In 1955 most children with CF did not live long enough to go to school.
• Median survival is over 40 years of age
• One half of all patients are now adults
• Nine CF therapies have been FDA approved
• One CF therapy treats the basic defect and more are likely
How did this happen?
Cystic Fibrosis Foundation: Enabling Success
Pathogenesis of CF Lung Disease

- Mutant CFTR
  - Depleted ASL
  - Defective mucociliary clearance

- Infection
- Obstruction
- Inflammation

Progressive, irreversible lung damage

Adapted from Chmiel et al. Clin Rev Allergy Immunol 2002
Symptom-based CF Therapies
What was the impact of these new symptom-based therapies and quality improvement?
Median Survival Age of Patients with Cystic Fibrosis

Source: Cystic Fibrosis Foundation, National Patient Registry
• CFF Therapeutic Development Program (TDP) started in 1998

  – Created to encourage industry and academia to focus on CF and CFTR as drug target

  – Components of TDP

    – Financial assistance

    – Research tools and scientific advice

    – Well organized clinical trial network
Vertex Screening Strategy

- Orally bioavailable drugs
- Two CFTR targets:

**Potentiators:**
Increase opening (gating) of CFTR channels

- G551D
- VX-770

**Correctors:**
Increase number and function of CFTR channels at the cell surface

- F508del
- VX-809
Ivacaftor Phase 3 Results (Sweat Chloride)

Change in sweat chloride concentration
mmol/L (mean, 95% CI)

-60
-55
-50
-45
-40
-35
-30
-25
-20
-15
-10
-5
0
5

Placebo
Ivacaftor

Estimates are model-based. Points and 95% CI are unadjusted (raw)
Phase 3 Results (G551D)

FEV1

PEx

CFQ-R

wt

Phase 3 Results of CF Therapies

Relative Change in FEV<sub>1</sub> % Predicted from Baseline (with 95% CI)

- **ivacaftor**
- **inhaled tobramycin**
- **dornase alfa**
- **azithromycin**
2012 - FDA Approves Ivacaftor
What else can we learn from G551D patients who will be treated with ivacaftor?
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
Effect of ivacaftor on pancreatic function in G551D Age 2-5: Evidence of partial rescue
Mucociliary Clearance: *The Movie*

**Baseline**

**Ivacaftor - 3 months**

Trachea

Stomach

*Courtesy of Dr. Tim Corcoran, U. Pittsburgh*
**P. aeruginosa** Culture Rate

Data courtesy of Dr. Steve Rowe and the GOAL Study Team
Ivacaftor Lung Function Benefit Persists

See: McKone et al. NACFC 2013
Effect of Decreased Rate of Decline in $\text{FEV}_1$

- **G551D With Ivacaftor**
- **F508del/F508del**

**Lung Transplant**
CFTR Potentiator (Ivacaftor)
Could work in 15% of CF population
Clinical trials are ongoing to enable FDA approval
## Ivacaftor Expansion Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Mutation Description</th>
<th>Population %</th>
<th>% Population (cumulative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>G551D</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>2013</td>
<td>other gating mutants</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>2014</td>
<td>R117h</td>
<td>8%</td>
<td>17%</td>
</tr>
</tbody>
</table>

**Predicted:**

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
<th>Population %</th>
<th>% Population (cumulative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-2016</td>
<td>residual function</td>
<td>15%</td>
<td>26%</td>
</tr>
</tbody>
</table>
What About the Most Common Mutation - F508del?

50% of US patients have F508del mutations on both alleles

90% of US patients have at least one F508del mutation
• Orally bioavailable drugs
• Two CFTR targets:

**Potentiators:** Increase opening (gating) of CFTR channels

**Correctors:** Increase number and function of CFTR channels at the cell surface
Phase 3 Study Design

Screen Day -28 to Day -1
Randomize 1:1:1 on Day 1

Phase I: 24-Week Dosing Period

- **N=167**
  - Lumacaftor 400 mg Q12H + Ivacaftor 250 mg Q12H
  - Lumacaftor 600 mg QD + Ivacaftor 250 mg Q12H
  - Placebo + Placebo

**SAFETY FOLLOW UP**
- At Week 28
- OR
- BLINDED (ACTIVE) ROLLOVER Up to 96 Weeks

Study VX12-809-105

Homozygous F508 subjects
Lumacaftor/Ivacaftor Improved FEV₁

Absolute Change from Baseline in Percent Predicted FEV₁

- **Placebo**
- **LUM 600 mg qd / IVA 250 mg q12h**
- **LUM 400 mg q12h / IVA 250 mg q12h**

* P<0.025

Ramsey, Boyle, Elborn...Wainwright et al. Poster #250 NACFC 2014
Symposium 10.3, Wainwright, Friday 11:30 AM
• FEV1 absolute improvement- 3%
• Pulmonary exacerbations reduced by 30-40%
• Weight gain

• Next steps: NDA to be submitted this year
What about patients that only have one copy of F508del?

Their F508del response should be approximately one half that of homozygous patients.
Lumacaftor/Ivacaftor does not improve FEV$_1$ in F508del Heterozygotes
Effect of 28 days of VX-661/ Ivacaftor on FEV$_1$ in F508del Homozygotes

**CFTR Corrector: VX-661**

- Works with similar mechanism to lumacaftor to traffick F508del-CFTR to cell surface
- Longer Half-life; Less drug-drug interactions than lumacaftor; No evidence of early chest tightness

Donaldson, Pilewski....Rodman, et al. ECFS 2014
Overview of VX-661-Ivacaftor

- In F508del-CFTR homozygous subjects, VX-661-ivacaftor demonstrates statistically significant and clinically meaningful improvement in lung function
  - Absolute percent predicted FEV1 improvement = 4.5-4.8%
  - Relative percent predicted FEV1 improvement = 7.5-9.0%

- In F508del/G551D heterozygous subjects, lung function is significantly increased when VX-661 is added to a physician-prescribed Kalydeco regimen
  - Absolute percent predicted FEV1 increased 5.2%
  - Relative percent predicted FEV1 increased 8.4%
VX-661-Ivacaftor Proposed Pivotal Studies

- F508/F508 pivotal (VX14-661-106)
  - Placebo-controlled study of 24 week duration enrolling approx. 500 subjects

- F508/non-responsive pivotal (VX14-661-107)
  - Placebo-controlled study of 12 week duration enrolling approx. 280 subjects

- F508/residual function pivotal (VX14-661-108)
  - Placebo-controlled and ivacaftor monotherapy controlled study; 8 week cross-over design, enrolling approximately 300 subjects

- F508/gating pivotal (VX14-661-109)
  - Ivacaftor monotherapy controlled study of 8 week duration (4 week run-in with ivacaftor alone), enrolling 150 subjects

- Program-wide Open Label Extension (OLE) study (VX14-661-110)
  - For participants of any pivotal study and study VX13-661-103
Ongoing Efforts to Identify the Next Generation F508del CFTR Correctors
The Next Generation of CFTR correctors will target different parts of F508del-CFTR to further stabilize CFTR folding and dramatically increase the amount of CFTR trafficked to the cell surface.
New Screening Program Highlights

• A large diversified chemical space is being screened
  – Strategically diverse chemical libraries
  – Millions of compounds screened last year

• Novel screens are being performed
  – Primary screens in human bronchial epithelial cells
  – Screens with CFTR domains (NBD1 stability)
  – Airway surface liquid maintenance

• Goal is to have efficacy greater than that seen with Kalydeco in G551D patients

• Timeline
  – Clinical trials could start next year
  – Projected approvals: 2019-2023
Goal of Second Generation Program on CFTR Activity

![Bar chart showing CFTR Activity for G551D and F508del/F508del variants with different treatments: Untreated, Kalydeco, VX-809, VX-809 + Kalydeco, VX-809 + Kalydeco + 2cd Corrector.](image)
CFTR Modulators and US CFTR Genotype Distribution

Our Goal is CFTR Modulation for 100% Patients!
Potential Pulmonary Treatments For The Last 5% of Patients

• Nonsense mutations (3%)
  – New novel screening programs underway
  – Ataluren

• Mutations unlikely to respond to small molecules (2%)
  – DNA transfer
  – mRNA transfer
  – Restore airway surface liquid
    • ENaC inhibition
    • Alternative chloride channel activation
    • Novel delivery of hypertonic saline solutions
  – Mucus rheology altering agents
Personalized CF Regimens

• Maximize CFTR function
  – Initially based on the patient’s CFTR mutations
  – Ultimately a personalized response may be used

• Symptomatic therapies will be utilized as needed
  – Infants and young children with excellent CFTR restoration may not need other therapies
  – Understanding impact of various levels of CFTR restoration will help us determine what additional therapies are needed to maintain health
  – Older patients with established disease will probably continue to need other therapies
Long-term Issues

- Cost of therapies
- Burden of therapies
- Access to therapies
- Adherence to therapies

- Is there a better way?
Thank you!

PRESTON W. CAMPBELL, III, M.D.
Executive Vice President for Medical Affairs