CF ATLANTA Research & Development Program at Emory University and Georgia Tech (CF@LANTA)

Clinical & Translational Research Core

Arlene Stecenko, MD
Director, Emory + Children's Cystic Fibrosis Care Center
Chief, Pediatric Pulmonary, Allergy/Immunology, Cystic Fibrosis, and Sleep
Director, Clinical & Translational Research Core for CF@LANTA RDP
November 4, 2015
Overarching Goal CF@LANTA

• Promote interdisciplinary research in CF pathogenesis & translate new knowledge into improved preventive & personalized therapies

• Centered around 700 CF patients followed at our care center
Overall Organization of CF@LANTA
Overall Goals of Clinical & Translational Research Core

- Promote human subjects research in CF, with an emphasis on CF diabetes and on acute pulmonary exacerbations
  - **Banking**: Develop a biospecimen repository where each biologic sample has a complimentary & detailed description of the clinical phenotype at the time of collection
  - **Prospective**: Provide tailored specimen collection to match specific investigators' needs
  - **Creativity**: Stimulate new ideas. Bring new investigators to CF
Specific Aims

1. Develop Standard Operating Procedures (SOPs) for Biospecimen Collection
2. Manage CF Biospecimen Repository (CFBR) & Build Portfolio of Banked Specimens
3. Manage CFF Clinical Data Registry & Enhance Depth/Quality of Data Collected
4. Provide Translational & Clinical Research Support/Consultation for Human Studies
5. Provide Biostatistics & Data Management
Aim 1. Develop Standard Operating Procedures (SOPs) for Biospecimen Collection

- Four SOPs Refined: Exhaled breath condensate (EBC), sputum (microbes & supernatant), serum & platelet poor plasma
- Collection & storage personalized for current core investigators needs as well as future needs
- Dr M. Brown trained all research staff for Emory Adult CF & Emory+Children’s Pediatric CF programs on processing
- Dedicated lab space on third floor identified and being equipped with all needed equipment and supplies
- To do site visit at Scottish Rite CF Pediatric program
Format SOPs

- Collaborative effort core investigators, CFBR research staff, CFBR Director
- Once approved, only CFBR Director can make changes
- Format – purpose, equipment, supplies, solutions, processing, labelling, storage, clinical state at time of collection (stable vs APE vs recovering from APE, oral intake, FEV1 – baseline and at time sample taken, what inhaled antibiotic when sample taken)
Aim 2. Manage CFBR: Study Methods for CFBR

1. Identify eligible patients attending the adult or pediatric CF clinics at Emory or Children’s
2. Approach patients in clinic, explain the study, and consent if willing to participate
3. Ask participating patients each time they are in clinic or the hospital if they want to donate samples
4. Collect blood, sputum, bronchoalveolar lavage fluid, and/or nasal scrapings from the subject
5. Process samples immediately and store
6. Link each sample to clinical data
Aim 2. Manage CFBR & Build Portfolio of Banked Specimens

- Build on work done since CFBR started in Aug 26, 2010
- With additional resources from the RDP, recruited more research coordinators and replaced data manager
- Emory/Children’s team → Jane Wei, Julie Flores, Chris Driggers, Miti Gandhi, Joy Dangerfield, Eric Hunter
Aim 2. Manage CFBR & Build Portfolio of Banked Specimens - cont’d

- Prioritized work flow based on currently funded research studies requiring specimens. Realized needed samples when clinically stable (cross sectional studies) and also during an acute pulmonary exacerbations (APE)
- Identified 220 high value CF patients at Emory (adult and pediatric) based on having 1 to 3 APEs per year.
- Focus: collecting every time in clinic and when hospitalized \(\rightarrow\) clinically stable, pre-APE (no symptoms, clinically stable, and about to have an APE within the next 3 months), APE severe enough to require hospitalization, response to treatment for APE, recovery from APE
Aim 2 Results:
Inception in Aug 2010 to October 2015

- 497 adult and pediatric CF patients enrolled
  - Emory Adult CF Clinic - 194 out of 280 patients (69%) enrolled
  - Emory Pediatric CF Clinic - 114 out of 230 patients (50%) enrolled
  - Scottish Rite Pediatric CF Clinic - 138 out of 170 patients (81%) enrolled

- 3,321 specimens collected
- 7,589 aliquots banked
Number of Specimens Collected Per Year Excluding bacterial isolates

2009: 35
2010: 157
2011: 164
2012: 84
2013: 546
2014: 636

2015 data = 10 months only
Aim 3. Manage CF Clinical Data Registry & Enhance Depth/Quality of Data Collected

- CFF Registry
  - Clinical data on each patient at clinic and during hospitalization
  - Includes demographics, health outcomes (lung function, nutrition, pulmonary exacerbations), airway microbiology, adherence to CFF care and prevention guidelines, treatments, and complications
  - Problem - data cross sectional by group and not longitudinal by cohort or individual
Aim 3. Manage CF Clinical Data Registry &
Enhance Depth/Quality of Data Collected - cont’d

- Importing key data from CFF Clinical Registry each year from 2010 onward for each patient to CFBR
- Longitudinal clinical data on Master Sheet
  - Demographics
  - Baseline FEV1 each year
  - OGGTT each year
  - Airway microbiology each year
Aim 3. Manage CF Clinical Data Registry & Enhance Depth/Quality of Data Collected - cont’d

- Enhanced CFF Registry data in CFBR
  - Longitudinal data in individual or cohorts of subjects from 2010
  - Follow disease progression with aging or development of complication (CFRD, APE)
  - Follow disease improvement with intervention - Quality improvement, new therapies
Aim 3. Manage CF Clinical Data Registry & Enhance Depth/Quality of Data Collected - cont'd

- Linkage between CFF Registry & CFBR
  - Basic CFBR linkage = Cross sectional by sample and clinical state at time of sample
  - Advanced CFBR linkage = Longitudinal by clinical progression
Combination of CFF Clinical Registry & CF Biospecimen Repository: A Powerful Tool

Co-infection with Staph aureus and Pseudomonas aeruginosa
A Longitudinal Analysis of Chronic MRSA and *P. aeruginosa* Co-infection in Cystic Fibrosis: A Single-Center Study

Maret L. Maliniak, Arlene A. Stecenko, Nael A. McCarty

- 354 CF patients at Emory Adult CF clinic and Emory+Children’s Pediatric CF clinic followed from 2007 to 2013
- Classified according to whether had chronic co-infection with MRSA and pseudomonas, chronic infection with either, or neither
- Correlated infection status with rate of decline in FEV1 and in rate of APE needing intravenous antibiotics
Results: Maliniak

- Rate of Decline in % FEV1.0
  - Adjusted for age, sex, baseline FEV1, CFRD, B cepacia, average rate of decline significantly greater with co-infection compared to either alone, or neither
  - Co-infection = 2.77% decrease/year

- Rate of APE

AVERAGE NUMBER OF APEs NEEDING IV ANTIBIOTICS PER YEAR BY INFECTION STATUS

<table>
<thead>
<tr>
<th>Infection Status*</th>
<th>Adjusted IRR†</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Co-infection vs. Chronic PA alone</td>
<td>1.24</td>
<td>1.01, 1.52</td>
<td>0.04</td>
</tr>
<tr>
<td>Chronic Co-infection vs. Chronic MRSA alone</td>
<td>1.34</td>
<td>1.03, 1.74</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic Co-infection vs. Intermittent infection</td>
<td>1.56</td>
<td>1.21, 2.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic Co-infection vs. No MRSA/PA</td>
<td>2.00</td>
<td>1.54, 2.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Aim 4. Provide Translational & Clinical Research Support/Consultation for Human Studies

- Support both cross sectional and longitudinal studies
- Increase efficiency - one patient may provide samples for more than one study at the same time
- Consistency of definitions
- Decrease misclassification of clinical state
  - Defining CF without diabetes as absence of clinical diagnosis of diabetes and treatment with insulin
  - Defining clinical stable CF as absence of clinical diagnosis of APE
Roadmap for APE Studies

VERSION September 3, 2015

No Acute Pulmonary Exacerbation

Patient Clinically Stable

Patient Clinically Stable (with no APEs in previous 3 months)

3 Months

Patient Clinically Stable

APE Definition: Increase in symptoms (cough, sputum production) and/or new findings on chest exam PLUS decrease in Baseline FEV1 by 10% or more

Definition of Baseline FEV1: Represents the avg of the best 7% FEV1 for each quarter in the previous calendar year

Definition of Clinically Stable: No increase in symptoms, lung exam at baseline, FEV1 within 10% of baseline, and not placed on oral antibiotics

Acute Pulmonary Exacerbation

Patient Clinically Stable (with no APEs in previous 3 months)

APE 5 Days or Less Prior to IV Antibiotics and Admission

APE with 48 hrs of Admission and starting IV Antibiotics

APE @ End of IV Antibiotics (2-4 weeks)

Clinical Visit 3 Months (+/- 2 weeks) Post Date of Admission for APE

Clinical Visit 6 Months (+/- 2 weeks) Post Date of Admission for APE

Inclusion Criteria:
- Clinically Stable for ≥ 2 clinic visits in a row OR
- Clinically Stable then subsequent 3 month APE
- Normal OGGT within 6 months OR
- Prednisone OGGT within 6 months OR
- C-reactive protein ≤ 10 mg/L
- CF or healthy controls
- No APE in previous 3 months
- APE severe enough to require admission
- Complete at least 14 days of IV antibiotics
- CPF in hospital to require admission
- Normal OGGT done in previous 6 months prior to enrollment
- 14 days prior to enrollment

| CF, healthy controls, disease controls |

<table>
<thead>
<tr>
<th>PT</th>
<th>Age Group</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiducia</td>
<td>15 yrs</td>
<td>50</td>
</tr>
<tr>
<td>Joanne</td>
<td>10-30 yrs</td>
<td>50</td>
</tr>
<tr>
<td>Robin</td>
<td>All</td>
<td>300</td>
</tr>
<tr>
<td>Day</td>
<td>8-10 days</td>
<td>20</td>
</tr>
<tr>
<td>CPFIR</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>
# Roadmap for APE Studies: Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APE Definition</strong></td>
<td>Increase in symptoms (cough, sputum production) and/or new findings on chest exam PLUS decrease in Baseline FEV1 by 10% or more</td>
</tr>
<tr>
<td><strong>Definition of Baseline FEV1</strong></td>
<td>Represents the avg of the best % FEV1 for each quarter in the previous calendar year</td>
</tr>
<tr>
<td><strong>Definition of Clinically Stable</strong></td>
<td>No increase in symptoms, lung exam at baseline, FEV1 within 10% of baseline, AND not placed on oral antibiotics</td>
</tr>
</tbody>
</table>
### Roadmap for APE Studies: Funded Studies

<table>
<thead>
<tr>
<th>PI</th>
<th>Age Group</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facundo</td>
<td>≥ 7yrs</td>
<td>50</td>
</tr>
<tr>
<td>Joanna</td>
<td>10-39</td>
<td>30</td>
</tr>
<tr>
<td>Rabin</td>
<td>All</td>
<td>280</td>
</tr>
<tr>
<td>Jay</td>
<td>8-18yrs</td>
<td>20</td>
</tr>
<tr>
<td>Stecenko</td>
<td>8-21yrs</td>
<td>20</td>
</tr>
<tr>
<td>CFBR</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

**Inclusion Criteria**
- Clinically Stable for 2 clinic visits in a row OR Clinically Stable then subsequent 3 month APE
- Normal OGTT w/in 6 months OR Prediabetic OGTT w/in 6 months OR CFRD on insulin
- CF or Healthy controls
- No APE in previous 3 months
- APE severe enough to require admission
- Complete at least 14 days of IV antibiotics
- APE severe enough to require admission
- Normal OGTT done in previous 12 months prior to enrollment

*CF, healthy controls, disease controls*
Roadmap for APE Studies: Specimen Collection

No Acute Pulmonary Exacerbation

Patient Clinically Stable

3 Months

Patient Clinically Stable (with no APEs in previous 3 months)

FAC

Sputum Supernatant

Sputum

3 Months

Patient Clinically Stable

Acute Pulmonary Exacerbation

Patient Clinically Stable (with no APEs in previous 3 months)

Patient Clinically Stable then within three months has an APE severe enough to require hospitalization

APE 5 Days or Less Prior to IV Antibiotics and Admission

APE with In 48hrs of Admission and starting IV Antibiotics

APE @ End of IV Antibiotics (2-4weeks)

Clinic Visit 3 Months (+/- 2 weeks) Post Date of Admission for APE

Clinic Visit 6 Months (+/- 2 weeks) Post Date of Admission for APE
Additional Goals for Next 8 Months

- Develop joint services with other Cores in RDP
  - Cell Models Core → nasal epithelial cells & airway epithelial cells from lung transplant
  - Analytic Core → human samples for measures of redox balance/oxidative stress
- Start Director’s Fund
- Market Clinical Core’s expertise
- Other suggestions?