

**Origins of a Patient Care Network for PCD:
Genetic Disorders of Mucociliary Clearance Consortium**

Michael R. Knowles, M.D.
Cystic Fibrosis/Pulmonary Research and Treatment Center
The University of North Carolina at Chapel Hill

Essential Features of Patient Care Network For an Orphan (Rare) Disease

Essential Features

Requires

- | | |
|--|--|
| 1. Identifying pertinent patients... .. | Ability to diagnose the disorder |
| 2. Educated health care team..... .. | Understanding clinical features;
experience |
| 3. Ability to “evolve” and improve. | Size; communication; research |
-

Keys to success

1. Patient advocacy group: feedback; push; pull together
2. Compelling clinical disease
3. Compelling science
4. Resources: intellectual and fiscal (organization and NIH)

Cystic Fibrosis over 50 Years: Example of Patient Care Network for an Orphan Disease

1. 1955 – Cystic Fibrosis Foundation (CFF) established
2. 1955-60 – Sweat Cl⁻ (diagnostic) test discovered
3. 1960-70 – Clinical Care Centers established (now 120)
4. 1982 – Research Development Program initiated (now 10 Centers)
5. 1989 – CF gene (CFTR) identified, which assisted diagnosis and discovery (now studying other genes that impact on severity of disease)
6. 1990s – Two new therapies (Pulmozyme; TOBi) introduced (macrolides in 2002)
7. 1998 – Therapeutic Development Network established (now 18 Centers)
8. 2003 – Extensive Standardization of Care Program established

Results:

1. Median age of survival improved from 6 to 33 years
2. Fundraising matured; allows development, and supplements the NIH
3. A dozen possible new therapies in the pipeline to be tested.

What about PCD?

Essential features

1. Diagnosis...Getting better; new approaches; genetics rapidly developing
2. Educated health professionals...Improving; Consensus Statement coming
3. Ability to improve...Size, communication, and research progressing

Keys to success

1. PCD Foundation organized...New experience/growing
2. Clinical disorder is compelling...Clinical research underway
3. Science is compelling...Cilia, biology, genetics
4. Resources...NIH grants
5. Time...way ahead of CF schedule

Genetic Disorders of Mucociliary Clearance (MCC) Consortium

11/02 – Congress authorized Office of Rare Diseases (ORD) at NIH to fund research into orphan diseases

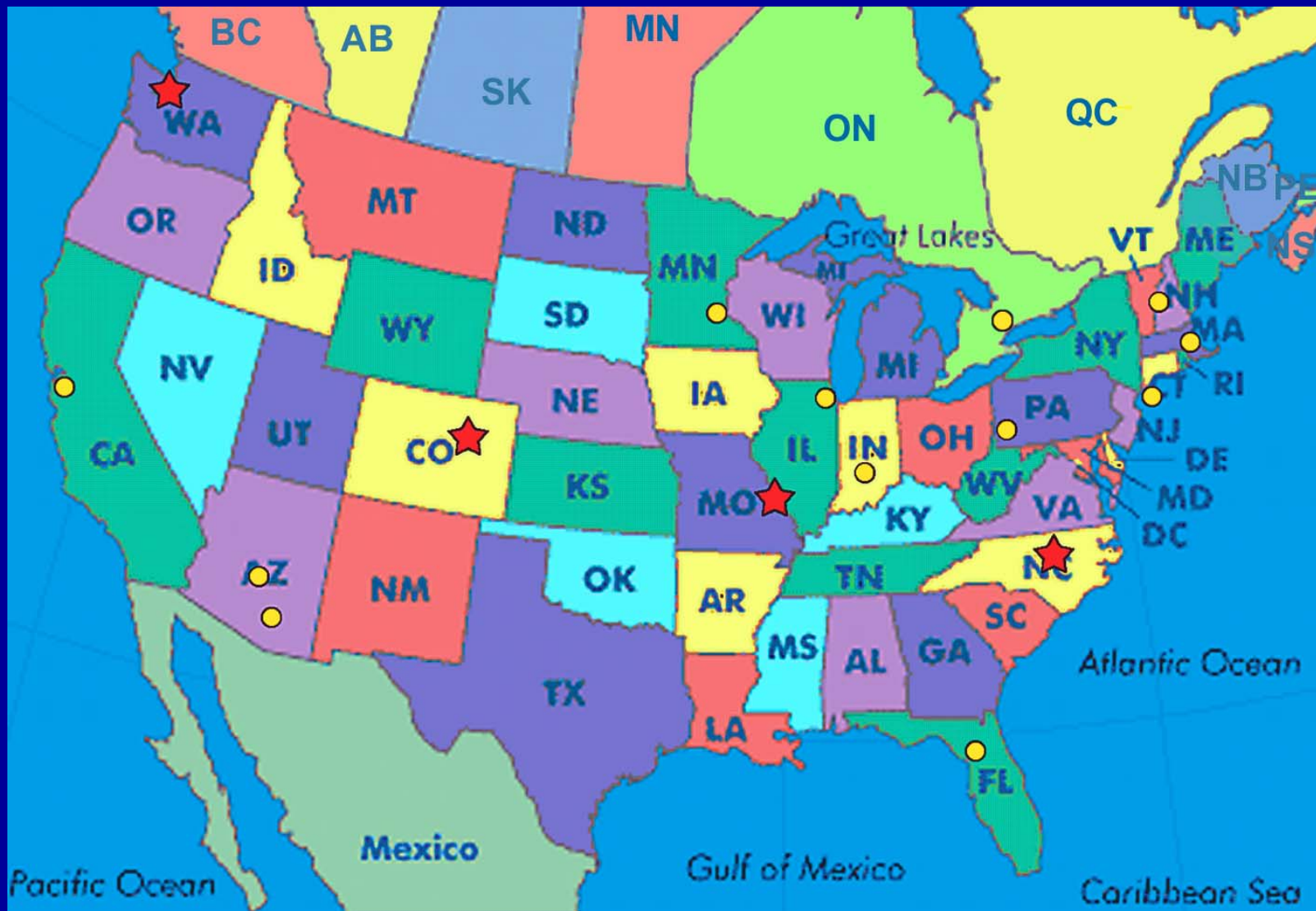
2003 - Grant competition (9/60 were eventually selected)

9/04 - 5-year grant for MCC Consortium; includes PCD, variant CF, and PHA

10/04 to present -

1. Establishing organization of MCC Research Centers; later, other clinical centers
2. Developing standard diagnostic procedures
3. Developing clinical research protocols focused on:
 - Clinical features and diagnosis (reviewed at NIH 7/21/05)
 - Longitudinal study (being developed)
4. Interacting/communicating with Rare Lung Disease Consortium (Cinn., 4/05)
5. Educating basic scientists (Gordon Conference, Calif., 2/05)
6. Establishing Rare Disorders Clinical Research Network (RDCRN)

PCD Research and Clinical Center Network



Goals of Research and Clinical Center Network

1. Establish more readily available diagnostic and therapeutic expertise
2. Use NIH resources to rigorously define key aspects of clinical disease, and identify genetic causes of disease
3. Build population of patients in Centers, so can study longitudinal course of disease, and develop extensive clinical experience
4. Develop consensus guidelines on diagnosis and treatment
5. We hope to study in PCD patients the benefits of different therapeutic approaches, including novel therapies requires large enough population of patients (hence focus on diagnosis).

PCD Update: Diagnostic Methodologies

1. Nasal nitric oxide (NO) – low NO correlates with PCD
 - Extending technology to 3 other sites in Network
 - Developing ability to measure in infants/children
2. Ciliary ultrastructure
 - Established SOPs for obtaining and processing nasal ciliated cells
 - Computerized methodology to analyze ciliary defects in electron micrographs
 - Developing pathology tests of cilia, using antibody staining techniques
3. Ciliary beat patterns
 - Developing methods to culture cells from nose
 - Using high speed videomicroscopy to precisely measure ciliary beating
 - If successful, could be used to test drugs *in vitro* (test tube)
4. Genetic testing
 - Doing collaborative research with 5 sites (UNC; Germany; U.K.; Paris; St. Louis)
 - Cross-testing samples for confirmation (~15-20% of PCD by genetic tests)
 - Developing clinically-available diagnostic genetic panel

PCD Update: Clinical Disease

1. Establishing Network of Centers
2. Trying to establish Clinical Registry Database
3. Developing Diagnostic and Treatment Guidelines
(ATS-sponsored; 2 workshops with N. American experts)
4. Multicenter cross-sectional study of clinical disease parameters (lung function; microbiology; CXR/CT scan findings)
5. Designing prospective longitudinal studies through MCC Consortium (including infants/children) to better define clinical pathogenesis of disease

If there are enough patients in the Network, it will provide the opportunity for clinical trials of drug therapy.

PCD Update: Basic Science

1. Ciliary dysfunction associated with different ultrastructural and genetic defects in PCD.
 - Will provide easier diagnosis, and guide therapeutic strategies
2. Mechanism whereby nasal (airway) NO is low in PCD
 - Will give understanding of cellular mechanism of disease, and perhaps therapeutic insights (sweat Cl⁻ test used for diagnosis in CF for 35 years before CF genetic mutation shown to involve Cl⁻ channel).
3. Identify disease-causing genetic mutations in PCD
 - Will improve diagnostic capability, and probably define a whole new set of people with “mild” PCD that has not been previously recognized.
 - Will enhance opportunity to devise new therapy, and identify larger number of patients to test.
4. Animal models (genetic modulation of mice)
 - Confirm certain genes might cause PCD
 - If get mice with PCD, can perform studies much more rapidly in mice than humans; speed therapeutic development
5. Involve “basic scientists” (Gordon Conference)
 - Synergy of thought and action

Conclusion

1. Essential features for Patient Care Network for PCD are present (pertinent patients, educated health care professionals, ability to evolve/improve)
2. Keys to success are present (PCD Foundation; compelling clinical disorder and science; resources)
3. NIH-funded Mucociliary Clearance Consortium is special bonus, and timely.

In summary, the progress towards a PCD clinical care and research network is strikingly ahead-of-schedule relative to other rare disorders, with excellent opportunities for growth and progress. Consolidation of current assets, and patience, along with perseverance, offer rich hope for the future.