Cystic Fibrosis: Update and Progress Made

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Cystic Fibrosis

- Autosomal recessive genetic disorder affecting all exocrine tissues. More than 2000 disease-causing mutations have been identified.
- Multiorgan involvement with most frequent organs:
  - Upper and lower respiratory tract
  - Pancreas
  - Sweat gland
  - Reproductive tract
  - Hepatobiliary tract
- Classic triad: recurrent sinopulmonary disease, elevated sweat chloride and pancreatic insufficiency.
- Non-classic presentations are possible. Adults comprise most of these individuals.
- Orphan disease with about 70,000 affected individuals worldwide.

The frequency of CF mutations varies in different populations

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence</th>
<th>Carriers</th>
<th>F508del</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasians</td>
<td>1 / 3,300</td>
<td>1 / 29</td>
<td>79%</td>
</tr>
<tr>
<td>Hispanics</td>
<td>1 / 9,000</td>
<td>1 / 46</td>
<td>46%</td>
</tr>
<tr>
<td>African-Americans</td>
<td>1 / 15,300</td>
<td>1 / 60</td>
<td>48%</td>
</tr>
<tr>
<td>Asian Americans</td>
<td>1 / 32,100</td>
<td>1 / 90</td>
<td>30%</td>
</tr>
</tbody>
</table>

Over 2,000 mutations in CFTR have been found, but not all are disease-causing. 70% of patients with CF have one copy of F508del.
Clinical Presentation of CF

**Classic CF**
- No functional CFTR
- Chronic sinusitis
- Earlier and more severe deterioration of lung function
- Severe hepatobiliary disease
- Pancreatic insufficiency
- Greater incidence of malnutrition and severe liver disease

**Non-classic CF**
- Some functional CFTR
- Chronic sinusitis
- Later onset and milder lung disease
- Pancreatic sufficient, less likely to have CF-related diabetes
- In general – later diagnosis, milder disease, and more responsive to treatment

__Cystic Fibrosis Transmembrane Conductance Regulator__

The critical genetic defect underlying CF was identified in 1989
The gene is located on the long arm of chromosome 7
The gene spans 250kb containing 27 exons, encoding for a mRNA of 6500 nucleotides, and a protein of 1480 amino acids

_Cartoon diagram of CFTR_
Besides CFTR, the apical membrane contains other transport proteins. These include:

- ENaC, the epithelial Na⁺ channel
- CaCC, the Ca²⁺-activated Cl⁻ channel
- P2Y₂-R, purinergic receptors

Intracellular Signals

P2Y₂-R
Healthy Cells

CF Cells

Pathophysiology of CF Lung Damage

Airway Colonization in CF

Diagnosis

- Appropriate clinical symptoms or
- Family history (sibs, or first cousins)
- Sweat chloride / pilocarpine iontophoresis
- CF genotype/gene sequencing
- Nasal potential difference
- Newborn screening
  - IRT/DNA
  - Need to confirm with other tests
  - No need for clinical symptoms

Median survival by colonization status 1991-1995

- Colonization Status
  - All patients
  - colonized P.A.
  - colonized B.cepacia
  - Never colonized P.A. or B.cepacia
- Median Survival [yrs]
  - 30
  - 29
  - 21
  - 51
Newborn Screening has decreased the age of diagnosis

Common Clinical Presentations

- Meconium ileus 13%
- Respiratory symptoms 45%
- Failure to thrive 27%
- Steatorrhea 20%
- Neonatal screening 11%
- Family history 15%

SWEAT TEST

- Always need pilocarpine iontophoresis
- Adequate collection >75 mg of sweat
- Sweat chloride:
  - >60 meq/l most frequently CF
  - 40 to 55 indeterminate
  - >35 in infants most likely CF
  - ~1% CF pts normal CL levels
  - Sweat chlorides tend to increase with age
False Positive Sweat Test
- Hypothyroidism
- Hypoadrenalism
- Nephrogenic Diabetes Insipidus
- Severe Malnutrition
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Ectodermal Dysplasia
- Glycogen Storage Disease
- Poor collection

False Negative Sweat Test
- Severe Edema
- Poor collection
Cystic Fibrosis: Daily therapies

**Respiratory**
- Airway Clearance: bronchodilator agent to help with mucus clearing
- Active airway clearance therapy
- An inhaled antibiotic

**Nutritional**
- Dietary supplements (high fat high protein)
- Increased fat-soluble vitamins (A/D/E/K)
- Salt supplements

**Gastrointestinal**
- Pancreatic Enzyme replacement
- Acid blockade
- Agents that improve intestinal motility

**Endocrine**
- Insulin
- Growth hormone
- Vitamin D (other agents for bone health)

**Anti-Infective**
- Antibiotics (oral, inhaled, intravenous)
- Anti-inflammatory
- Ibuprofen
- Azithromycin

**One Day’s Treatment**
CYSTIC FIBROSIS - Treatment

ANTIBIOTICS
- Oral-based on sputum culture results
- Inhaled: options are tobramycin, aztreonam, colistin, ceftazidime
- Intravenous: based on sputum culture results

NUTRITION
- Pancreatic enzyme replacement: weight based regimen
- Vitamin deficiencies: fat soluble vitamins especially
- High calorie diet: goal to maintain BMI within normal

CHEST PHYSIOTHERAPY
- Many modalities

BROMOCRIPTINATES
- Albuterol

ANTIBIOLAMATORY AGENTS
- Azithromycin
- Steroids: in the correct setting, ABPA, concomitant asthma

MUCOLYTICS
- Dnase
- Hypertonic saline

Excellent glycemic control

Pediatric and Adults Almost Equal in Number

Current Therapy just a Band Aid
CF research over the decades

- 1980 to 90's identified the salt defect in CF
- Identification of CF gene and gene product
- Gene replacement therapy
  - Problems with longevity of replacement
  - Safety issues with certain vectors
- Low hanging fruit
  - Azithromycin
  - Hypertonic saline
  - Improved airway clearance
  - Nutritional therapies
- 2000's small molecule focus
  - Fueled by better understanding of form and function of CFTR

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**Table 2.7. Clinical disease phenotype associated with some mutations in the CFTR**

<table>
<thead>
<tr>
<th>Long disease and pancreatic exocrine dysfunction (ES) trait treated</th>
<th>Long disease, pancreatic exocrine sufficiency (PS), and bronchitis or normal lung</th>
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</tr>
</thead>
<tbody>
<tr>
<td>A455E</td>
<td>B117delCFTR</td>
<td>B117delCFTR</td>
</tr>
<tr>
<td>G551W</td>
<td>N1303K</td>
<td>D428H</td>
</tr>
<tr>
<td>D1279I</td>
<td>A584V</td>
<td>R752N</td>
</tr>
<tr>
<td>R1177 + 1 G to T</td>
<td>A455G</td>
<td>A455E</td>
</tr>
<tr>
<td>D1092Y</td>
<td>S549R</td>
<td>R752H</td>
</tr>
<tr>
<td>S1253N</td>
<td>S549R</td>
<td>R752Q</td>
</tr>
<tr>
<td>S1487N</td>
<td>S549R</td>
<td>R752P</td>
</tr>
<tr>
<td>S1487Q</td>
<td>S549R</td>
<td>R752K</td>
</tr>
</tbody>
</table>

CFTR, cystic fibrosis transmembrane conductance regulator.

*Di as referred to references 5, 6, 9, 28, 46, 47, 69, 76, 85, 91-93, 95, 162.

*Refers to the length of the polypetide chain in position 844, e.g., 5T or 7T or 9T (69, 113).

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**CF is Not One Genetic Disorder**

**CFTR mutation classes**

- Normal
- Class I synthesis
- Class II maturation
- Class III regulation
- Class IV conductance
- Class V quantity

'**severe**' mutations
- Pancreatic insufficiency
- Decreased survival

'**mild**' mutations
- Pancreatic sufficiency

Mutation specific treatment approaches seems logical
Reduced Quantity
Reduced Function

Treatment approaches
Correctors
Potentiators

Drug Discovery: High Throughput Screening for CFTR-specific Drugs
- A cell-based fluorescent membrane potential assay was developed
- 228,000 chemically diverse drugs were screened
- Lead scaffold was selected based on:
  - Potency
  - Selectivity
  - Chemical tractability
- Cells glow yellow when ion flux occurs
  - These “hits” are drug candidates

High-Throughput Screening
>10,000 Primary Assays/day
CFF Pipe
line is critical to patients with CF

CFF.org
clinicaltrials.gov

Vertex Screening for CFTR Modulators

Screen Chemical Compounds (hundreds of thousands)
Identify Hits (hundreds)
Validate Hits (~ten)
Select and Optimize Leads (~2)
Nominate Development Candidates in each category (potentiator & corrector)
File IND
Clinical Trials
File NDA

Vertex Collaboration
~13 years

Potentiator: OSE111
Clinical Trials
Phase 1 in 2006
Phase 2 in 2007
FDA approved in 2012

Corrector VX 609 plus
Potentiator VX 770
Phase 3 ongoing for patients with most common mutation F508del
NDA application in process

Potentiator: Approved Dec 2014 for R117H mutations
Phase 3 Results of CF Therapies

Have We Made Progress?

Port CF
The Future for CF

- Individualized CFTR modulation based on protein defect
- Advancement in gene therapy
  - Will it be needed if CFTR modulation is started early in life???
- Older patients with established bronchiectasis will continue to need current standard of care therapy
  - Will need improvement in lung transplantation
- Continued improvement in life expectancy with goal of CF = Cure Found