Clinical Translational Research in Cystic Fibrosis – "Where are we in 2011 and where will we be in 5 years?"

Bonnie W. Ramsey, M.D.
Endowed Professor of Pediatrics
University of Washington School of Medicine
Director, Cystic Fibrosis Foundation
Therapeutics Development Network Coordinating Center
Seattle Children's Research Institute

cystic fibrosis foundation THERAPEUTICS inc.

UW Medicine SCHOOL OF MEDICINE

Seattle Children's HOSPITAL · RESEARCH · FOUNDATION

Disclosure Statement

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

AlgiPharma AS
Amgen, Inc.
Aradigm Corporation
Axcan Pharma, Inc.
Bayer Healthcare AG
Chiesi Pharmaceuticals Inc.
CSL Behring L.L.C.
Gilead Sciences
GlaxoSmithKine
Inspire Pharmaceuticals, Inc.
KaloBios
MerLion Pharmaceuticals GmbH
Mpex Pharmaceuticals, Inc.
MPM Asset Management LLC
N30 Pharmaceuticals, LLC
Novartis Pharmaceuticals Corp.
Pharmaxis Ltd.
PTC Therapeutics, Inc.
Solvay Pharmaceuticals, Inc.
Transave, Inc.
Vectura Ltd.
Vertex Pharmaceuticals Incorporated

I also receive grant funding from CFF and the National Institutes of Health

Today's Presentation

- Examples of success in CF translational research
- What resources does the CF community already have?
- What are our challenges?
- What are the next steps for clinical translational research as we focus on early lung disease and young children?

Pathogenesis

Defective CF Gene

↓

Defective/Deficient CFTR

↓

Decreased Chloride Secretion
Increased Sodium Absorption

↓

Bronchial Obstruction

↓

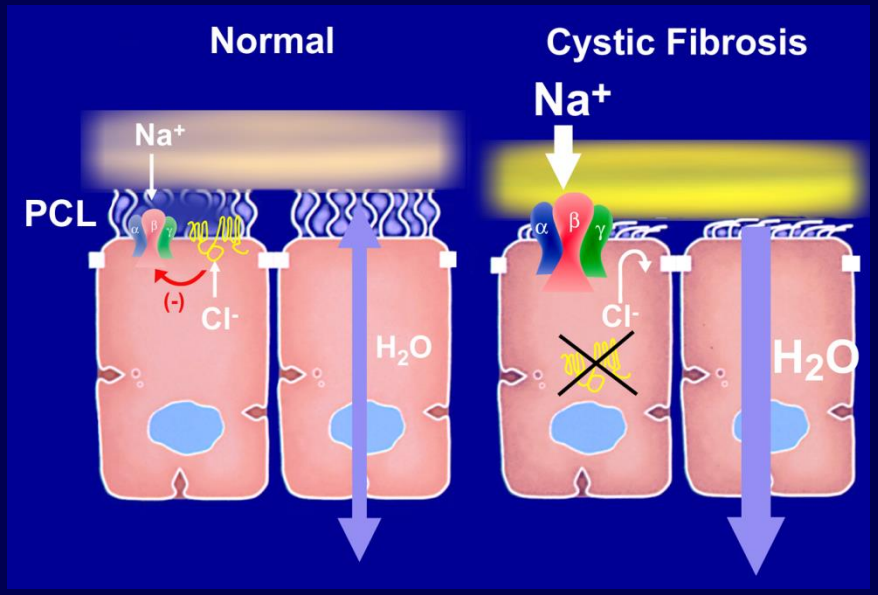
Infection

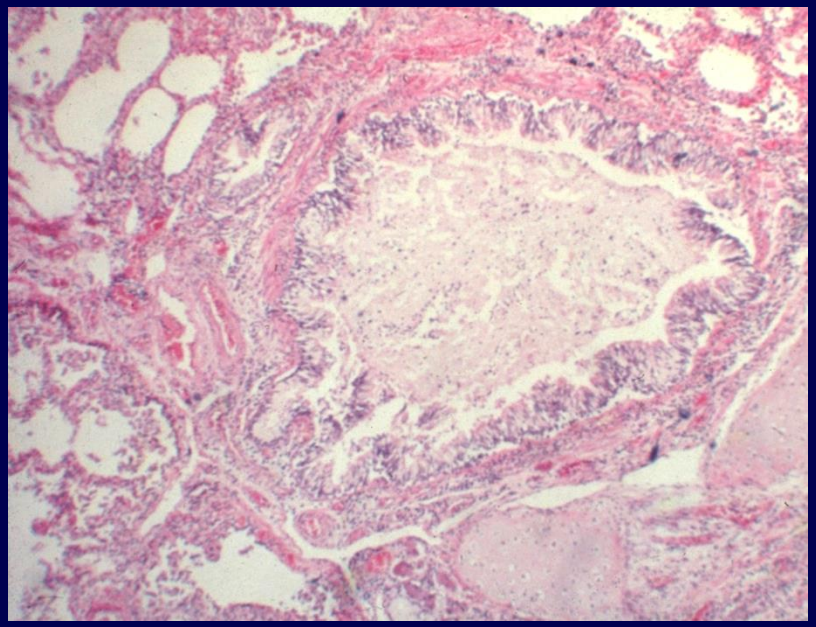
↓

Inflammation

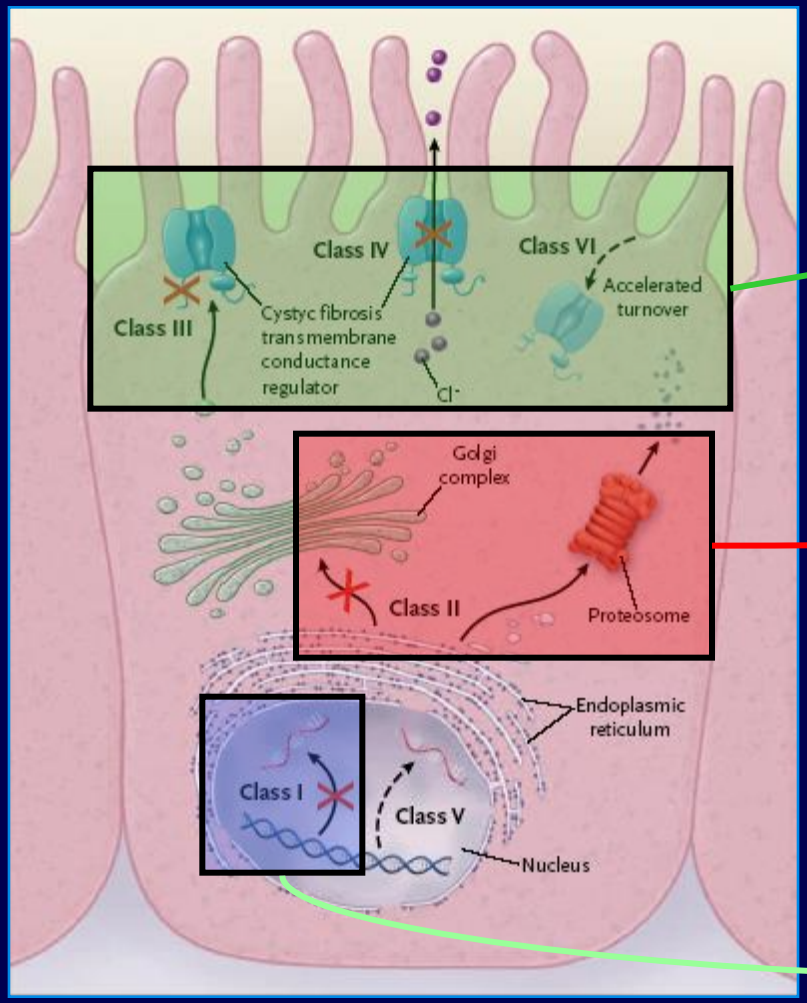
↓

Bronchiectasis





Therapeutic Approaches by Class



CFTR Potentiator

CFTR Processing Corrector

Translational Readthrough

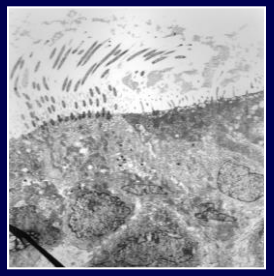
Rowe SM, et al., *NEJM* 2005;352(19):1992-2001

Drug Discovery Process Leading to VX-770

High Throughput Screening → **Medicinal Chemistry** → **Biology Activity in Cell Cultures*** → **Animal Studies** → **Human Studies**

100,000's
of molecules

1000's



100's
In vitro
Biological effect

10's
Safety
pharmacology
toxicology

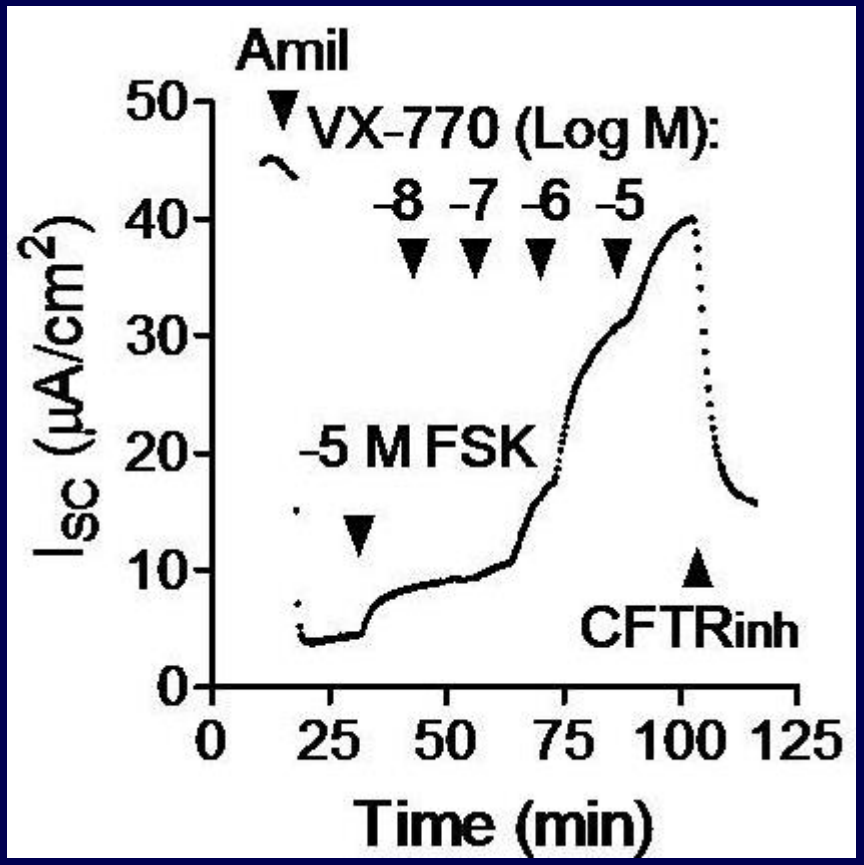
7-10

*Human bronchial epithelial cells

Supported by CFF and Vertex

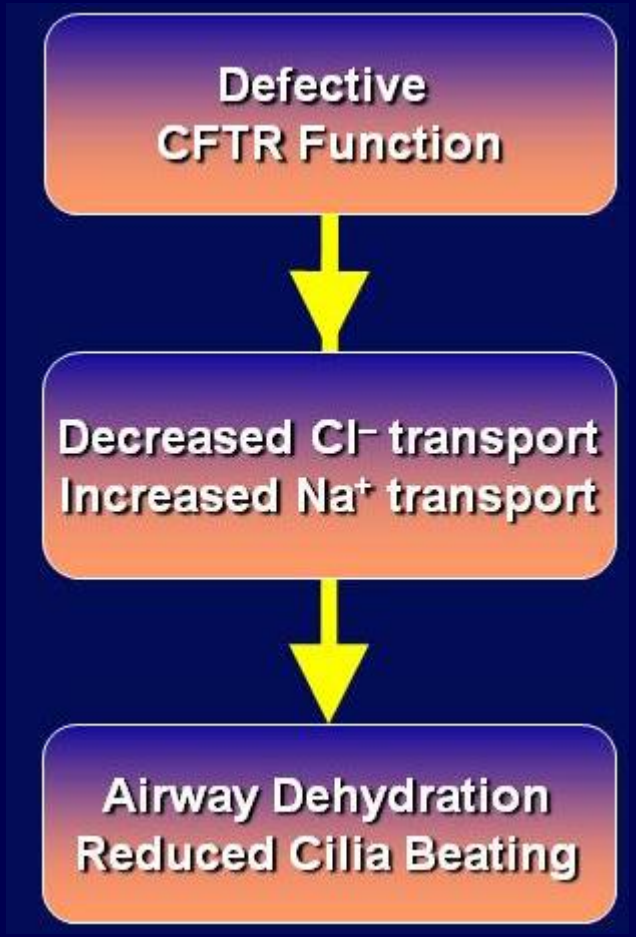
VX-770, A Potentiator, Increases G551D/F508del-CFTR Activity

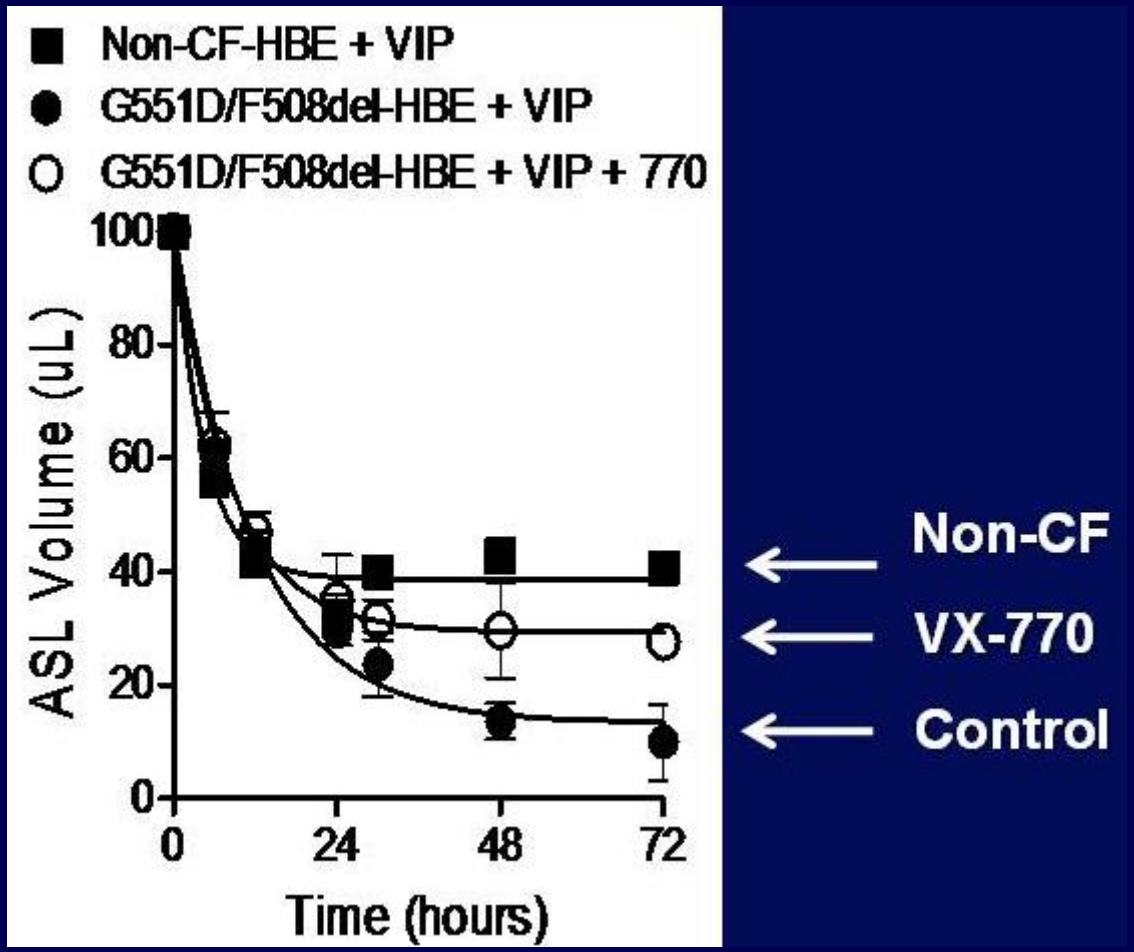
Ussing chamber studies using G551D/ΔF508-HBE cultures



Van Goor F, et al, *PNAS* 2009;106(44):18825-30

VX-770, A Potentiator, Increases G551D/F508del-CFTR Activity





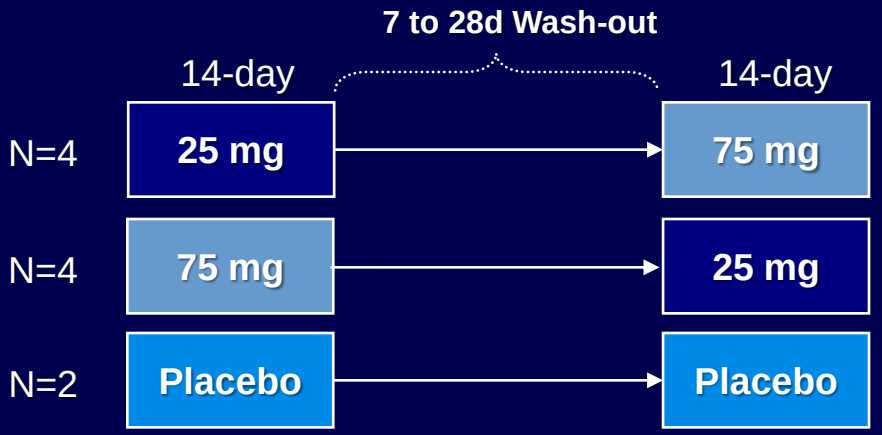
Van Goor F, et al, *PNAS* 2009;106(44):18825-30

VX-770 Phase 2A Study Design

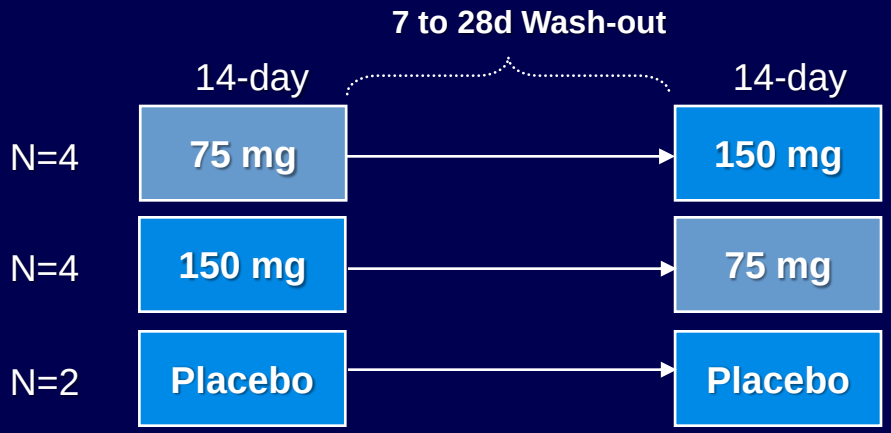
Part 1

Randomized,
Double-Blind,
Placebo Controlled

Group A:
10 Subjects
(G551D Mutation)

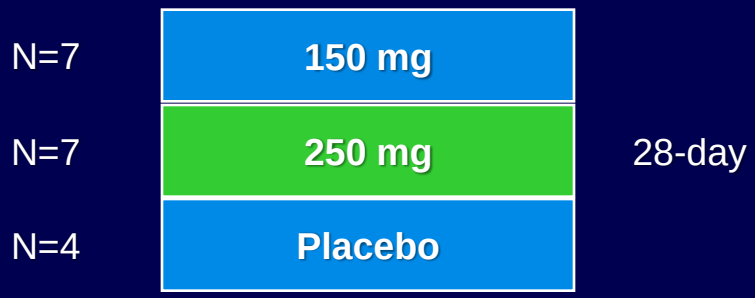


Group B:
10 Subjects
(G551D Mutation)



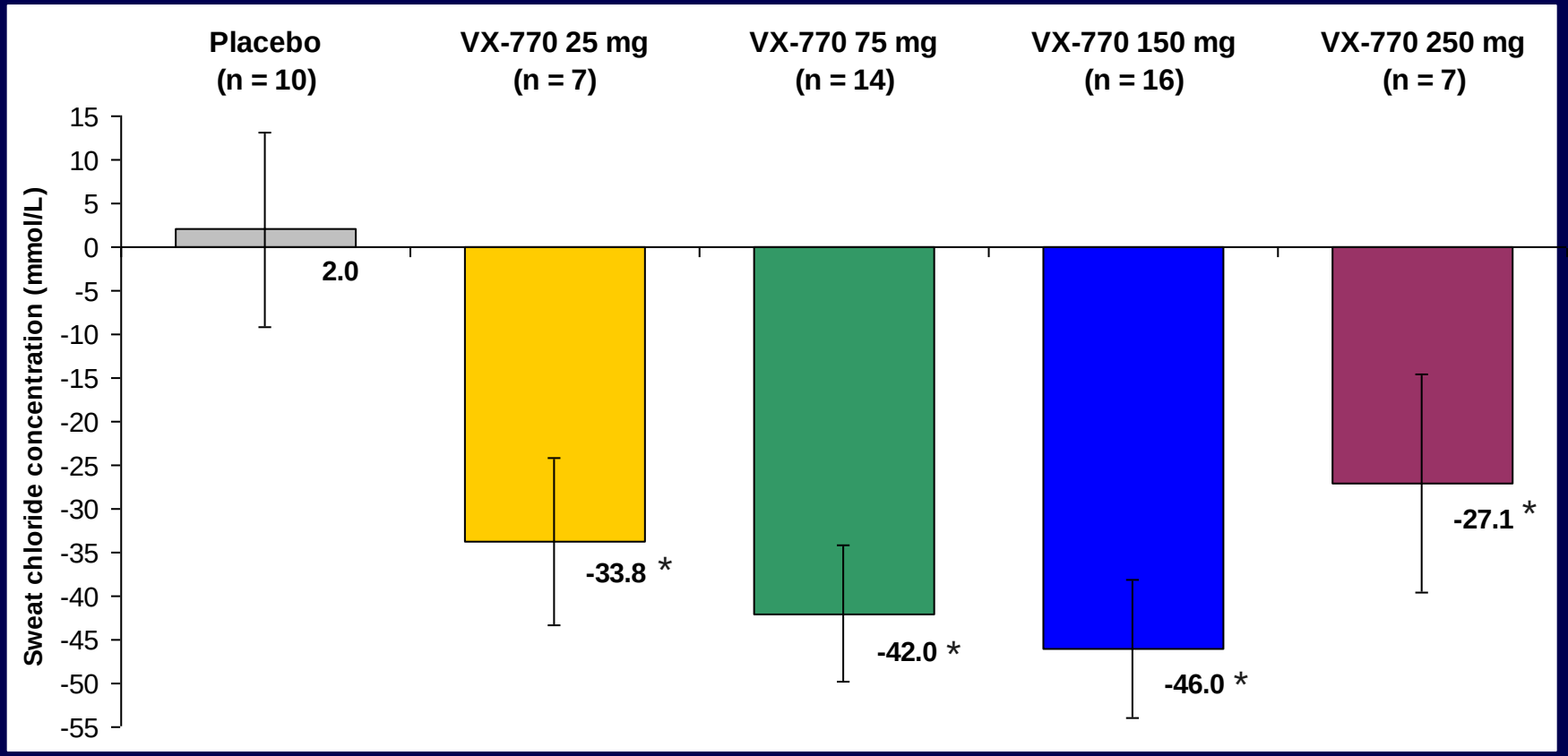
Part 2

18 Subjects
(G551D Mutation)



Sweat Chloride Change from Baseline

Combined Part 1 and 2 data through Day 14 - Mean (95% CI)



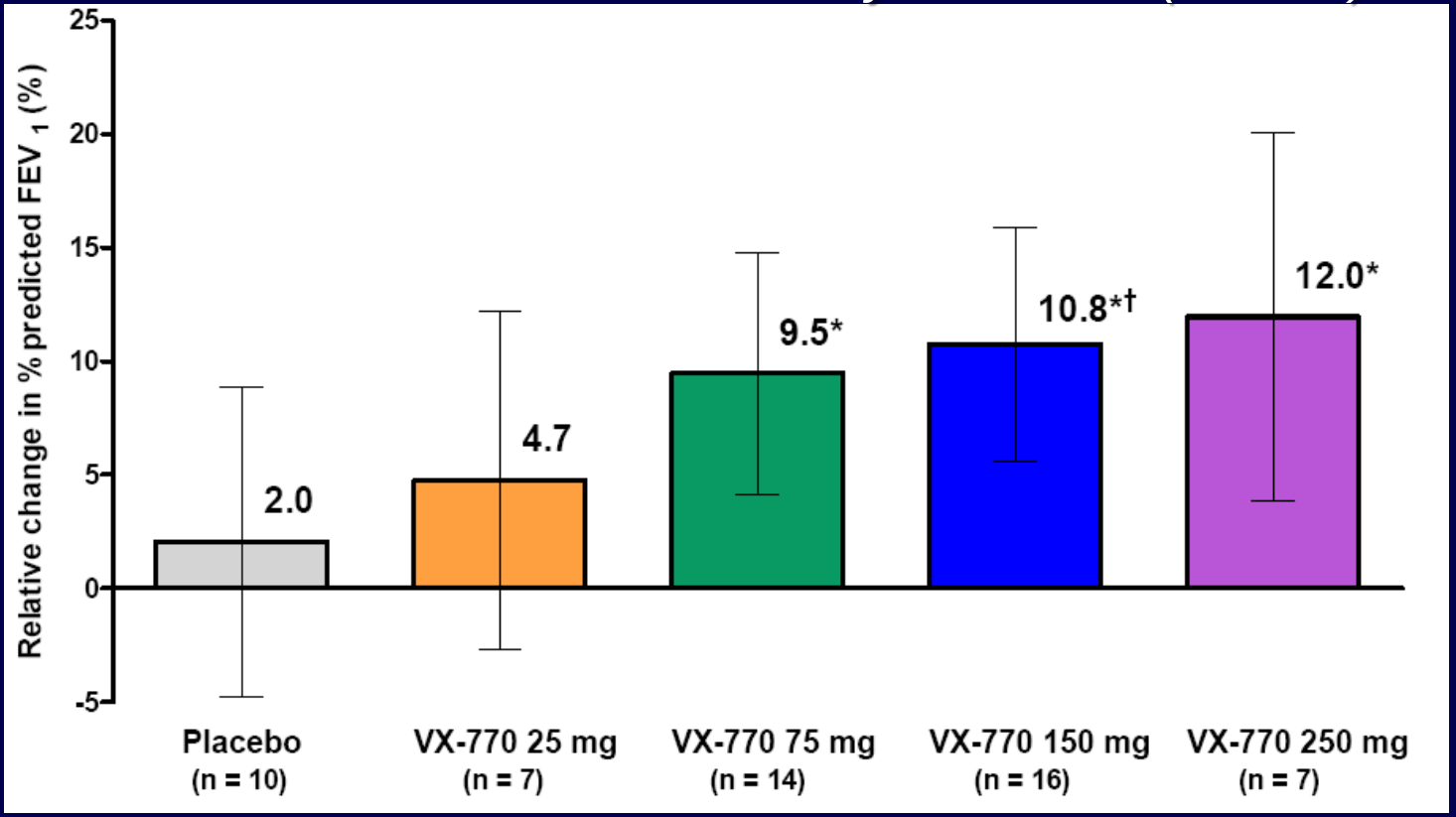
*$p < 0.01$ within-group and vs. placebo
Linear trend for dose groups $p < 0.001$

Accurso, F. et al , *NEJM* 2010;363:1991-2003

Relative Change in FEV_1 % Predicted

VX-770 improvements in lung function were statistically significant

Combined Part 1 and Part 2 to Day 14 - Mean (95% CI)



* $p < 0.01$ within-subject
† $p < 0.01$ within-subject
‡ $p < 0.05$ within-subject

Accurso, F. et al , *NEJM* 2010;363:1991-2003

VX-770 Registration Program in CF

endeavor PROGRAM
Aspiring to transform CF treatment

Orphan Drug and Fast Track Designation

Three separate registration studies:

strive — Primary trial to enroll ages 12+ with G551D mutation

envision — Patients aged 6 to 11 with G551D mutation

discover — Phase 2 study of CF patients homozygous for the F508del mutation

Vertex News Release (1)
February 23, 2011

"Phase 3 study of VX-770 (Strive) showed profound and sustained improvements in lung function (FEV_1) in patients with cystic fibrosis and G551D mutation"

- Strive enrolled 161 patients worldwide with CF and at least one G551D mutation
- Patients received VX-770 (n=83) 150mg pill or placebo pill (n=78) twice daily for 48 weeks

Vertex News Release (2)
February 23, 2011

Results (VX-770 compared with placebo)

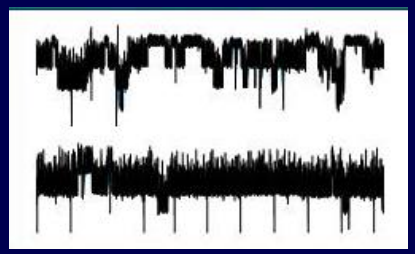
	24 weeks	48 weeks
➢ FEV_1		
• Mean absolute change	10.6%	10.5%
• Relative change	16.7%	16.9%
➢ Pulmonary exacerbation requiring antibiotics		↓ 55%
➢ Weight		↑ 3.1kg (6.8 lbs)
➢ Sweat chloride (baseline 100 mmol/L)		↓ < 60 mmol/L

Strategies to Rescue F508del-CFTR: Restore Both Trafficking and Gating

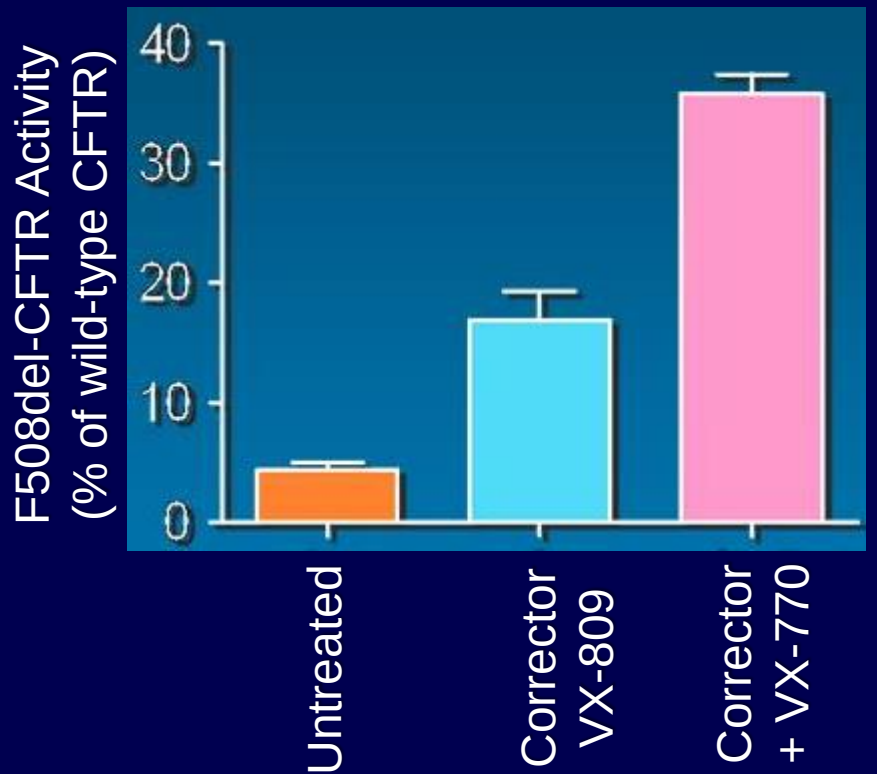
VX809 Corrector

$$I_{CFTR} = n * Po * g$$

VX-770



Additivity of Corrector and Potentiator in F508del-HBE Cells



Two Phase 2a Clinical Trials in ΔF508/ΔF508 Patients

- VX-770 (Discover Trial)
  - 140 patients with CF and ΔF508 mutations to test safety
    - Drug was safe except some cough and rash
    - Results
      - FEV_1 ↑ 1.6% at 16 weeks
      - Sweat chloride ↓ 2.6 mmol/L at 16 weeks

Phase 2a VX-809 Trial Study Findings (2/5/2010) (n=89)

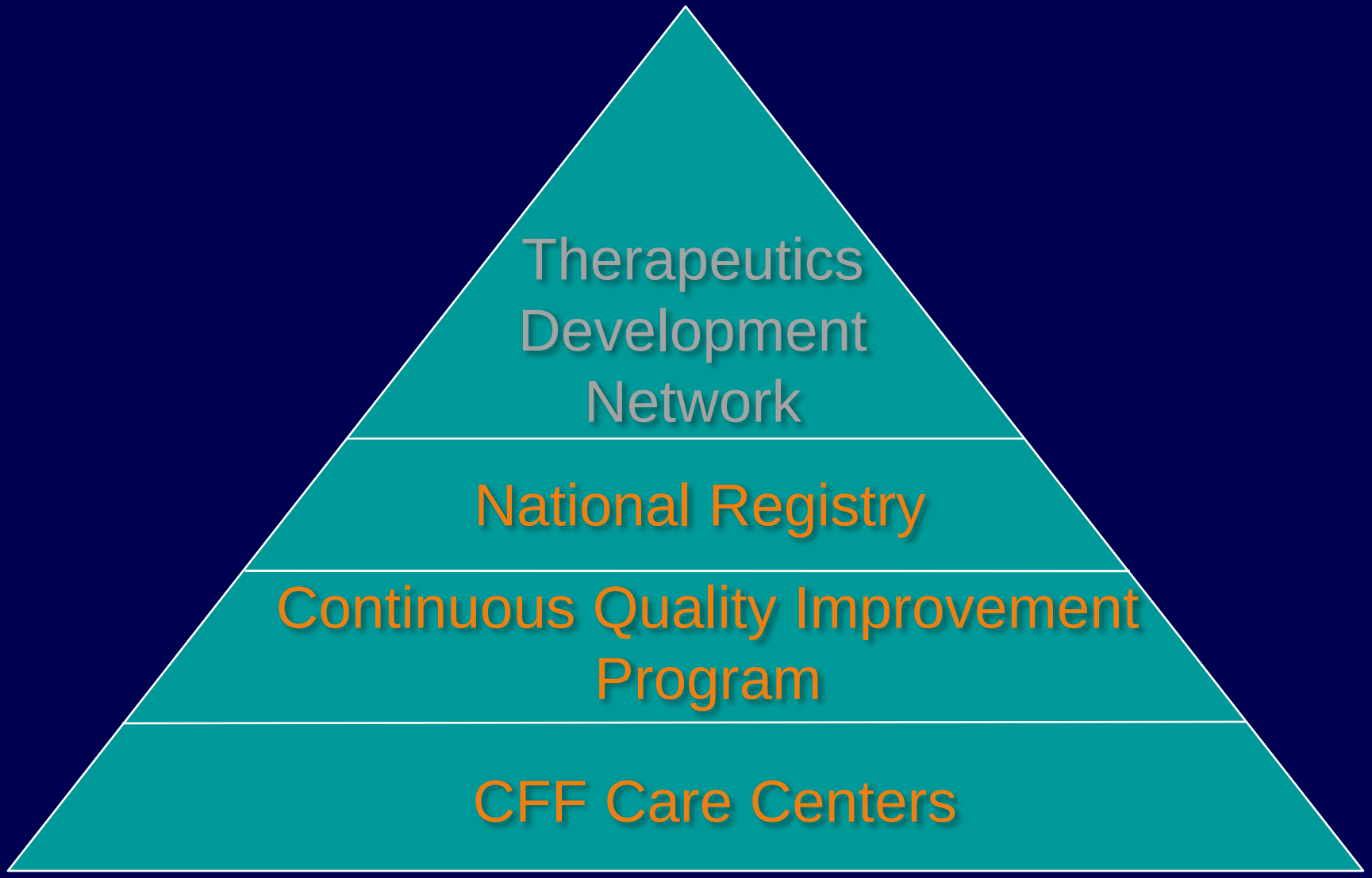
- Safety – well-tolerated; one patient per arm discontinued for adverse events
- CFTR activity measured by sweat chloride

Treatment Arm	Mean Change in Sweat Cl^{-*}	P-value
25 mg	0.10 mmol/L	N/S
50 mg	-4.61 mmol/L	N/S
100 mg	-6.13 mmol/L	0.0498
200 mg	-8.21 mmol/L	0.0092

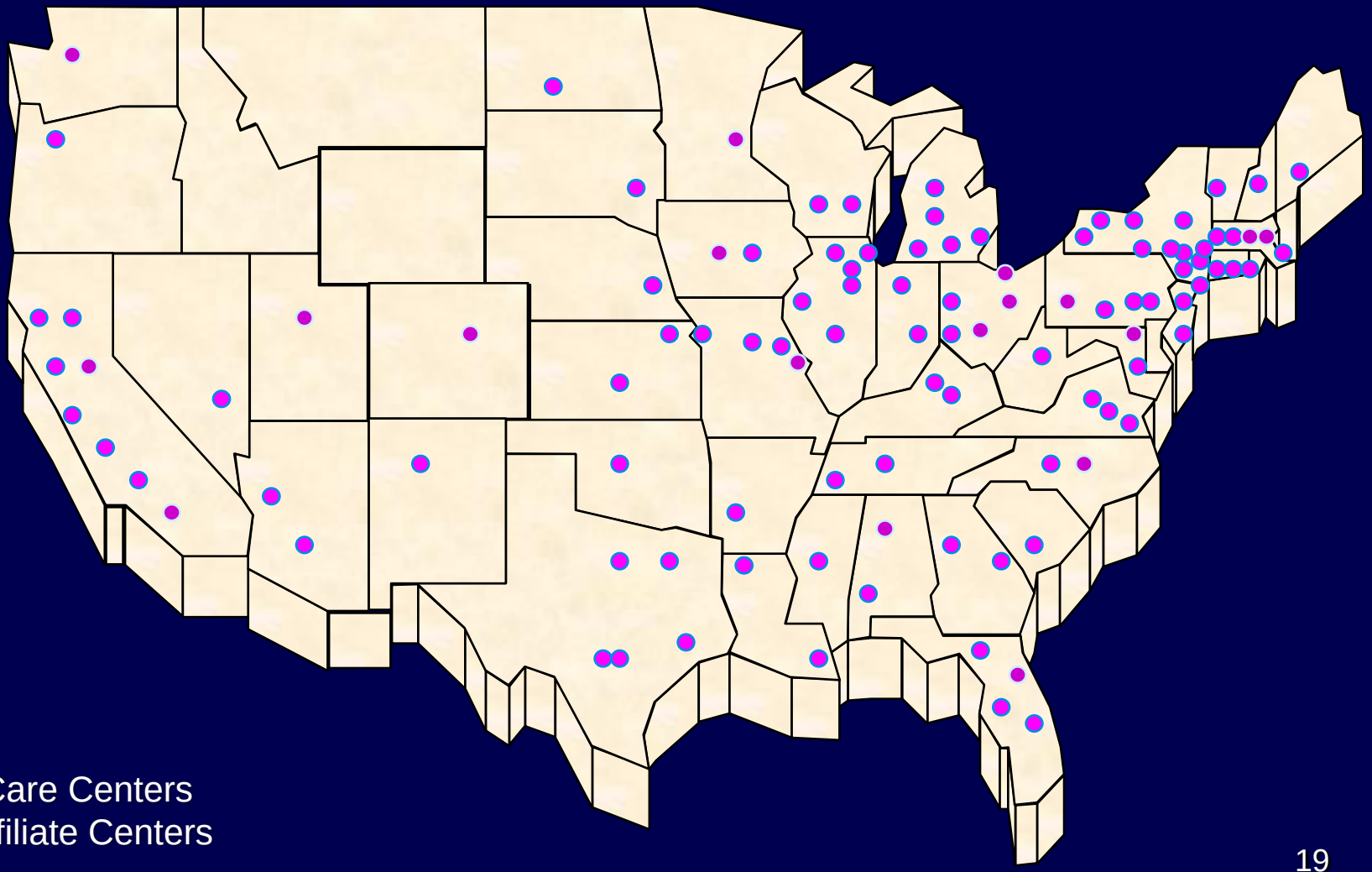
* compared with placebo arm

- Vertex has moved forward with combined VX-770 and VX-809 clinical trials

CFF Infrastructure that Supports Successful Clinical Research



Cystic Fibrosis Foundation (CFF) Care Centers



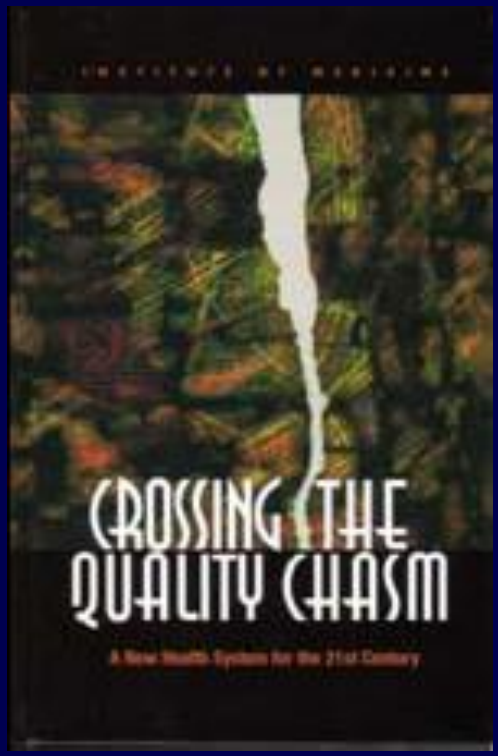
116 Care Centers
51 Affiliate Centers

Key Features of CFF Care Centers that Support Clinical Research

- Multi-disciplinary teams supported by an annual CFF grant
  - MDs, RNs, dietary, social work, respiratory therapy, genetics, etc.
- **Commitment to** teaching and **research**
- Accreditation process with peer review site visits every three years
- **Standardized treatment plans** (inpatient and outpatient) to reduce variability
- **Ongoing collection of clinical data** for patient registry
- Foundation for 77 Therapeutics Development Network (TDN) centers

CFF Continuous Quality Improvement (CQI) Program

- Inspired by 2001 Institute of Medicine (IOM) report, CFF initiated CQI programs at all CF Care Centers
- Key priorities of this program:
  - Understanding the relationship between process and outcome in clinical care
  - The use of guidelines, data registries and front line data support
  - Involving patients in the care process
  - Understanding the impact of new therapies in ongoing clinical practices

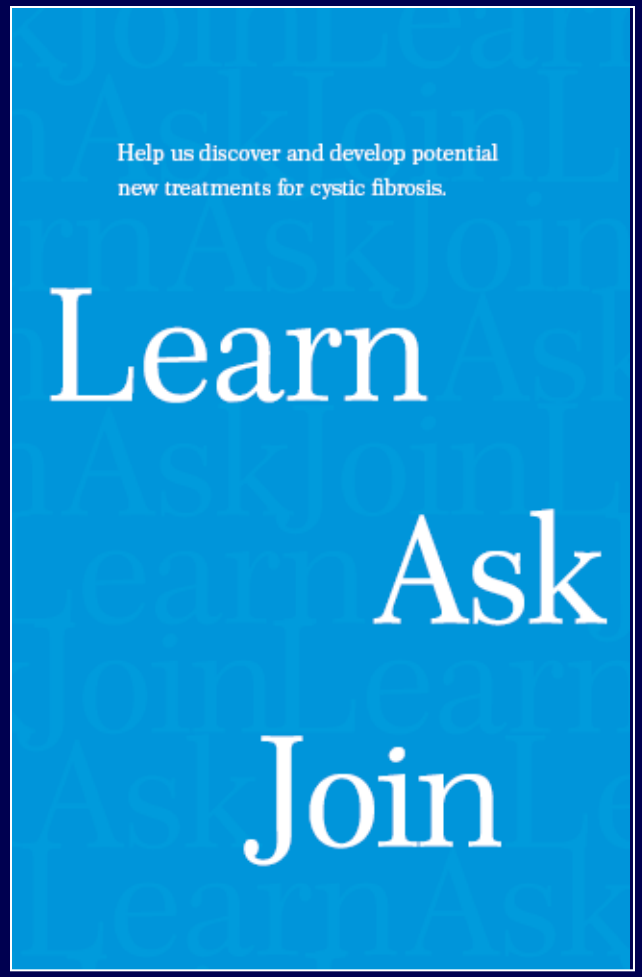


How CFF CQI Supports Research

- Further decreases variability in care standards
- Helps to understand confounding factors leading to variability
- Creates culture of inquiry
- Promotes transparency and close partnership with families (parent advisory committee)

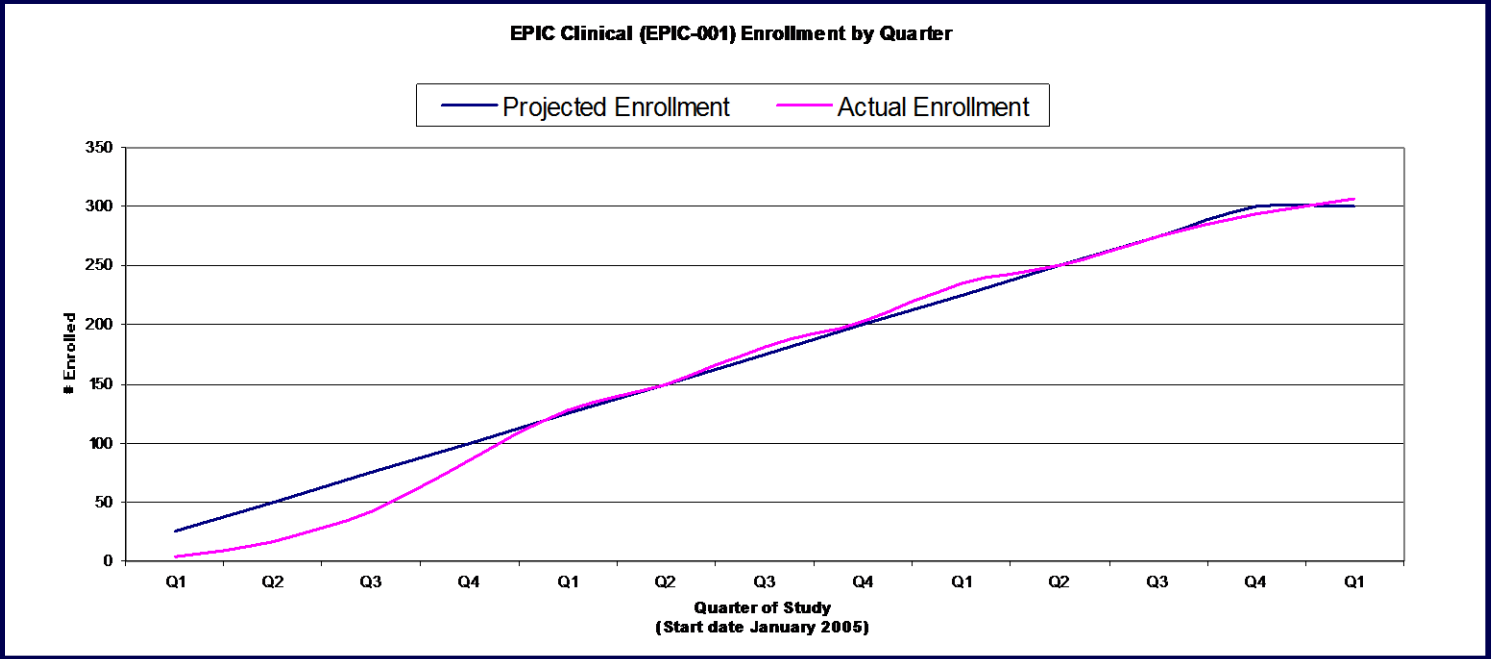
What is CFF Doing to Reduce Barriers to Participation in Research Studies?

- Changing the culture:
  - "Learn, Ask, Join"
  - "I Am The Key"



www.cff.org

Enrollment Success in the CF Population

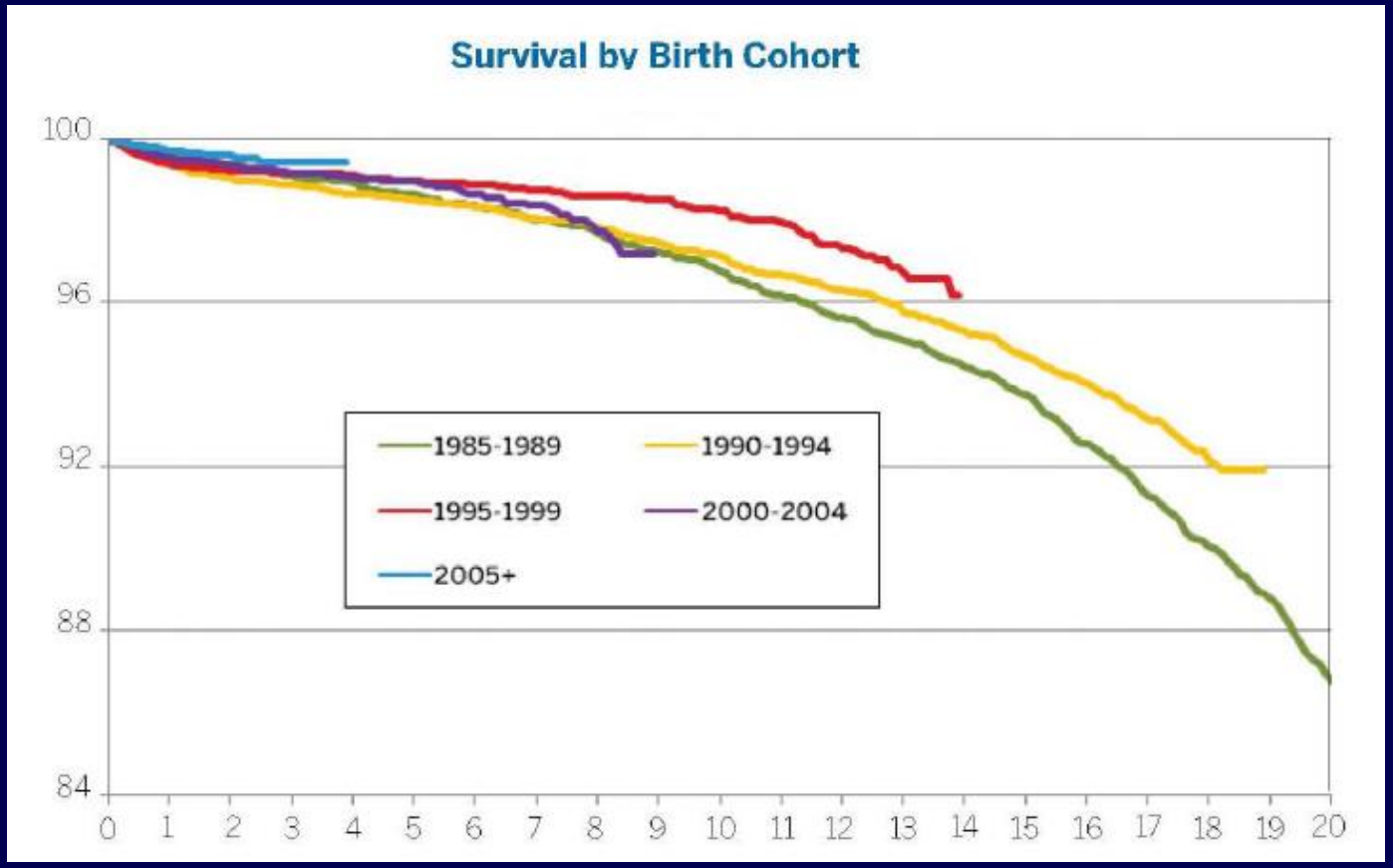


- Well trained research staff
- Patients easily identified and screened through registry
- Low screen failures (< 10%)
- Families very knowledgeable and committed
- Low attrition rate (< 10%)

A Powerful Research Tool

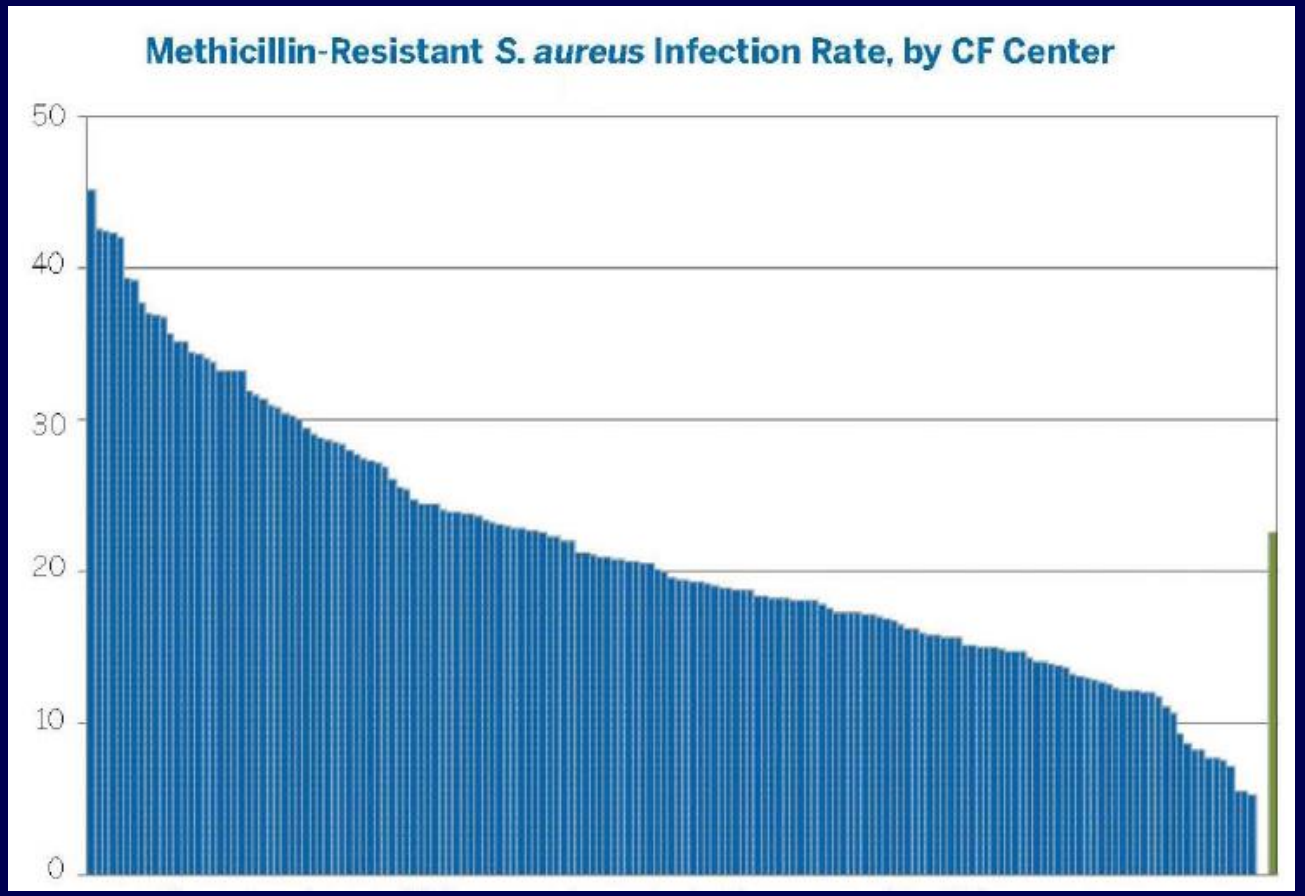
Cystic Fibrosis Foundation | Adding *tomorrows* every day.

Patient Registry – A Powerful Research Tool
Example 1: Natural History Studies



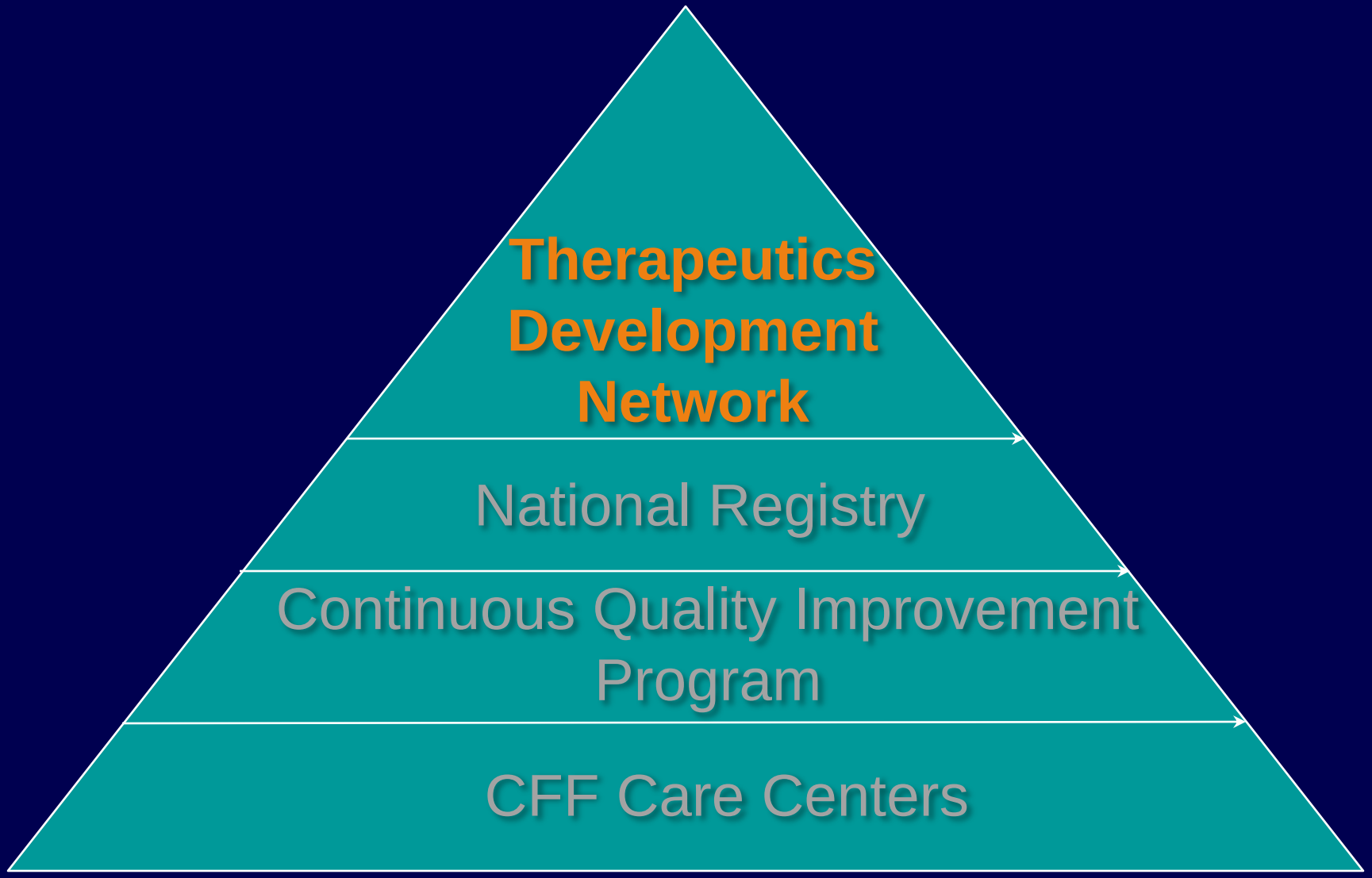
Of patients born between 1985 and 1989 (the earliest cohort shown here in green), 88% survived to age 19. For patients born between 1990 and 1994, 92% survived to age 15.

Patient Registry – A Powerful Research Tool Example 2: Identifying Optimal Patient Populations



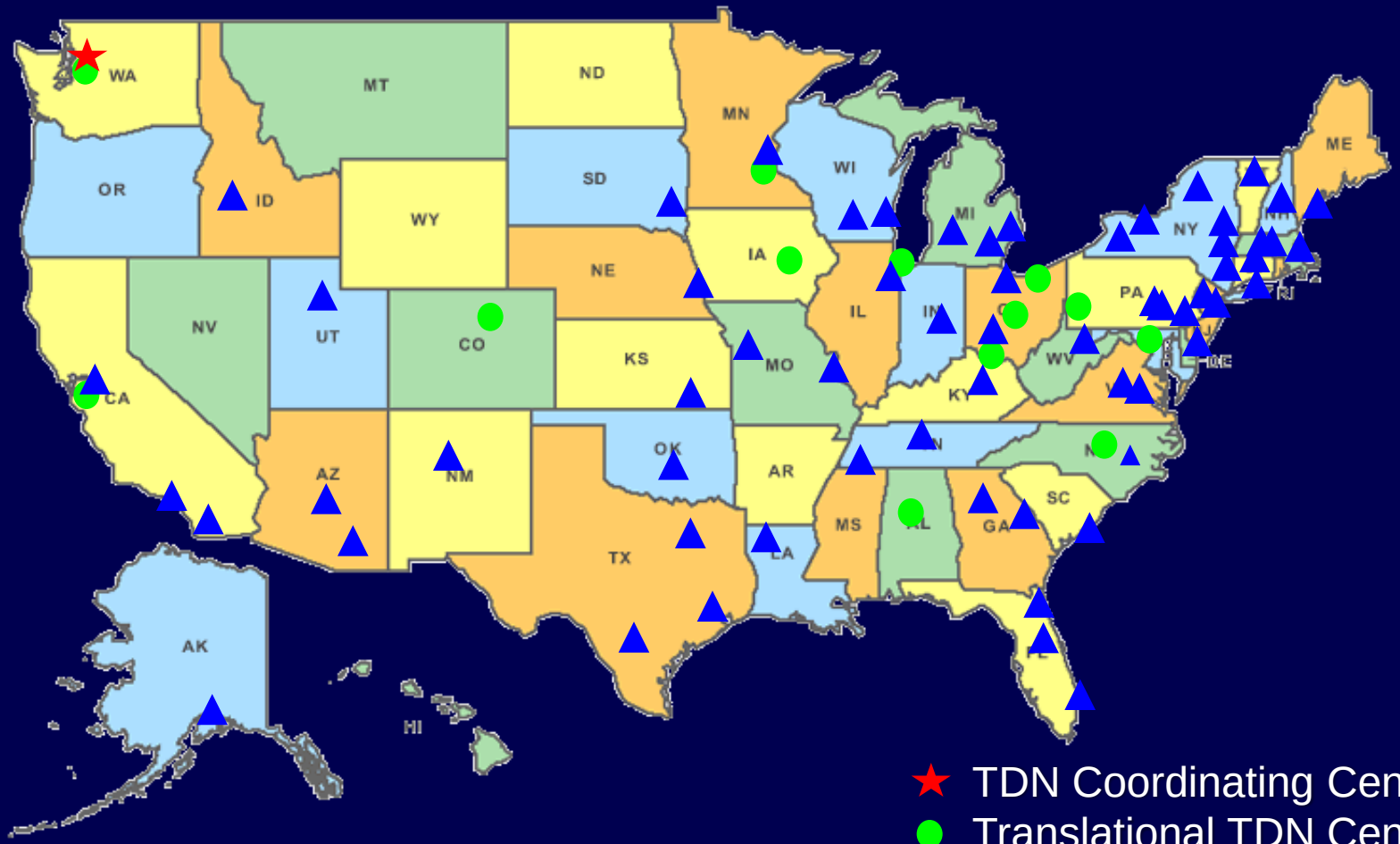
The national rate is 22.6 percent (green bar). The range is 0 to 45.2 percent.

CFF Infrastructure that Supports Successful Clinical Research

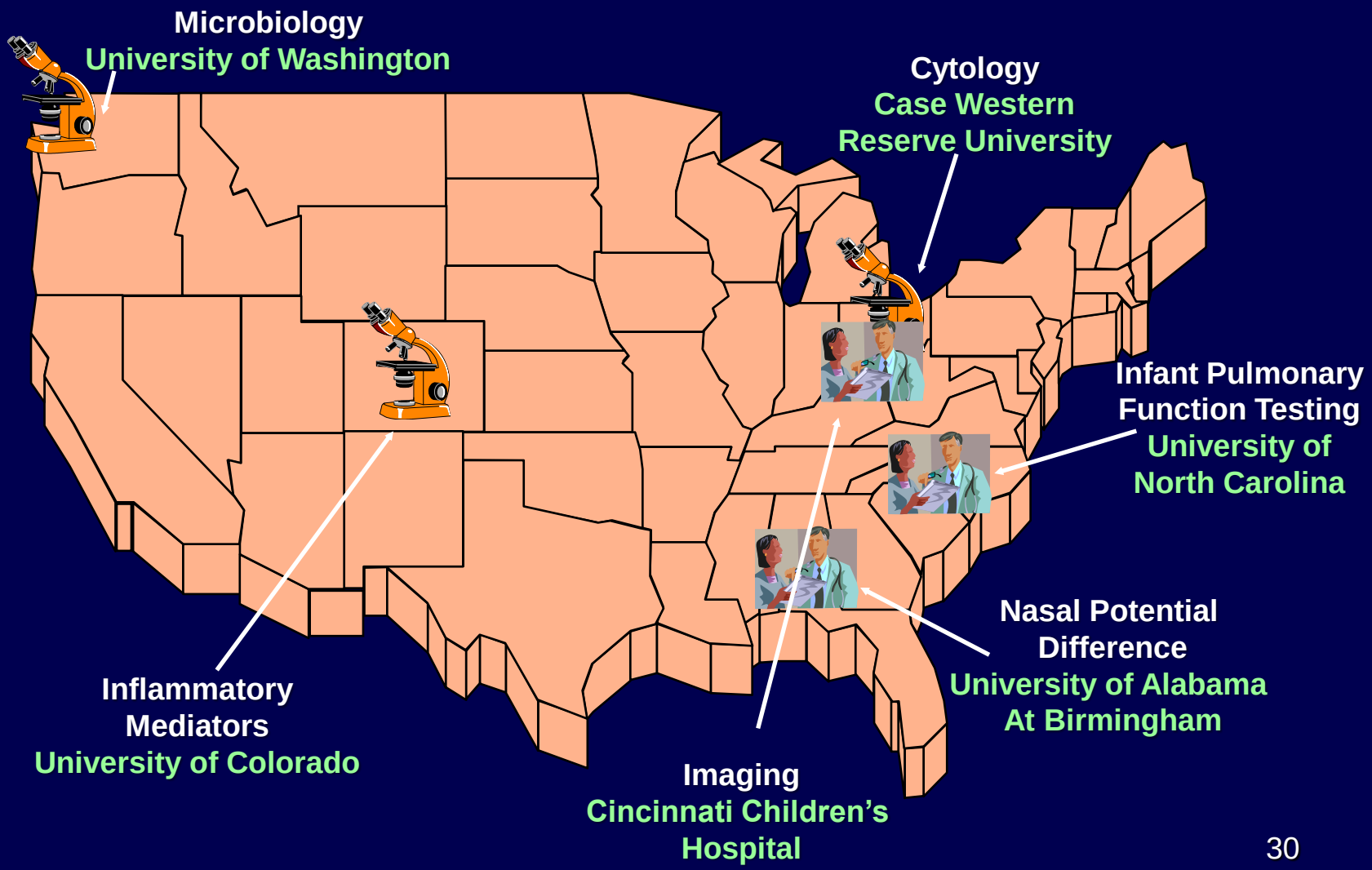


CFF Therapeutics Development Network (TDN)

Established in 1998



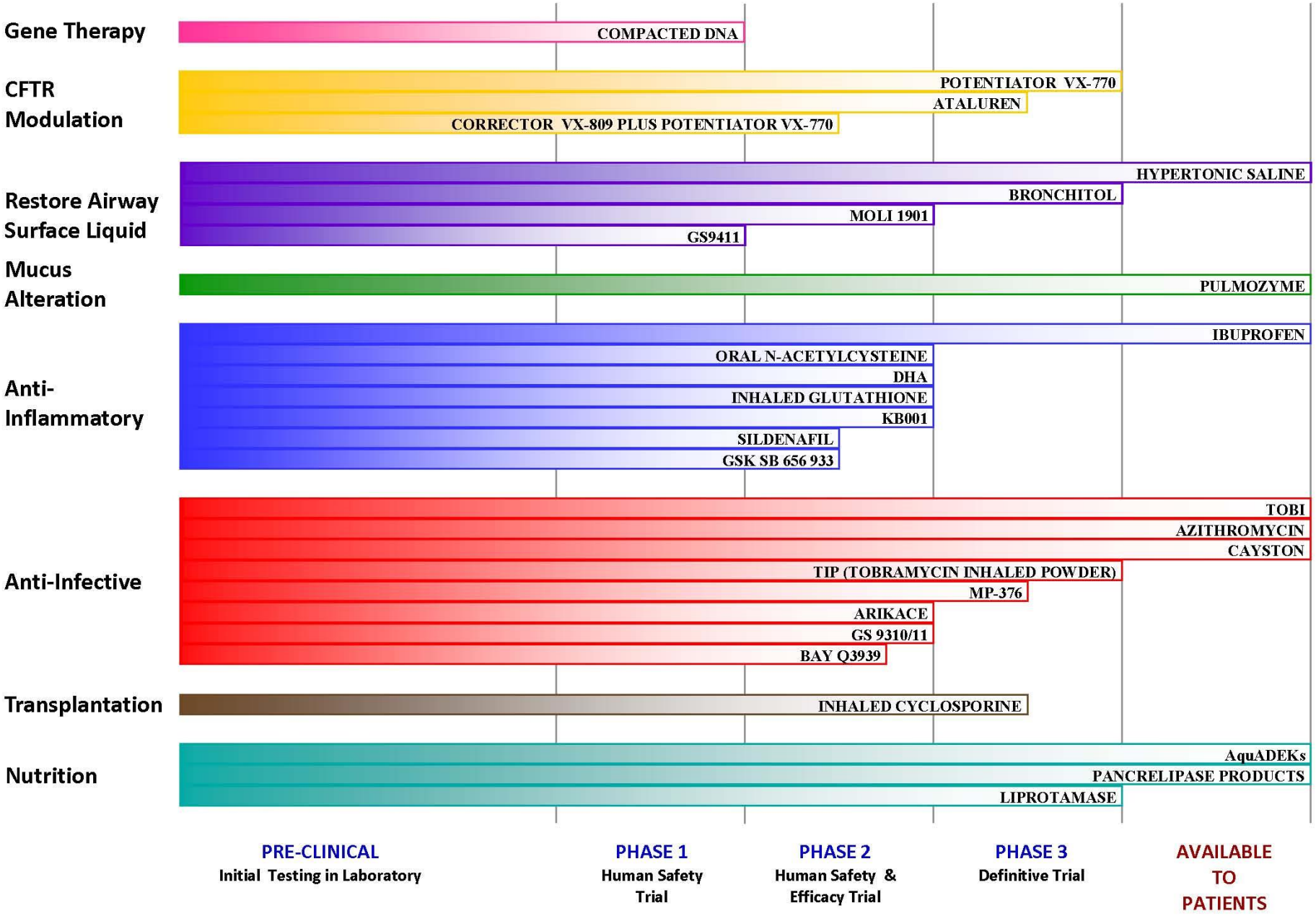
National Resource Centers



CFF TDN Accomplishments

- Over 100 therapeutic and observational trials successfully completed utilizing network sites and resources
- Over 30 investigational new drugs reached Phase 1 and 2
- Approximately 12 therapies have reached Phase 3 trials
- Four therapeutic pathways have been completed with FDA approval
  - Inhaled Aztreonam (Cayston®)
  - Three Pancreatic Enzyme Preparations (Zenpep®, Creon®, Pancreaze®)

Cystic Fibrosis Foundation Therapeutics Pipeline



February 23, 2011

Challenges We Face in the Next 5 Years (1)

- Disease progression is slowing
  - Magnitude of change in outcome measures reduced and prolonged
  - Sample size and study durations increase
- More approved therapies are available
  - Safety considerations (e.g., drug – drug interactions)
  - Comparative effectiveness studies will be necessary
- Baseline population characteristics are changing
  - Example – Patient population in inhaled aztreonam studies (2007-2009) had the same FEV_1 range as inhaled tobramycin studies (1995-1997) but were 10 years older!
  - Importance of concurrent placebo group rather than historical controls

Challenges We Face in the Next 5 Years (2)

- Moving to younger, milder patients
  - Developing age appropriate clinical endpoints
  - Safety monitoring in young, vulnerable population — short-term and lifetime follow-up
- Finite patient population and funding
  - Setting priorities across the world community
  - Using resources wisely and efficiently

Key Priorities for the CF Research Community in the Next 5 Years

- Ensure patient safety and family trust
- Ensure responsible use of shared resources
- Better understand natural history of early lung disease
- Facilitate outcome measure development
- Develop new approaches to study designs

Priority #1: Continue to Ensure Patient Safety

- Established CFFT Data Safety Monitoring Board (Wayne Morgan, Director)
- Established centralized medical monitoring program (Chris Goss, Medical Director)
- Accumulating safety laboratory data and adverse event profiles (CFF TDN virtual data bank)
- Needs for the next 5 years
  - Expand safety database and sharing of safety data across studies (CFF, NIH, industry) – at a minimum include placebo populations
  - Continue to collect normative and natural history data – especially in infancy

Priority #2: Responsible Utilization of Clinical Resources

- Joint European (ECFS CTN) and US (CFF TDN) review of large multi-center clinical trials through TDN Protocol Review Committee
- Central database (CCSM) tracking all US multi-center trials at 77 TDN sites, enabling accurate enrollment projections
- Percent of patient population at TDN sites newly enrolled in studies during previous 12 months
  - Interventional
    - Range across sites = 0.5 - 27%
    - Median = 9%
  - Observational
    - Range across sites = 0 - 56%
    - Median = 10%

Responsible Utilization of Shared Resources: Current Repositories

Resource	Data	Specimens	Oversight
TDN virtual data repository	Placebo data for RCT's	----------	NRCC (Sam Moskowitz, Chair)
TDN NRC banked specimens	Variable data linked to TDN studies	• Bacterial pathogens (UW) • Sera • BAL	NRCC
CFFT Specimen Bank (ProMedx)	Standard template of identifying data	• Sera • Microbiology	CFFT Biomarkers Committee (S. Sagel, Chair)
Wisconsin NBS study (2012)	Identifying data for specimens	• Sera (ProMedx) • Micro (UW)	CFFT Biomarkers Committee
International CF Modifier Consortium	DNA Sequencing data	DNA	Consortium Steering Committee (currently not open to non-investigators)

Priorities for Shared Resources

- Proactive consenting of patients/families for banking
- Central database with “search engine” to track specimens and linked data
- Transparency and open access to large repositories
- Partnership of CFF, NIH and industry to support effort

Priority #3
Better Understand Natural History of Early Disease

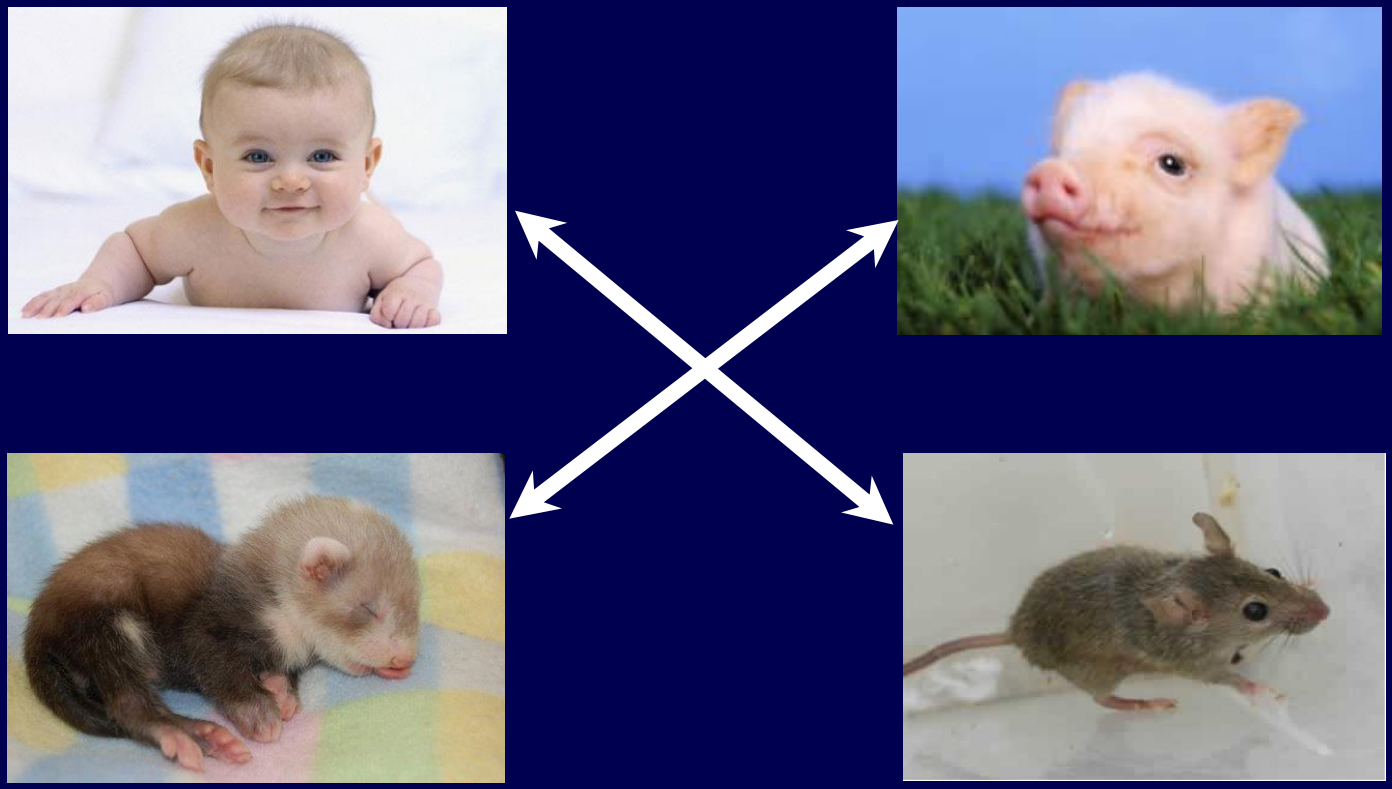
Priorities from NHLBI Workshop Sept. 20-21, 2010:

- Leverage Newborn Screening to elucidate the natural history and clinical manifestations of early lung disease
- Develop a spectrum of biomarkers of early CF lung disease, measures of structural lung disease in connection with physiologic functions
- Explore the role of CF modifier genes and their associated variants in early lung disease
- Develop enabling technologies/tools/animal models of early lung disease (e.g. better imaging technologies)

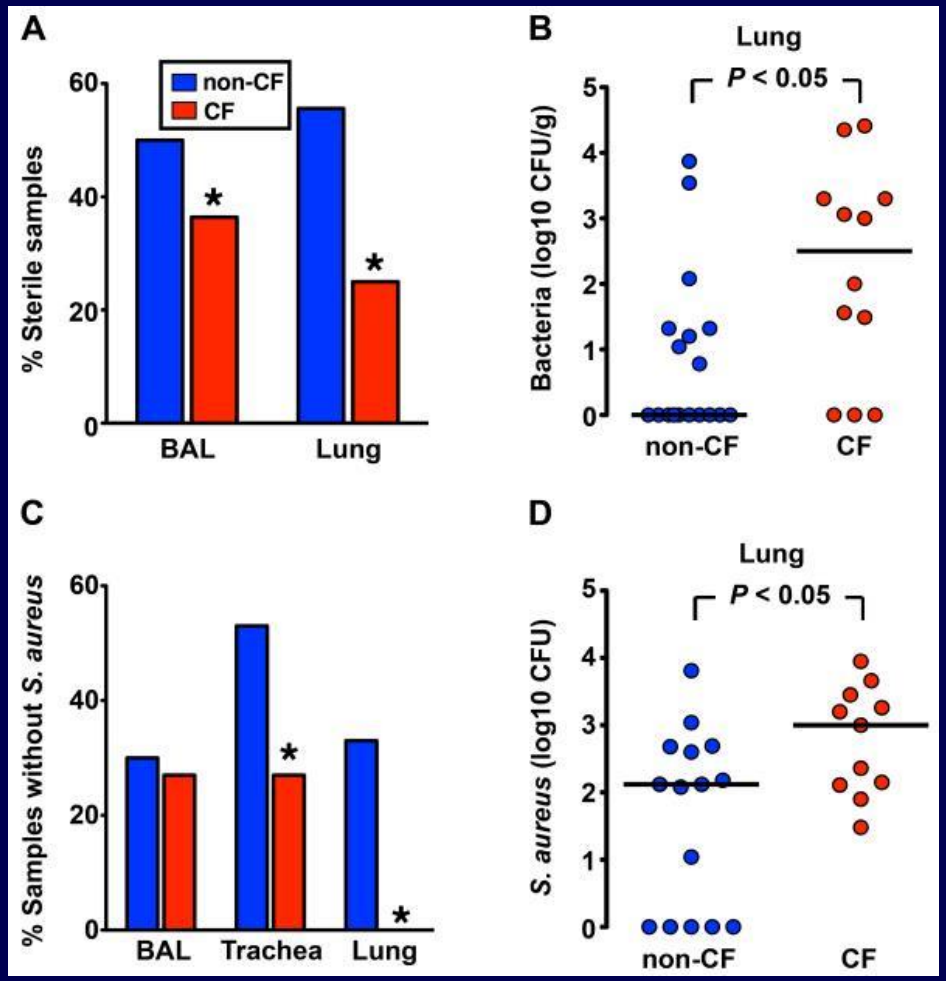
Baby Observational and Nutritional Supplement Study (BONUS)

- To define and describe weight gain and growth in first year of life in CF newborns
- Explore nutritional, microbiologic and inflammatory characteristics that may be associated with optimal or poor growth
- Enzyme sub-study
  - Evaluate effect of the doses of pancreatic enzyme replacement on fat and protein malabsorption
- Establish a data and specimen repository for future studies
- Starting in late 2011
- 125 infants at 30 sites

Incredible Opportunity from Cross-Species Investigations



Newborn CF Piglets Fail To Eradicate Bacteria



David A. Stoltz, "Cystic Fibrosis Pigs Develop Lung Disease & Exhibit Defecetive Bacterial Eradication at Birth" (2010) *Science Translational Medicine Vol 2 Issue 29: pg. 5, Fig . 7*.

Priority #4: Facilitate Outcome Measures Development

Level 1: Clinical Efficacy Measures

Level 2: Validated Surrogate Endpoints

Level 3: Non-Validated Surrogate Endpoints

Level 4: Biomarkers

Kindly provided by Nicole Hamblett

FDA Workshop September 23-24, 2010

"Issues in the Design of Clinical Trials of Aerosolized Antimicrobials for the Treatment of Cystic Fibrosis"

- Purpose of the open forum was for the FDA to gain perspective about clinical management of CF lung disease and outcome measures being used for both clinical care and research studies
- Three key clinical outcomes of interest to the Anti-microbial Division were discussed:
  - Patient related outcome measures
  - Pulmonary exacerbation definition
  - FEV_1

FDA Workshop Take Away Messages

- FDA is keenly interested in completing the validation of at least one patient related outcome (PRO) measure of respiratory symptoms
  - Two leading candidates:
    - CF Questionnaire – Revised (CFQ-R)
      Quittner AL et al., *Chest* 2009;135(6):1610-8
    - CF Research Symptom Diary
      Goss, CH et al., *JCF* 2009;8(4):245-52
- FDA and European Medicines Agency (EMeA) would like an international effort to develop a universally-accepted definition of a pulmonary exacerbation
- FEV_1 and other pulmonary functions are not accepted by all FDA divisions as a primary endpoint; important secondary endpoint
- FDA encourages the CF community to lead the effort to validate outcome measures

Biomarkers

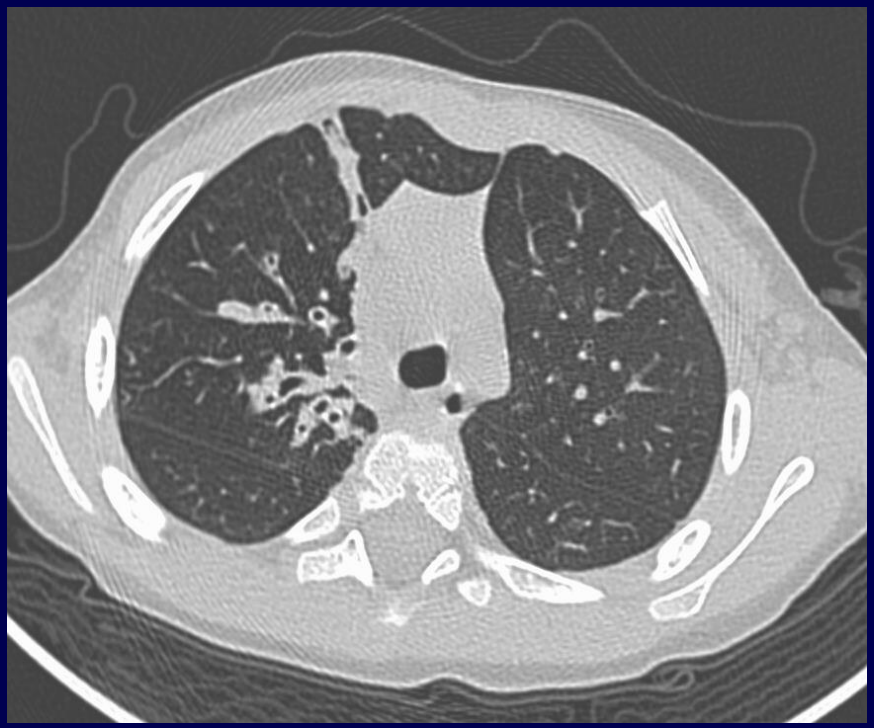
- Biomarkers serve an important role in drug development
  - As measures of biologic activity:
    - Identifying therapeutic targets
    - Screening candidate drugs
  - As correlates for clinical efficacy:
    - Providing proof of concept in early stage trials
    - Understanding mechanism of action
    - Identifying responders to treatment

Kindly provided by Nicole Hamblett

Candidate Biomarkers for Early Disease

- Measures of CFTR function
  - Sweat Chloride
  - Nasal Potential Difference
- Measures of airway hydration and Mucociliary Clearance (MCC)
- Measures of early lung disease
  - HRCT Imaging
  - Infection
  - Inflammation

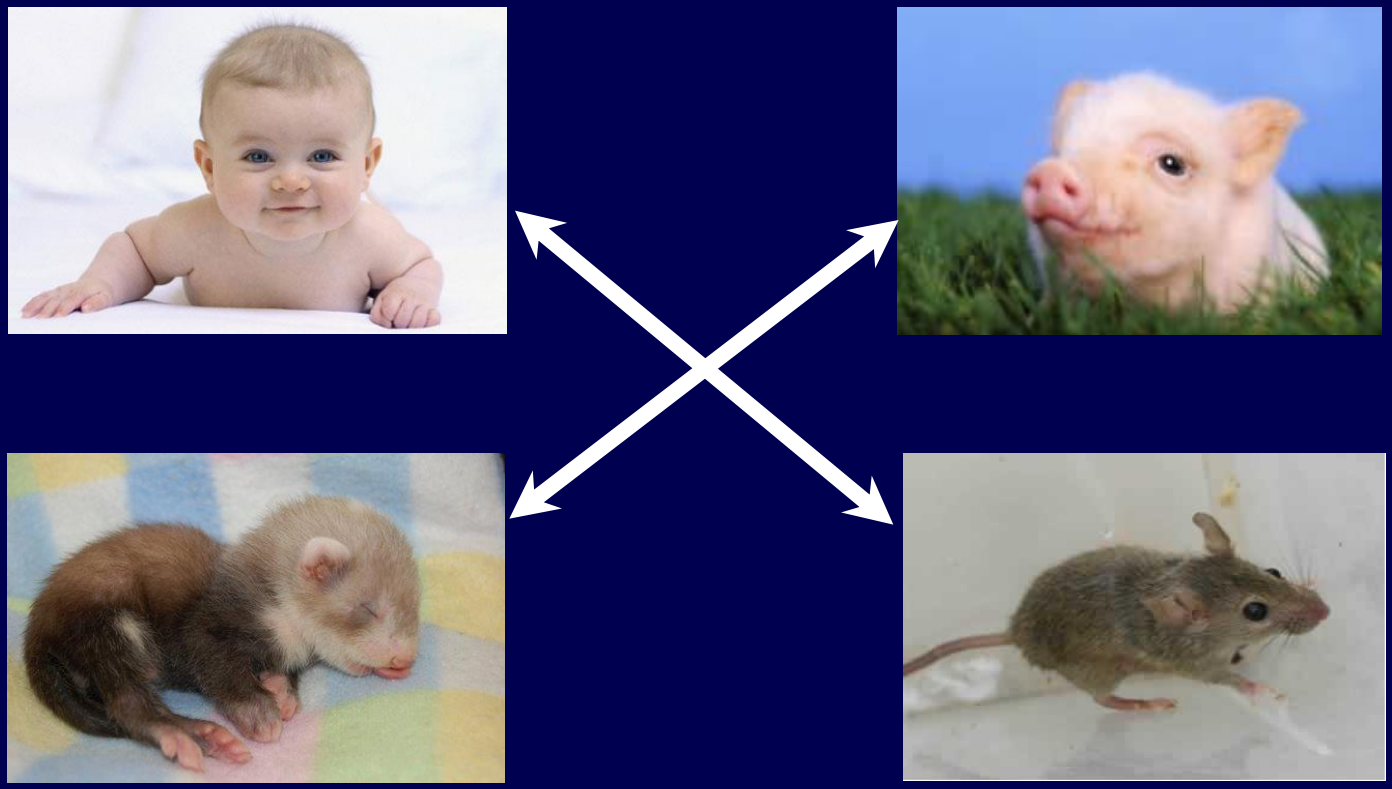
HRCT Reveals Early Structural Damage



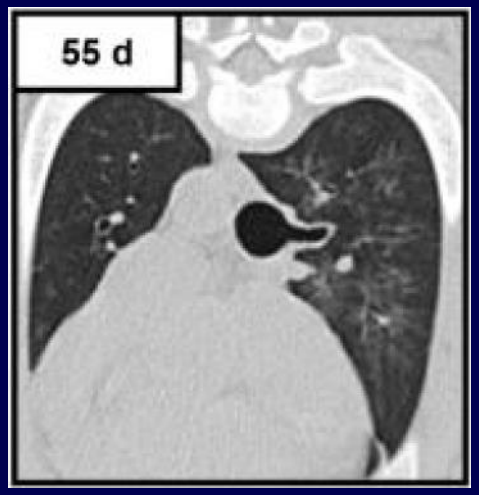
- HRCT detects regional structural damage prior to ↓ PFTs
- Emerging measure of early lung disease in CF

Long FR , *PATS* 2007; de Jong PA, *Eur Respir J* 2004; Davis SD, *AJRCCM* 2007

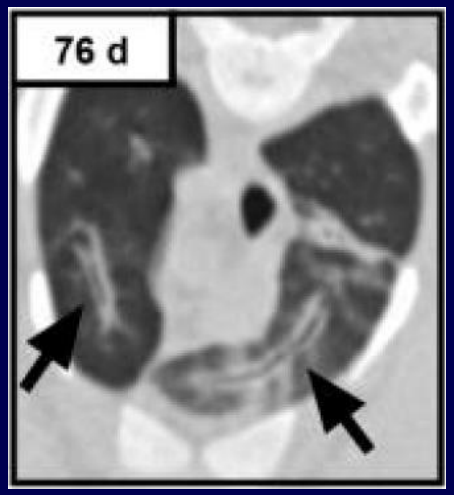
Incredible Opportunity from Cross-Species Investigations



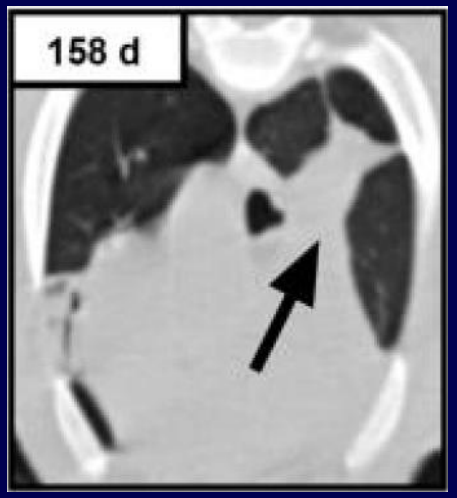
CF Pigs Develop Pulmonary Disease



Non-CF



CF



CF

David A. Stoltz, "Cystic Fibrosis Pigs Develop Lung Disease & Exhibit Defecetive Bacterial Eradication at Birth" (2010) *Science Translational Medicine Vol 2 Issue 29: pg. 5, Fig . 7*.

Priority #5
New Approaches to Study Designs

- With multiple approved CF therapies available, we can no longer rely on randomized placebo-controlled clinical trials
- Next generation will look at comparisons of approved agents
- Unlikely that industry will conduct these trials
- The CF community will need to move towards comparative effectiveness research

Comparative Effectiveness Research (CER)

- IOM Report:
  - Defines CER as the "generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care."

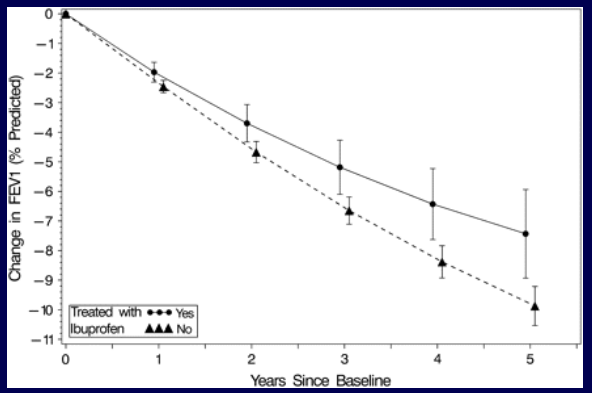
Institute of Medicine. Initial Priorities for Comparative Effectiveness Research. 2009. Washington D.C., National Academies Press

Types of CER Studies

- Prospective observational studies
  - Cohort and case control
  - Before/after
- Retrospective observational studies
  - Cohort and case control
  - Before/after
- Cost benefit analyses
- Practical clinical trials

Examples of Observational Studies of Therapeutic Interventions in CF

- Observational assessment of Ibuprofen in US CFF Patient Registry
  - Difference, **0.48%** pred./year (95% CI, 0.19 to 0.78)
- 2 Randomized, controlled trials:
  - 4 year study (N=85)
    - FEV_1 % of predicted rate of decline slower in ibuprofen group
      - **-1.48%** compared to **-3.57%** per year
  - Canadian Ibuprofen 2 year study DB RCT (N=142)
    - Sign. reduction in the rate of decline of FVC % pred. (**0.07** +/- 0.51 vs **-1.62** +/- 0.52; P = .03)



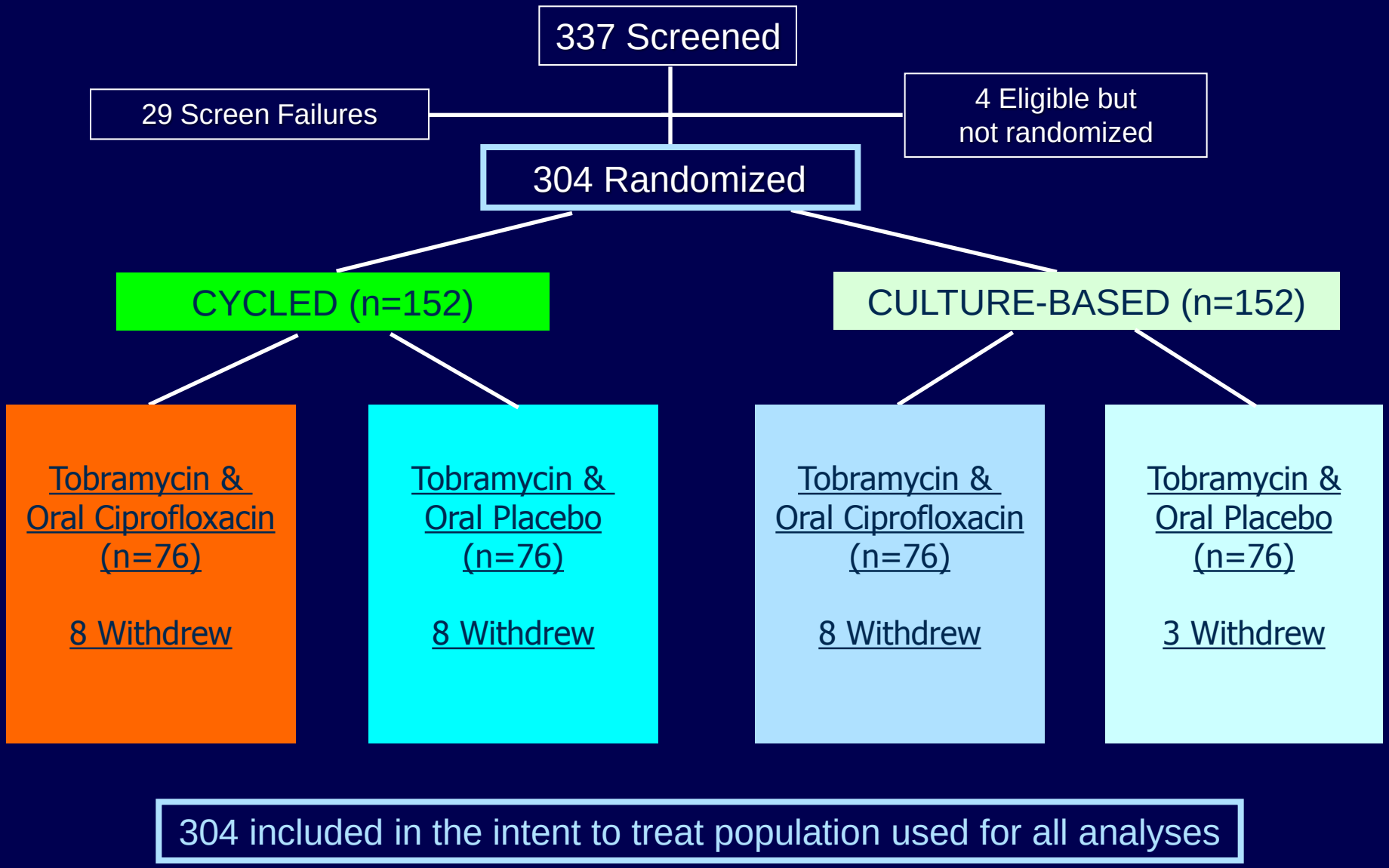
Konstan, MW et al. *AJRCCM*. 2007;176:1084
Konstan, MW et al. *NEJM*, 1995; 332:848
Lands, LC et al. *J. Peds*. 2007;151:249

Practical Clinical Trials (PCTs)

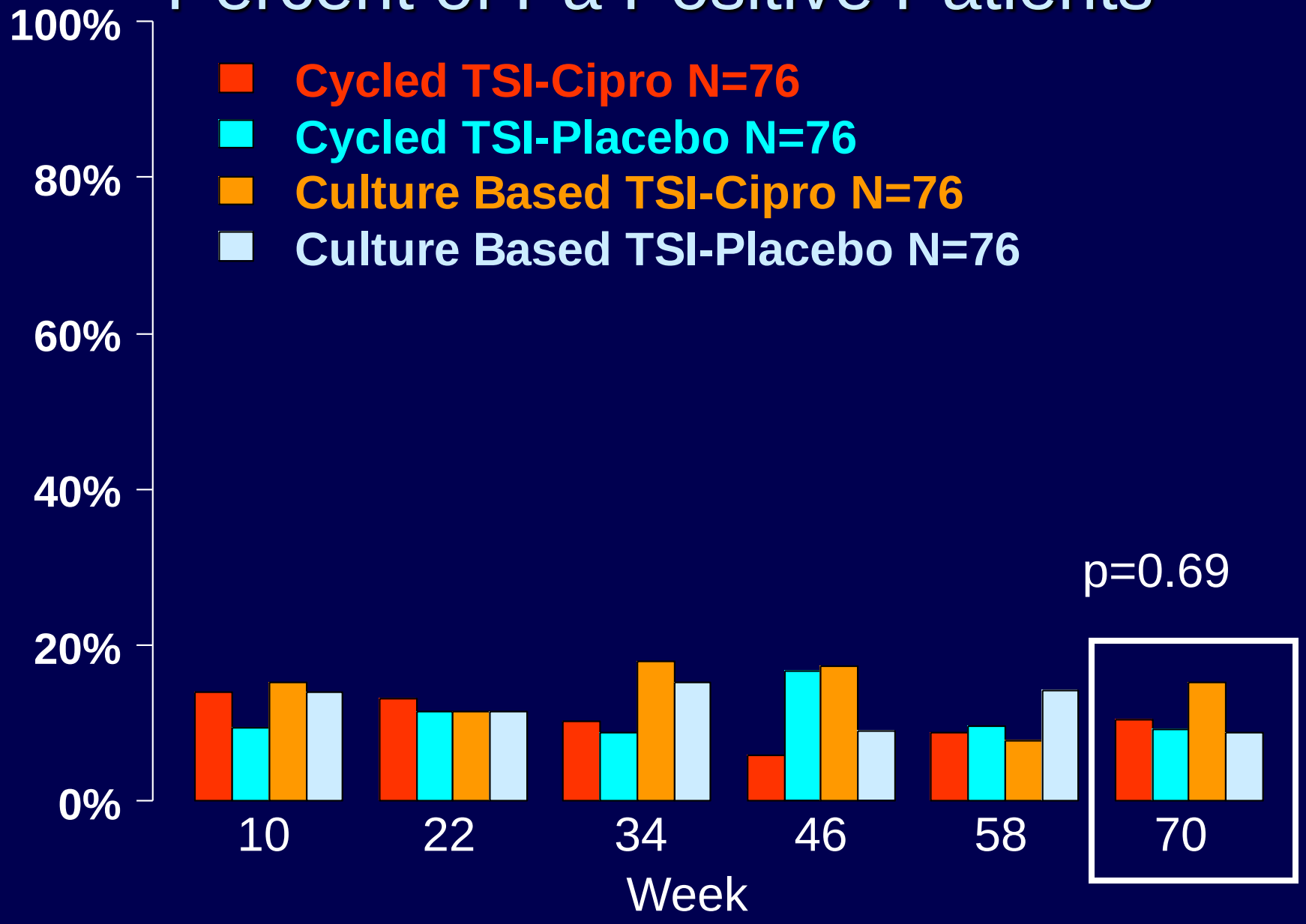
- Distinct from classic randomized clinical trials which explain the “how” and “why” a treatment works:
  - Highly defined population to maximize effect
  - Well defined primary efficacy outcome
  - Required for development of new therapies
- PCT are designed to assist decision makers on optimal clinical approaches
  - Based on diverse “real world” populations
  - Most helpful for comparing approved therapies
- Outcomes are much broader with longer follow-up
  - Quality of life
  - Patient /family satisfaction
  - Cost analysis

An Example of CF PCT

Early Pseudomonas Infection Control Clinical Trial



EPIC Results:
Percent of Pa Positive Patients



Staphylococus Aureus Resistance – Treat or Observe (Star-Too)
Sponsor: CFFT

- Primary objectives:
  - Evaluate the microbiologic effect and safety of a 2 week MRSA eradication protocol
- Selection criteria:
  - 90 individuals with CF, 4 to 45 years of age, with recent MRSA respiratory tract infection
  - Patients randomized to either treatment or observation
- Treatment arms:
  - Oral antibiotics for 14 days
    - Trimethoprim sulfa (Bactrim®)
    - Rifampin
  - Topical antibiotics daily for 5 days
  - Environmental decontamination for 21 days
- Observation arm:
  - Only receive treatment if symptomatic
- Follow-up: 6 months
- Outcome measures:
  - Frequency of eradication of MRSA from oropharyngeal cultures
  - Frequency of pulmonary exacerbations
  - Safety and adherence to protocol

Future CER Studies in CF

- Careful retrospective and prospective cohort studies will be an integral component of CER in CF
  - Limitations of cohort data need to be addressed with new methodologies
- CF is ideally positioned to implement expanded CER research because of the CFF Patient Registry and other ongoing prospective cohorts (EPIC Observational Study)
- Immediate opportunities
  - Newborn screening
  - Impact of quality improvement projects
  - Comparison of newly approved therapies such as inhaled antibiotics

Where Will the CF Community Be in 2015? (1)

- At least one FDA approved therapy targeting the underlying defect in CF is available to patients
  - Corrects CFTR function
  - Improves airway hydration and mucociliary clearance
- Key biomarkers to characterize and elucidate the primary pathophysiology of CF lung disease have been developed through natural history and animal model studies

Where Will the CF Community Be in 2015? (2)

- Through comparative trials, the international CF community better understands treatment combinations to maintain pulmonary gastrointestinal health in CF patients:
  - Antibiotic combinations
  - Treatment of exacerbations
  - Airway clearance

Active TDN Reviewed Studies - March 2011

Title	Sponsor	Study Type	Patients	Status
CFTR Modulators/Correctors				
1) VX-770-105	Vertex	Open Label Extension	110	Enrolling
2) VX-770-106	Vertex	Phase 2 FEV1 >90% LCI	24	Protocol Reviewed
3) VX-809-102	Vertex	Phase 2 Combination w/ VX-770	160	Enrolling
4) PTC 124	PTC	Open Label Extension	190	Enrolling
Anti-Infectives				
1) MPEX 207 MPEX 209 (inhaled levofloxacin)	MPEX	Phase 3 Phase 3 vs. TOBI	270 330	Enrolling Protocol Reviewed
2) CIPRO DPI (inhaled ciprofloxacin)	Bayer	Phase 2b	180	Enrollment Complete
3) STAR-TOO (Early MRSA treatment)	CFFT	Phase 2	90	Protocol Reviewed
4) Arikace (108/109) (inhaled liposomal Amikacin) Arikace (110)	Insmed	Phase 3	300 500	Protocols Reviewed
Anti-Inflammatory				
1) Spiriva (B1.205.438)	Boeringer-Ingellheim	Phase 3	360	Enrolling
2) Pharma NAC	CFFT	Phase 2	70	Enrollment Complete
3) GSK-SB-656-933	GlaxoSmithKline	Phase 2	112	Enrollment Complete
Restore Airway Surface Liquid				
1) Hypertonic Saline in Infants	CFFT/NIH	Phase 2	321	Enrollment Complete
2) Mannitol DPI	Pharmaxis	Phase 3	300	Enrollment Complete

Thank You

Special thanks to:
Bob Beall
Preston Campbell
Chris Goss
Nicole Hamblett
Pamela Hoang
Marie Linavat
Bruce Marshall
Diana Oliden
Margaret Rosenfeld
Steve Rowe
Jill Van Dalfsen
Lisya Van Housen

Cystic Fibrosis Foundation

cystic fibrosis foundation THERAPEUTICS inc.

UW Medicine SCHOOL OF MEDICINE

Seattle Children's HOSPITAL · RESEARCH · FOUNDATION