Cystic Fibrosis-Update

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Lecture Outline

• Epidemiology of CF
• Pathophysiology and genetics
• Diagnostics
• Targeting the genetic defect
CF Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal Article / Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1938</td>
<td>CF of the pancreas and its relation to celiac disease.</td>
</tr>
<tr>
<td>1951</td>
<td>Heat prostration in fibrocystic disease of the pancreas and other conditions.</td>
</tr>
<tr>
<td>1953</td>
<td>Abnormal electrolyte composition of sweat in CF</td>
</tr>
<tr>
<td>1955</td>
<td>Creation of CFF – spearheaded by families of children with CF</td>
</tr>
<tr>
<td>1959</td>
<td>A test for concentration of electrolytes in sweat in CF utilizing pilocarpine by iontophoresis.</td>
</tr>
<tr>
<td>1964</td>
<td>A therapeutic regimen for patients with CF.</td>
</tr>
<tr>
<td>1966</td>
<td>CFF patient registry formed</td>
</tr>
<tr>
<td>1979</td>
<td>Dried-blood spot screening for CF in the newborn.</td>
</tr>
<tr>
<td>1983</td>
<td>Chloride impermeability in CF.</td>
</tr>
<tr>
<td>1988</td>
<td>Effect of nutrition on survival is confirmed</td>
</tr>
<tr>
<td>2003</td>
<td>Evidence for benefit leads to recommendation for universal CF NBS</td>
</tr>
</tbody>
</table>

Epidemiology of CF

- **Prevalence**
  - United States ~ 30,000 (1 of every 3,500 babies born)
  - Worldwide ~ 70,000

- **Change in patient demographics**
  - Increased life expectancy
  - Improved overall lung function

Newborn Screening for CF

• Mandated nationwide
• 66% of new diagnoses made in the first year of life
• Step-wise process:
  – Measurement of IRT
  – If elevated, then repeat IRT or CFTR genotyping
  – If still elevated or mutation detected, then sweat chloride test
• Sweat chloride test = best initial diagnostic test

<table>
<thead>
<tr>
<th>Age ≤ 6 mo</th>
<th>Age &gt; 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF is unlikely</td>
<td>&lt; 30 mmol/L</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30-59 mmol/L</td>
</tr>
<tr>
<td>Consistent with CF</td>
<td>≥ 60 mmol/L</td>
</tr>
</tbody>
</table>

Cystic Fibrosis Foundation, 2015.

Diagnostic Complexity

• Patients not identified via NBS
  – Normal or equivocal sweat chloride test results
• 6.8% patients diagnosed ≥ 16 years old
• Clinical presentation
  – Often diagnosed in adolescence or adulthood
  – Genetic mutation – less common defect
  – Mild disease – respiratory, GI, pancreatic
  – Atypical symptoms – infertility, sinusitis
  – Infection with typical CF respiratory pathogens

CF Pulmonary Function Decline

Median % Predicted FEV₁ vs Age

Gender Gap

2007
1990

Parallel lines

Cystic Fibrosis Foundation Patient Registry 2007.

Improved Patient Survival:
Evidence-Based Strategies

NBS program and step-wise diagnostics
Pancreatic enzyme replacement
Specialized CF care centers
Complete nutritional management
Enhanced chest physiotherapy
Aggressive antibiotic regimens

Pathophysiology of CF

• Heterogeneous, autosomal recessive disorder
• Over 2,000 mutations in the CFTR gene have been described
• CFTR protein is a chloride channel
• Mutated CFTR protein leads to lower or absent chloride transport

Cystic Fibrosis Foundation, 2015.

CFTR Channel

• CF is due to genetic mutations that affect the CFTR protein
  ➢ Impacts synthesis and transfer of the CFTR protein to the apical membrane of epithelial cells
  ➢ Influences gating or conductance of chloride and bicarbonate ions through the channel
• CFTR dysfunction results in:
  ➢ Imbalance of ion transport and epithelial secretions in the lungs, GI tract, pancreas, and liver

CFTR Channel

Normal CFTR and ENaC activity:
Healthy ASL
Normal mucociliary clearance

Defective CFTR, compromised chloride transport, and ENaC overactivity:
Dehydrated ASL
Poor mucociliary clearance

CF-Related Lung Disease

Abnormal CFTR
- Reduced ASL
- Impaired mucociliary clearance

Inflammation
Infection
Obstruction
Structural damage
Bronchiectasis
Pulmonary insufficiency
Respiratory failure
Aerosolized Antibiotics

- **Rationale for use**
  - To deliver a high dose of medication to the site of infection
  - To minimize systemic exposure and toxicity
  - To overcome sputum binding
  - To optimize PK / PD parameters

- **Agents**
  - TSI = tobramycin solution for inhalation
  - AZLI = aztreonam lysine inhalation solution
  - TIP = tobramycin inhaled powder

# TSI for Chronic Airway Infection

## Study design
- Longitudinal, regression analysis
- N = 12,740 patients from CFF patient registry
- Study duration = 10 years

## Study results
- TSI use was associated with a 21% reduction in the odds of subsequent year patient mortality ($P < 0.05$)

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### Clinical Study	Study Design	N	Dosage	Study Results
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Ramsey$^1$	RCT	520	300 mg twice daily for 28 days, 3 on/off cycles	Improvement in microbial response, pulmonary function ($P < 0.05$) Less hospitalizations, fewer IV antibiotics used
Moss$^2$	OL	93	300 mg twice daily for 28 days, 12 on/off cycles	Improvement in pulmonary function sustained for study duration ($P < 0.05$)
Murphy$^3$	OL	184	300 mg twice daily for 28 days	Decrease in hospitalizations, concurrent antibiotic use ($P < 0.05$)

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AZLI vs TSI for Chronic Airway Infection


Protein Repair: Mutation-Specific Treatment

Fajac, et al., ECFS 2011; Symposium 12 Oral

AA = amino acid
Most Common Mutations
CFF Patient Registry, 2013

<table>
<thead>
<tr>
<th>Patients* (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del</td>
<td>86.4</td>
</tr>
<tr>
<td>G542X</td>
<td>4.6</td>
</tr>
<tr>
<td>G551D</td>
<td>4.4</td>
</tr>
<tr>
<td>R117H</td>
<td>2.8</td>
</tr>
<tr>
<td>N1303K</td>
<td>2.5</td>
</tr>
<tr>
<td>W1282X</td>
<td>2.3</td>
</tr>
<tr>
<td>R553X</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Homozygotes = 46.5%
Heterozygotes = 39.9%

97% of patients have had their mutations identified through genetic testing

* Patients with one or two alleles

CFTR Mutations Reduce the Amount or Function of CFTR at the Cell Surface

CFTR Mutations

Defect in CFTR Protein

Reduced Quantity of CFTR at Cell Surface
Reduced Function of CFTR at Cell Surface

Normal
Approach to Restoring CFTR Function

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

**Correctors:**
Increase the cellular processing and delivery of CFTR proteins to the cell surface

CFTR Modulation

- Address the underlying genetic anomaly of CF
- Restore the function of the CFTR protein
- CFTR modulators:

<table>
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<th>Modulator</th>
<th>Description</th>
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<tr>
<td>Ivacaftor</td>
<td>CFTR potentiator</td>
</tr>
<tr>
<td>Ataluren</td>
<td>Premature stop codon suppressor – enables the formation of a functioning protein in patients with nonsense genetic mutations</td>
</tr>
<tr>
<td>- Lumacaftor</td>
<td>CFTR correctors – move defective CFTR protein to proper place in cell membrane and improve its function as a chloride channel</td>
</tr>
<tr>
<td>- VX 661</td>
<td></td>
</tr>
</tbody>
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Cystic Fibrosis Foundation, 2015.
## Mutation Classification

<table>
<thead>
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<th>Class</th>
<th>Mutation</th>
<th>CFTR</th>
<th>Examples</th>
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<td>I</td>
<td>Nonsense; frame-shift</td>
<td>No functional CFTR</td>
<td>G542X</td>
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<tr>
<td>II</td>
<td>Missense; amino acid deletion</td>
<td>CFTR trafficking defect, some CFTR</td>
<td>F508del</td>
</tr>
<tr>
<td>III</td>
<td>Missense</td>
<td>Abnormal channel function, block in regulation</td>
<td>G551D</td>
</tr>
<tr>
<td>IV</td>
<td>Missense</td>
<td>Abnormal channel function, altered conductance</td>
<td>R117H, D1152H</td>
</tr>
<tr>
<td>V</td>
<td>Missense; splicing defect</td>
<td>Reduced synthesis of CFTR</td>
<td>3849+10kbC→T, 5T</td>
</tr>
<tr>
<td>VI</td>
<td>Missense</td>
<td>Decreased stability of CFTR</td>
<td>4326delTC</td>
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## Ivacaftor: STRIVE Clinical Trial

![Graph showing change in FEV1 (% Predicted) from Baseline over 48 weeks for Placebo and Ivacaftor](image)

Treatment effect = 10.5% \( P < 0.05 \)

**Ivacaftor**

- **Mechanism of action**
  - Increases the time that activated CFTR channels at the cell surface remain open; thereby, restoring CFTR function
- **FDA approved for patients with the following genetic mutations:**

<table>
<thead>
<tr>
<th>G551D</th>
<th>R117H</th>
<th>G178R</th>
<th>S549N</th>
<th>S549R</th>
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<tr>
<td>G551S</td>
<td>G1244E</td>
<td>S1251N</td>
<td>S1255P</td>
<td>G1349D</td>
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<td>G542X 12%</td>
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<td>CFTR trafficking defect, some CFTR</td>
<td>F508del 86%</td>
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<td>III</td>
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<td>Abnormal channel function, block in regulation</td>
<td>G551D 5%</td>
</tr>
<tr>
<td>IV</td>
<td>Missense</td>
<td>Abnormal channel function, altered conductance</td>
<td>R117H, D1152H 5%</td>
</tr>
<tr>
<td>V</td>
<td>Missense; splicing defect</td>
<td>Reduced synthesis of CFTR</td>
<td>3849+10kbC→T 5T A455E 5%</td>
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<tr>
<td>VI</td>
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<td>Decreased stability of CFTR</td>
<td>4326delTC Rare</td>
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### Combination Approach: CFTR Potentiator Ivacaftor Doubled the *In Vitro* Activity of VX-809

*Van Goor et al. Pediatr Pulmonol 2009;44(S32):154absS9.4*
Ivacaftor with Lumacaftor

A. Change from Baseline in Percentage of Predicted FEV₁

B. Time to First Pulmonary Exacerbation

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Ataluren with TSI


Ataluren without TSI

**BMI Trend**

24 year woman with G551D/d508F

- **Before Kalydeco**
- **After Kalydeco**

**CF Severe Pulmonary Exacerbations**

42 year old man with R117H-5T/del508F
Sinus Disease

Pre-Ivacaftor  
Post-Ivacaftor

Restoring CFTR Function  
Decreases Rate of Decline in FEV$_1$

**Sawicki, McKone…Konstan et al, Poster 207**

* $p < 0.001$. 
Effect of Decreased Rate of Decline in FEV$_1$

![Graph showing the impact of FEV$_1$ on age and the effect of Ivacaftor and F508del/F508del mutations on lung transplant and FEV1 prediction.]

**FEV1 change doesn't predict CFPE reduction-Orkambi**

![Bar graph comparing the event rate per patient over 48 weeks for placebo, LUM/VA, <5, and LUM/VA, ≥5 across all PEx, PEx requiring IV Antibiotics, and PEx requiring Hospitalization.](chart.png)
A second corrector further enhances *in vitro* F508del CFTR function

![Graph showing chloride transport in F508del and F508del/G542X mutants with and without correctors.](image)

**CFTR Modulation**

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Ataluren</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Ivacaftor + Lumacaftor</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Ivacaftor + VX 661</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Riociguat</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>QBW251</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>N91115</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Cystic Fibrosis Foundation, 2015.
CF-Summary

• Genetic Disease- CFTR
  – Autosomal Recessive
  – Defect in Ion Transport: Cl-, Na, H₂O

• Cycle- Infection, Inflammation, Mucus
  – Innate Immunity-likely primary defect
  – Antibiotics, Mucolytics, Anti-inflammatory, Rehydrators

• CFTR Modulation
  – Protein Repair
  – Gene Therapy
  – RNA editing
  – ENaC Inhibition