions
• Gallium and iron are same size (ionic radius)
• Fool bacteria to use Gallium instead of iron
• Proof-of-concept Phase 1b Study
  – 20 adults with CF and chronic Pseudomonas
  – Improved lung function that persisted
• W17.6: Abstract 307

What are future questions for treating infections with increasing access to CFTR modulators?

- If CFTR modulators are used prior to infection:
  - Will people remain infection-free?
  - Will infections occur later?
  - Will emerging pathogens become problematic?
- Our current treatment paradigms may change.
- Our research and clinical approaches to infections will evolve.
A prospective study to evaluate biological and clinical effects of significantly corrected CFTR function
2 year prospective observational study of short- and long-term clinical effectiveness of next generation modulators

Objectives:
- Impact on lung function, sweat Cl⁻, symptoms, BMI
- Focused sub-studies, e.g., microbiology, inflammation, gastrointestinal issues
- Biobank for future studies

400 people with CF
- ≥12 years of age
- F508del heterozygote/minimal function allele (~60%)
- F508del homozygous (~40%)
- Stable health
- Willing to maintain current therapies for ≥ 6 months
Amazing Tool Box Available

- Highly motivated partners: individuals with CF, families, and care centers
- Research Tools
- Collaborations
- Funding resources
- Industry partnerships
- Infrastructure to conduct studies
- Biobanks
- New ideas
It Takes a Village

Patrick Flume
Nicole Hamblett
Luke Hoffman
John LiPuma
Dave Nichols
Jerry Nick
Lynne Quittell
Pradeep Singh
Valerie Waters

OPTIMIZE Study Team
STOP Trial Study Team
TEACH Trial Study Team
PATIENCE Study Team
PREDICT Study Team
PROMISE Trial Study Team
Dublin Study Group
SCVSA Study Group

Team at CF Foundation:
Aliza Fink, Genevieve Maul,
Stephanie McDermott,
Susan Schept, Jenna Vince

#NACFC
Infection-related Symposia, Workshops, and Posters

Symposia
• S12 – Microbial Adaption in the CF Airway
• S21 – Controversies in Airway Infection

Workshops
• W11 – Airway Innate Defense Defects in CF
• W17 – Epidemiology & Management of Infections
• W27 – Microbial Ecology of CF Airways

Infection-related posters
Presented at the Cystic Fibrosis Foundation’s NACFC 2018