How To Set Up A Successful Clinical Trials Network

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Co-PI, UW Institute of Translational Health Science

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In my former capacity as Director of the Cystic Fibrosis Foundation Therapeutics Development Network Coordinating Center, I have received grants or contracts from the following companies in the past 3 years:

<table>
<thead>
<tr>
<th>Novartis Pharmaceuticals</th>
<th>CURx Pharmaceuticals Inc</th>
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<tr>
<td>N30 Pharmaceuticals</td>
<td>PulmoFlow</td>
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<tr>
<td>Aptalis Pharma, Inc.</td>
<td>Gilead Sciences Inc</td>
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<td>Insmed Inc.</td>
<td>Pulmatrix</td>
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<tr>
<td>Pharmaxix Ltd.</td>
<td>Pharmagenesis (Cornerstone 281)</td>
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<td>Celtaxsys</td>
<td>Breathe Easy Ltd</td>
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<tr>
<td>KaloBios</td>
<td>ProQR Therapeutics BV</td>
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<tr>
<td>Kamada</td>
<td>Eli Lilly</td>
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<td>12th Man Technologies</td>
<td>Achaogen</td>
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<td>Vertex Pharmaceuticals</td>
<td>Genentech</td>
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<tr>
<td>Nordmark</td>
<td>Respira Therapeutics Inc</td>
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<td>Corbus Pharmaceuticals</td>
<td>Bristo-Myers Squibb</td>
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<td>Parion Sciences</td>
<td>INC Research</td>
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<td>Flatley Discovery Lab LLV</td>
<td>Cornerstone Therapeutics</td>
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<tr>
<td>Savara Pharmaceuticals</td>
<td>GlycoMimetics Inc</td>
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<td>Mpxex Pharmaceuticals, Inc</td>
<td>Catabasis</td>
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<tr>
<td>Aridis Pharmaceuticals LLC</td>
<td>Grifols Therapeutics</td>
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<tr>
<td>National Institutes of Health</td>
<td>Cystic Fibrosis Foundation</td>
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</table>
Advantages of Collaborative Multicenter Studies (Kraemer et al, *Arch Gen Psychiatry* 1990;47:1163)

- Large participant pool permitting more generalizable cohorts
  - Critical need among orphan disease populations
- Enhancement of training and expertise at the sites
- Broad expertise of multiple investigators contributing to the scientific questions and process
- Standardized processes to enhance data quality and reduce variability
What is the Cystic Fibrosis Therapeutics Development Network (CF-TDN)?

• A non-profit clinical trials network, established in 1998 to facilitate development and conduct of all phases of clinical trials and identify appropriate outcomes for future studies

• TDN is a program supported and managed by Cystic Fibrosis Foundation Therapeutics Inc (CFFT)
  • TDN Coordinating Center is located at Seattle Children’s Research Institute

• Funding history
  • Infrastructure: Grant support from Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT) and NIH (1999-2007)
  • Study specific: CFFT, industry, NIH
Why did the CFF choose to start the CF TDN in 1998? (1)

- CF community had a long history of negative, underpowered single site clinical studies
- CF Foundation had been involved in two successful development programs (Pulmozyme®, 1993 and TOBI®, 1998) but wanted to take a more active role in catalyzing and “derisking” therapeutic development for industry
- Scientific breakthroughs emerging in 1990s provided a window of opportunity for novel drug development
- CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; discovered in 1989

- **CFTR** gene encodes a protein (CFTR channel) that functions as a regulated channel for chloride and other ions to pass through the membrane of epithelia in multiple organs.
Emerging Allele-Specific Therapies

- F508del CFTR Processing Corrector (F508del, possibly others)
- CFTR Potentiators (G551D, R117H, R1070W...)
- Translational Readthrough (G542X, W1282X, R1162X,...)

Three approaches will include > 90% of genotypes

The CF Foundation has “really paved the way for other small disease nonprofits to take drug discovery into their own hands.”

—Harvard Business School Professor Robert Higgins
What was unique about the CF TDN network?

- Integral part of an audacious translational program to develop novel therapies to change the lives of patients with CF
- Partnership of a Foundation and NIH (NCATS)
- Partnership of a Foundation and Industry
- Spanned pediatric and adult patients
- Created a significant infrastructure to ensure long-term sustainability
  - Well-supported sites
  - Large coordinating center
  - Robust data systems
  - Specialized national resource centers
CFTDN Goals

• Conduct efficient, successful studies
• Protect the safety and rights of study participants and provide equitable access to CF clinical studies
• Perform innovative ancillary studies
• Develop novel biomarkers and outcome measures
• Promote the continued advancement of junior faculty
• Make efficient use of limited resources by utilizing archived data and specimens
2017 CF Therapeutics Development Network

# TDC: 89 Sites  #NRC: 7 Sites

National Resource Centers

- Center for Biochemical Markers (CBM)
  Scott Sagel, Director
- Center for Microbiology (CCFM)
  Luke Hoffman, Director
- Center for CFTR Detection (CCD)
  Marty Solomon and Steve Rowe, Directors
- Center for Diagnostic Imaging (CDI)
  Paul Guillerman and Scott Nagle, Directors
- Center for Interpretive Cytology (CIC)
  Jim Cheresh, Director
- Center for Pediatric Lung Function (CPLF)
  Stephanie Davis and Jessica Pittman, Directors
- Center for Sweat Analysis (CSA)
  Scott Sagel, Director

January 2017
Therapeutics Development Centers

- Selected from CFF-accredited Adult and Pediatric Care Centers
- Chosen through a competitive process by CFFT
- CFFT infrastructure grants support:
  - Small portion of Adult and Pediatric PI salary
  - Adult and pediatric research staff
  - Site equipment
- Robust staff training and mentoring program
- Sites reviewed annually through performance tracking process; performance considered in competitive renewal every 2 years
TDNCC Overview of Responsibilities

- Supports electronic data capture (RAVE®) and management of all CFF studies
- Supports statistical design, analyses and manuscript preparation
- Maintains central tracking database
  - Supports governance structure
- Study design and implementation
- Site training and monitoring
- Study closeout
- Consultation
- Assistance with site communication and selection
Met Mission Statement:
“Facilitated clinical studies of new and existing therapies to cure and control CF”
TDN Study Activities by Cycle

- Close-out
- Enrolling
- Start-up

Years: 2004 to 2014
Highlights of CFTDN Studies (1998-2014)

• Since inception, network has primarily supported industry-based therapeutic development (70-75% of all studies)
• Initial studies were early Phase (1 and 2)
• Transition to larger Phase 3 trials
  • First CFFT Phase 3 – 2001
  • Industry moved to predominantly Phase 3 by 2009
• PI initiated studies have focused on outcome measure development (~25% of studies)
### Roles of Partners in CF Drug Development

<table>
<thead>
<tr>
<th>CFF*</th>
<th>Industry*</th>
<th>Academic(TDN)*</th>
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<tbody>
<tr>
<td>“De-risked” program with initial funding through Therapeutics</td>
<td>Pre-clinical development</td>
<td>Defined patient population (phenotype:genotype studies)</td>
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<tr>
<td>Development Awards</td>
<td>• Drug Screening</td>
<td></td>
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<tr>
<td></td>
<td>• Formulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Animal Toxicology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Manufacturing</td>
<td></td>
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<tr>
<td>Formed development committee</td>
<td>Regulatory FDA documents</td>
<td>Developed biomarkers and clinical endpoints</td>
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<tr>
<td>Found experts and developed teams</td>
<td>Funding and conduct of clinical trials</td>
<td>Assisted in clinical development plan and individual study</td>
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<tr>
<td>Support the Therapeutic Development Network</td>
<td></td>
<td>design</td>
</tr>
<tr>
<td></td>
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<td>Conducted studies at sites</td>
</tr>
</tbody>
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*Joint Development Committee oversaw program*
CF Therapeutic Program Goals

- Orally bioavailable drugs
- Two key CFTR targets:

**Class III mutations**

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

**Class II mutations**

**Correctors:**
Increase number and function of CFTR channels at the cell surface (also requires a potentiator)
Absolute Change from Baseline in FEV₁: % Predicted

# Key Therapeutic Trials Developed Through the TDN

<table>
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<tr>
<th>Therapy</th>
<th>Publication</th>
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</thead>
<tbody>
<tr>
<td>AAV gene therapy</td>
<td>Moss R, Human Gene Rx 2007;18:726</td>
</tr>
<tr>
<td>*Pancreatic enzymes</td>
<td>Borowitz D, J Pediatrics 2006;149:658</td>
</tr>
<tr>
<td>*Azithromycin</td>
<td>Saiman L, JAMA 2003;290: 1749 Saiman L, JAMA 2010;303:1707</td>
</tr>
<tr>
<td>*Hypertonic saline in infants</td>
<td>Rosenfeld M, JAMA 2012;307:2269</td>
</tr>
<tr>
<td>*Inhaled Mannitol</td>
<td>Aitken M, AJRCCM 2012;185:645</td>
</tr>
<tr>
<td>Inhaled Levofloxacin</td>
<td>Geller D, AJRCCM 2011;183:1510</td>
</tr>
</tbody>
</table>

*Available to patients
# Scientific Impact
Clinical Endpoints and Biomarkers

<table>
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<tr>
<th>Measure</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life measure</td>
<td>Quittner A, <em>Chest</em> 2009;135:1610</td>
</tr>
<tr>
<td>Biofilm susceptibility testing</td>
<td>Moskowitz S, <em>Peds Pulm</em> 2011;48:184</td>
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</table>
Lessons Learned for Successful Drug Development in an Orphan Disease

- Establish partnerships across industry, foundations, academics, federal agencies and patient/families
- Develop laboratory and clinical infrastructure in parallel and far in advance of first patient enrolled.
- Focus on deliverables and a common goal
  - Biology and mechanisms of action are secondary gains
  - Use the new drugs to further the science, e.g. GOAL study (S. Rowe, AJRCCM 2014)
Ongoing Challenges of a CTN in an Academic Setting

• Ensuring recognition and success of junior faculty
  • Solutions:
  • Encourage ancillary studies utilizing data and specimen repositories
  • Academic promotion letters written by CTN leader

• Overcoming bureaucratic barriers (e.g. contract negotiations)
  • Solution:
  • Work closely with CTSAs and institutional officers
Ongoing Challenges of a CTN in an Academic Setting

• Managing burn-out and turn-on of faculty and staff
  • Solutions:
  • Robust training programs
  • Anticipating workload
• Sustained infrastructure funding
  • Solutions:
  • Find partners in non-profit sector
  • Have a clear vision
Thank you!

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