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• To advance drug development and a search for a cure, the Cystic Fibrosis Foundation has contractual agreements with several companies to receive royalties related to drugs that are developed as a result of CF Foundation 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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Senior Vice President of Therapeutics Development
Cystic Fibrosis Foundation
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## Quality Care Awards

<table>
<thead>
<tr>
<th>Advocate Children’s Hospital – Park Ridge</th>
<th>University of Michigan, Michigan Medicine</th>
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<td>Pediatric Program</td>
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<td>University of Vermont Medical Center</td>
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<td>University of Virginia Pediatric and Adult Programs</td>
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<td>Toledo Children’s Hospital &amp; Northwest Ohio Cystic Fibrosis Center Pediatric and Adult Programs</td>
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<td>University of Rochester Medical Center Strong Memorial Pediatric and Adult Programs</td>
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<td>University of Alabama at Birmingham Adult Program</td>
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<td>SUNY Upstate Medical University Pediatric and Adult Programs</td>
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<td>University of Mississippi Medical Center Pediatric and Adult Programs</td>
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Francis S. Collins, MD, PhD
Director
National Institutes of Health
Presenter Disclosure

Francis S. Collins, M.D., Ph.D.

There are no relationships to disclose related to this presentation.
Presenter Disclosure

Francis S. Collins, M.D., Ph.D.

There are no commercial relationships to disclose related to this presentation.

Over thirty years, there are a lots of wonderful relationships with amazing people that relate to this presentation!
The Hunt for the Causative Gene

1938: CF recognized as a disease; classic, autosomal recessive inheritance — so the gene must be somewhere

1985: Mapped to chromosome 7 by family linkage studies

1987: Gene must be located somewhere in a ~2,000,000 base pair segment between MET and marker J3.11, but...
  - No cytogenetic abnormalities
  - No large deletions
  - No human genome project
Time for a New Approach: Let’s Collaborate!
February 20, 1989

Dear Francis,

My family is now in a desperate way! There has not been any income since June 1st, my children are in the streets and my wife is the sole breadwinner. I stay at CFF awaiting your call every day that the CF gene is in hand. I hear tid-bits now and then about transfecting experiments, stories about having cDNA libraries and new jumps, but the truth is there still is no gene.

The situation is getting more desperate. Now Bob Dresing is thinking about putting me out on the street... taking away my office because I have not been able to deliver the CF gene. We both are in need of some hope and optimism.

Needless to say, my desperate situation should not impart any pressure on you. Remember, “no pressure.”

Thank you for everything, but let’s hurry up a little.

Bob Beall, Ph.D. President of the CF Foundation
**CFTR Phe508del Mutation**
Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping


Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA

John R. Riordan, Johanna M. Rommens, Bat-sheva Kerem, Noa Alon, Richard Rozmahel, Zbyszko Grzelczak, Julian Zielenki, Si Lok, Natasa Plavsic, Jia-Ling Chou, Mitchell L. Drum, Michael C. Iannuzzi, Francis S. Collins, Lap-Chee Tsui

Identification of the Cystic Fibrosis Gene: Genetic Analysis

Bat-sheva Kerem, Johanna M. Rommens, Janet A. Buchanan, Danuta Markiewicz, Tara K. Cox, Arawinda Chakravarti, Manuel Buchwald, Lap-Chee Tsui
To Day is the most
Best day ever in my Life. They found a jean for
Cystic Fibrosis

J.H., 8 y/o CF patient.
Diary entry, Aug 25, 1989
The Long and Winding Road from Gene Discovery to Effective Treatment

1990: Understanding types, prevalence of CFTR mutations
- ~90% of CF patients have one or two copies of Phe508del
- ~4-5% of CF patients have $G551D$

1990 to now: Elucidating CFTR’s function and effect of mutations

1990 to now: Attempting correction by gene therapy to airway

Late 1990s to now: Identifying, testing compounds with potential to enhance chloride transport in CF patients….
Patients with Cystic Fibrosis Eligible for Molecularly Targeted Drugs (%)

- 2012: 5%
- 2013: FDA approves ivacaftor for G551D CFTR mutation, nine other rare mutations
Jane C. Davies, MD

Professor of Paediatric Respirology & Experimental Medicine
Honorary Consultant
National Heart & Lung Institute, Imperial College London
Royal Brompton Hospital, London, UK
Presenter Disclosure

Jane Davies, MD

The following relationships exist related to this presentation:

• Clinical Trial Advisory/Leadership roles:
  – Vertex, Proteostasis, Galapagos, Eloxx

• LCI Core Facility funding:
  – European CF Society
Entering the era of highly effective modulator therapy

Jane Davies
Imperial College London
Royal Brompton Hospital, UK
The Cystic Fibrosis Gene Is Found

Researchers have identified the major gene defect that causes cystic fibrosis. The discovery should lead to better diagnosis and perhaps improved therapies for the now fatal disease.

The race to find the cystic fibrosis gene is over. In three papers to be published in the 8 September issue of Science, researchers from Toronto and Ann Arbor report that they have cloned the gene and pinpointed the gene defect that causes most cystic fibrosis cases. "The data are virtually irrefutable that they have the right gene," says Louis Kunkel of Children's Hospital Medical Center in Boston, a cloning expert who led the successful search for the gene causing Duchenne muscular dystrophy.

Cystic fibrosis researchers have looked long and hard for their gene—and with good reason. The disease is the most common genetic disorder of Caucasian. In the United States, it strikes one child in every 3,000. An estimated 30,000 people have the disease today, and their prospects are grim. Most will die before their thirtieth birthday. Perhaps not surprisingly, news of the gene discovery began to leak out before the scheduled publication of the papers describing the research, and this in turn prompted the editor of Science to drop their normal embargo policy (see box on p. 924).

The discovery means that scientists can identify cystic fibrosis, including prenatal diagnosis, and also devise better treatments for those who carry a defective copy of the gene and run the risk of passing the disease to their children. It also raises hope for better cystic fibrosis treatments, perhaps new drugs or even gene therapy to replace the defective gene itself.

The race could have been considered until scientists could get a handle on the basic protein defect that causes cystic fibrosis. "Now we can finally study the basic defect and we may be able to treat the defect directly, not just the symptoms," says Lap-Chee Tsui, the leader of one of the groups that cloned the gene. No one can now predict, however, how long it might take to do this or even if it will prove to be possible. The search for the cystic fibrosis gene has taken years, and the work involved the collaboration of scientists from several institutions.

At the start of the search, the cystic fibrosis gene was known to carry any such convenient tag, unfortunately. In 1985, however, 2 years before Tsui and his colleagues joined forces with Collins and his team, the Toronto group had a big boost to their efforts. They identified the gene when they discovered a mutation on the chromosome in a patient with cystic fibrosis. This mutation was then mapped to chromosome 7. Wilton and his colleagues at the University of Utah in Salt Lake City further narrowed its location by identifying two "markers," the met allele and the DNA sequence designated J11, that flanked the gene (see diagram).

At the end, a collaborative effort by the groups of Tsui and John Riordan at Toronto's Hospital for Sick Children, together with Francis Collins at the Howard Hughes Medical Institute at the University of Michigan, bagged the gene. The researchers appear to have a clear victory. "We have a lot of papers in press but we don't have the gene," says chief investigator Robert Williamson of Saint Mary's Hospital Medical School in London, who has led the effort to clone the cystic fibrosis gene. "If we couldn't get it, we're very pleased that Francis and Lap-Chee were the ones to do it."

The collaboration between Tsui and Collins began in the fall of 1984, when the two researchers, who had previously been working independently, got together in San Diego at the annual meeting of the American Society for Human Genetics. "It was clear then that this was a very hard problem that was not going to be solved without a great deal of effort," Collins says.

The cystic fibrosis gene was such a tough nut to crack because, in the absence of information about the protein it encodes, researchers did not know what they were looking for among the estimated 100,000 genes in the human genome. Bioscientists have managed to clone a few other genes without knowing what their products were—the Duchenne muscular dystrophy gene is one of them—but some of the others, including the mutation for the disorder, were the Duchenne muscular dystrophy gene is one of them—but some of the others, including the mutation for the disorder.
CFTR functions as an ion channel
• No CFTR made (nonsense)
• Misfolded CFTR fails to reach cell surface

Designing CFTR modulator drugs: 3 groups

• Conductance abnormal
• Not enough CFTR/unstable
- No CFTR made (nonsense)
- Misfolded CFTR fails to reach cell surface

Other mutations lead to CFTR which reaches cell surface

- Defective gating (fails to open)
- Conductance abnormal
- Not enough CFTR/unstable

No CFTR for modulators to work on

Needs to re-fold and reach cell surface: ‘CORRECTORS’

Improve function: ‘POTENTIATORS’
Understanding Genetics and Impact on Protein Function Led to New Drug Development Programmes: 1st Drugs Potentiators
Understanding Genetics and Impact on Protein Function Led to New Drug Development Programmes

• First steps:
  – High throughput screening
  – Identification of hits leading through medicinal chemistry to ivacaftor
  – Phase 2 studies:
    • sweat Cl-, nPD, FEV₁
A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Drivdik, M.D., Matthias Greise, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Rajzen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Quiming Dong, Ph.D., Sally Rodriguez, Ph.D., Karl Yen, M.D., Claudia Ordóñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*
What Really Matters: Long-term Outcomes
Lung Health in the Longer Term: EXACERBATIONS

Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries

Nataliya Volkova 1,*, Kristin Moy 3, Jennifer Evans 3, Daniel Campbell 1, Simon Tian 4, Christopher Simard 4, Mark Higgins 3, Michael W. Konstan 5, Gregory S. Sawicki 6, Alexander Elbert 1, Susan C. Charman 1, Bruce C. Marshall 1, Diana Bilton 1,6

A

US CFFPR

<table>
<thead>
<tr>
<th>Year</th>
<th>R (95% CI)</th>
<th>Ivacaftor</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline year (2011)</td>
<td>1.13 (1.00-1.28)</td>
<td>0.71 (0.61-0.82)</td>
<td>0.60 (0.51-0.70)</td>
</tr>
<tr>
<td>Year 1 (2012)</td>
<td>0.80 (0.52-0.70)</td>
<td>0.58 (0.50-0.67)</td>
<td>0.58 (0.51-0.67)</td>
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</tbody>
</table>

Patients with PEx (%)


37.5 | 33.1 | 36.1 | 37.9 | 39.4 | 41.7 | 44.0


53.8 | 54.9 | 54.7 | 55.2 | 57.5

UK CFR

<table>
<thead>
<tr>
<th>Year</th>
<th>R (95% CI)</th>
<th>Ivacaftor</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline year (2011)</td>
<td>1.19 (1.04-1.36)</td>
<td>0.86 (0.74-0.99)</td>
<td>0.56 (0.46-0.69)</td>
</tr>
<tr>
<td>Year 1 (2012)</td>
<td>0.62 (0.52-0.75)</td>
<td>0.57 (0.47-0.67)</td>
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</tr>
</tbody>
</table>

Patients with PEx (%)


30.8 | 34.4 | 32.8

34.4 | 32.8

55.2 | 57.5

57.5
Lung Health in the Longer Term: **Pa INFECTION**
Lung Health in the Longer Term: FEV$_1$ DECLINE

Significant improvements in survival and need for transplantation
But only a minority of the CF population suitable for potentiator monotherapy
Prevalence of the 25 Most Common CFTR Mutations in People with CF Seen in 2018

- [84.7%] F508del
- [4.6%] G542X
- [4.4%] G551D
- [3.0%] R117H
- [2.3%] N1303K
- [2.2%] W1282X
- [1.8%] 3849+10kbC>T
- [1.8%] R553X
- [1.6%] 621+1G>T
- [1.6%] 1717-1G>A
- [1.4%] 2789+5G>A
- [1.1%] 3120+1G>A
- [1.0%] D1152H
- [0.9%] 5T
- [0.8%] I507del
- [0.8%] 3272-26A>G
- [0.8%] 2184insA
- [0.7%] R334W
- [0.7%] 1898+1G>A
- [0.7%] 3659delC
- [0.6%] G85E
- [0.6%] L206W
- [0.6%] R347P
- [0.6%] A455E
- [0.6%] R334W
- [0.5%] 3843+12del
- [0.5%] 508+1G>
- [0.5%] 741Trp
- [0.5%] 3272-26A>G
- [0.5%] 2184insA
- [0.5%] R334W
- [0.4%] 508+1G>
- [0.4%] 741Trp
- [0.4%] 3272-26A>G
- [0.4%] 2184insA
- [0.4%] R334W
- [0.4%] 508+1G>
- [0.4%] 741Trp
- [0.4%] 3272-26A>G
- [0.4%] 2184insA
- [0.4%] R334W
- [0.4%] 508+1G>
Progress Toward F508del

- Does not reach cell surface
- Degraded due to misfolding

- ‘Correctors’ aid trafficking
  - Early drugs insufficient alone
  - Combinations with potentiators successful
Lumacaftor/ivacaftor in People Homozygous for F508del

Wainwright C et al. NEJM 2015
Konstan M et al. Lancet Resp Med 2017
Tezacaftor/ivacaftor similarly effective, better tolerated

Both: Early impact on FEV₁ modest compared to ivacaftor
The Leap to Triple Combinations

Why are they needed?

CFTR Misfolding Very Complex: More Than One Approach Needed

Triple compounds:
2 correctors, different mechanisms
Potentiator ‘boost’
Elexacaftor in Triple Combination with Tezacaftor/Ivacaftor Increased F508del-CFTR Quantity and Function In Vitro

ELX/TEZ/IVA significantly increased chloride transport in F508del/MF-HBE and F508del/F508del-HBE cells compared with TEZ/IVA or ELX/IVA

ELX/TEZ/IVA increased steady-state levels of mature CFTR protein in vitro in F508del/MF-HBE and F508del/F508del-HBE cells compared with TEZ/IVA or ELX/IVA

MF, minimal function.
Primary endpoint for both studies: absolute change from baseline in ppFEV₁ at Week 4
Substantial Improvements in Lung Function and Rate of Pulmonary Exacerbations

LS, least squares; MF, minimal function; MMRM, mixed-effects model for repeated measures; PEx, pulmonary exacerbation; ppFEV₁, percent predicted forced expiratory volume in 1 second.

- Data are LS means based on an MMRM. PEx was defined as a new event or change in antibiotic therapy (IV, inhaled, or oral) for ≥4 sinopulmonary signs/symptoms. The event rate was calculated based on 336 days (48 weeks) in a year. A Poisson regression model was used to estimate the event rate for PEx. PEx leading to hospitalization and PEx treated with IV antibiotics were not controlled for multiplicity.

---

### LS Mean Absolute Change From Baseline in ppFEV₁ (SE), percentage points

- **Study 102, F/M**

### LS Mean Absolute Change From Baseline in ppFEV₁ (SE), percentage points

- **Study 103, F/F**

### Estimated Event Rate per Patient-Year

- **ELX/TEZ/IVA**
  - 63% reduction vs placebo (rate ratio, 0.29; 95% CI: 0.14, 0.61)

- **TEZ/IVA**
  - 71% reduction vs placebo (rate ratio, 0.22; 95% CI: 0.11, 0.43)
Individual Responses with Respect to Percentage of Predicted FEV₁

No. of Patients

-10 or less
-10 to -5
>5 to 0
0 to 5
5 to 10
10 to 15
15 to 20
20 to 25
25 to 30
>30

Absolute Change from Baseline in Percentage of Predicted FEV₁ through Wk 24

Placebo
Elexacaftor–tezacaftor–ivacaftor
Significant Improvements in Sweat Chloride, CFQ-R Respiratory Domain Score and BMI

Data are LS means based on an MMRM; dotted blue line indicates a change in 4 points, which is the minimal clinically important difference for pwCF with stable disease.1 Quittner AL, et al. Chest 2009; 135: 1610-1618.
Individual Responses with Respect to Sweat Chloride Concentration

- Placebo
- Elexacaftor–tezacaftor–ivacaftor

No. of Patients

-60 or less
>-60 to -50
>-50 to -40
>-40 to -30
>-30 to -20
>-20 to -10
>-10 to 0
>0 to 10
>10 to 20
>20

Bar chart showing the distribution of sweat chloride concentration responses to placebo and Elexacaftor–tezacaftor–ivacaftor treatments.
### Study 102, F/MF: ELX/TEZ/IVA Was Generally Safe and Well Tolerated

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=201), %</th>
<th>ELX/TEZ/IVA (N=202), %</th>
<th>Placebo (N=201), %</th>
<th>ELX/TEZ/IVA (N=202), %</th>
<th>Placebo (N=201), %</th>
<th>ELX/TEZ/IVA (N=202), %</th>
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<td><strong>Most Common (≥10%) AEs</strong></td>
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<td>Infective PEx</td>
<td>47.3</td>
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<td>Sputum increased</td>
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<td>Oropharyngeal pain</td>
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<tr>
<td><strong>SAEs, Discontinuations, Deaths</strong></td>
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<td>0.5</td>
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<td>Nasopharyngitis</td>
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<tr>
<td>Oropharyngeal pain</td>
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<tr>
<td>Hemoptysis</td>
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<td>Fatigue</td>
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<tr>
<td><strong>Other Events</strong></td>
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<tr>
<td>ALT/AST AEs</td>
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<td></td>
<td>4.0</td>
<td>10.9</td>
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<td>ALT/AST elevations</td>
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<tr>
<td>&gt;3× ULN</td>
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<tr>
<td>&gt;8× ULN</td>
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<td>1.0</td>
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<td>Rash events</td>
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<td>6.5</td>
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<td>AEs of creatine kinase elevation</td>
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<td>4.5</td>
<td>9.9</td>
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</table>

*AE, adverse event; SAE, serious AE; ULN, upper limit of normal; URTI, upper respiratory tract infection.

*Two patients in the placebo group were included in the ELX/TEZ/IVA safety set due to receipt of the incorrect study treatment.

*Group term that includes preferred terms of rash (eg, rash, rash generalized, rash pruritic).
Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele


Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial

Harry G M Heijerman*, Edward F McKone*, Damian G Downey, Eva Van Braeckel, Steven M Rowe, Elizabeth Tullis, Marcus A Mall, John J Welter, Bonnie W Ramsey, Charlotte M McKee, Gautham Marigowda, Samuel M Moskowitz, David Waltz, Patrick R Sosnay, Christopher Simard, Neil Ahluwalia, Fengjuan Xuan, Yaohua Zhang, Jennifer L Taylor-Cousar*, Karen S McCoy*, on behalf of the VX17-445-103 Trial Group†
Modulator Landscape

- No F508del, no gating, no RF (5-10%)
- RF/other
- Gating/MF or RF
- F508del/Gating
- F508del/RF
- F508del/MF
- F508del/F508del

'HIGHLY EFFECTIVE'

Elexa/Tez/Iva (FDA Oct 2019)

Iva (approved)

Tez/Iva (approved)

Lum/Iva (approved)

Tez/Iva (approved)

MF = minimal function
RF = residual function
Video of adult F/MF
Maximizing Impact
Can we achieve more by starting early?

- Almost certainly with the lungs
- Disease easier to prevent/delay than reverse
Good Idea, But Benefits Hard to Measure?
Lung Clearance Index
Benefits of Lumacaftor/Ivacaftor in Early Life: Much Clearer with LCI Than FEV$_1$

Also primary outcome in 6-11 years tez/iva and triple compounds

Ratjen et al. Lancet Resp Med 2017
Can we achieve more by starting early?

- Beyond the lungs?
- Evidence of pancreatic impacts
Early-Life Window for Pancreatic Disease

Long-term Impacts of Ivacaftor: CFRD

Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries

Nataliya Volkova, Kristin Moy, Jennifer Evans, Daniel Campbell, Simon Tian, Christopher Simard, Mark Higgins, Michael W. Konstan, Gregory S. Sawicki, Alexander Elbert, Susan C. Charman, Bruce C. Marshall, Diana Bilton.
Capturing the Full Potential for Benefit

A prospective study to evaluate biological and clinical effects of significantly corrected CFTR function.
| **CORE** | Clinical effectiveness; generate bio-specimen bank for researchers | Steven Rowe  
David Nichols |
|----------|---------------------------------------------------------------|---------------------------|
| **MUCUS** | Determine impact on MCC; relationships with mucus viscosity, pH, and functional microanatomy | Steven Rowe  
Scott Donaldson |
| **MICRO** | Determine whether microbiology and microbiome are altered | David Nichols  
Pradeep Singh  
Lucas Hoffman |
| **LIVER** | Discern the effect of CFTR modulation on liver enzyme elevation and biomarkers of hepatic fibrosis | Michael Narkewicz |
| **GI** | Determine effects on GI quality of life, pancreatic function, and microbiome/intestinal inflammation | Steven Freedman  
Sarah Jane Schwarzenberg  
Carla Frederick  
Daniel Gelfond |
| **ENDO** | Establish effects on diabetes/glucose metabolism, bone density, and other measures of nutrition and growth | Andrea Kelly  
Michael Stalvey |
| **INFLAM** | Examine changes in sputum and serum inflammatory measures | Scott Sagel |
| **HNE** | Biobank of HNE cells and assess ion transport in vitro | George (Marty) Solomon |
“But you keep expecting me to take more and more drugs…"
Priority (1)

What are the effective ways of simplifying the treatment burden of people with CF?
**SIMPLIFY: A Master Protocol for Testing Withdrawal of Chronic Therapies after HEMT**

**Design:** Parallel, randomized trials of hypertonic saline and dornase alfa

**Objective:** Test whether or not there are clinical changes after short-term withdrawal of chronic therapy in those taking Elexa/Teza/Iva

**Endpoints:** FEV$_1$pp, Safety, PROs, LCI, MCC

**Status:** Expected to begin in Q2 2020
So, Are We Done?

• No, more work to do:
  – Established disease:
    • unlikely to reverse
  – Pulmonary exacerbations:
    • reduced, not prevented
  – Chronic infection:
    • may not be cleared

• Interacting drugs/adverse reactions

• Regional differences in availability
Phase 2
Change in **Sweat Chloride** and **Lung Function** with Double and Triple Combinations

**Double Combination**
- Change in sweat chloride
  - LS Mean Change from Baseline in Sweat Chloride (mM)
  - Study Day
  - n=2
  - n=4

**Triple Combination**
- Change in lung function
  - LS Mean Change from Baseline in percent pPFV1
  - Study Day
  - Placebo
  - n=6
  - n=10

Data previously disclosed on October 17, 2018 and March 25, 2019.
Flatley Lab Pipeline

Pre-Clinical

Lead Identification | Lead Validation | Lead Optimization | Pre-Clinical Development
---|---|---|---
FDL169 CFTR Corrector
FDL169 Backup
FDL176 CFTR Potentiator
FDL176 Backup
FD2052160 Second Site CFTR Corrector
Dual Acting Modulators

Clinical

Phase I

Phase II

Flatley Discovery Lab
AbbVie CFTR Modulator Program

- Will develop CFTR potentiator licensed from the CF Foundation for potential use in combination treatments for CF.

- Currently investigating combinations of CFTR potentiator and corrector molecules
  - Phase II dose-finding study:
    - ABBV-2222 (corrector)
    - ABBV-3067 (potentiator)
    - homozygous F508del
Remaining Challenges

• For some patients current CFTR modulator pipeline not optimal:
  – No CFTR produced:
    • Plenary I: encouraging progress, early days
  – Rare mutations:
    • Understudied
    • Poorly understood
    • May respond to therapies: different approach to testing needed
Systems to Predict Efficacy of CFTR Modulators

(A) **In vitro**
Cell lines (FRTs, HBEs)
- Cell lines with CFTR (over)expression
- Ussing chamber

(B) **In vitro**
Induced pluripot. stem cells
- iPSCs
- Ussing chamber

(C) **Ex vivo**
Primary HNECs/HBECs
- HBECs
- Ussing chamber
- HNECs

(D) **Ex vivo**
Intestinal organoids
- Intestinal organoids
- FIS assay

**Mutation-specific In vitro Theratyping**

**Patient-specific Ex vivo Theranostics**

Credit: Margarida Amaral
Review

CFTR modulator theratyping: Current status, gaps and future directions☆

John Paul Clancy a, John H. Donaldson c, Donald R. VanDevanter e, Michael P. Boyle f, Martina Gentzsch g, Jorge Wallenburg j, Eric J. Sorscher k, Margarida D. Amaral l, Jennifer Anjaparavanda P. Naren m, Robert J. Bridges o, Philip J. Thomas p, Garry E. Stringer q, Anthony G. Durmowicz r, Martin Mense t, Kris D. Bocek u, William Skach v, Elizabeth Joseloff v, Hemmann Bihler v, John Mahoney v, Drucy Borowik v.
Remaining challenges

- Global inequities in access
- The expanding & ageing population:
  - Continuing development of symptomatic therapies
  - New issues and priorities
Estimates on the evolving patient landscape

Estimates of Patients by Health Status

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

End of 2016 ~5 year vision ~10 year vision ~20 year vision

Note: Healthy defined as FEV₁ >90%, Moderate as FEV₁ 40-90%, and Advanced disease as FEV₁ <40%

Source: Revised Model for July 2018 CFF Medical Strategy Retreat
'HIGHLY EFFECTIVE' (FDA Oct 2019)

No F508del, no gating, no RF (5-10%)

RF/other
Gating/MF or RF

F508del/Gating
F508del/RF
F508del/MF
F508del/F508del

Iva (approved)
Tez/Iva (approved)
Lum/Iva (approved)
Getting Closer to Our Shared Vision

• Best drugs
• All patients
• As quickly as possible
Francis S. Collins, MD, PhD
Director
National Institutes of Health
Don't Give Up On Me (Andy Grammar)
- 'Cause I'm not givin' up
- I'm not givin' up, givin' up, no not yet
- Even when I'm down to my last breath
- Even when they say there's nothin' left
- So don't give up on...

- I'm not givin' up
- I'm not givin' up, givin' up, no not me
- Even when nobody else believes
- I'm not goin' down that easily
- So don't give up on me
Dare To Dream

Dare to dream, dare to dream
All our brothers and sisters
breathing free
Unafraid, our hopes unswayed
‘Til the story of CF is history