

Cystic Fibrosis Drug Discovery and Development: More Than Venture Philanthropy

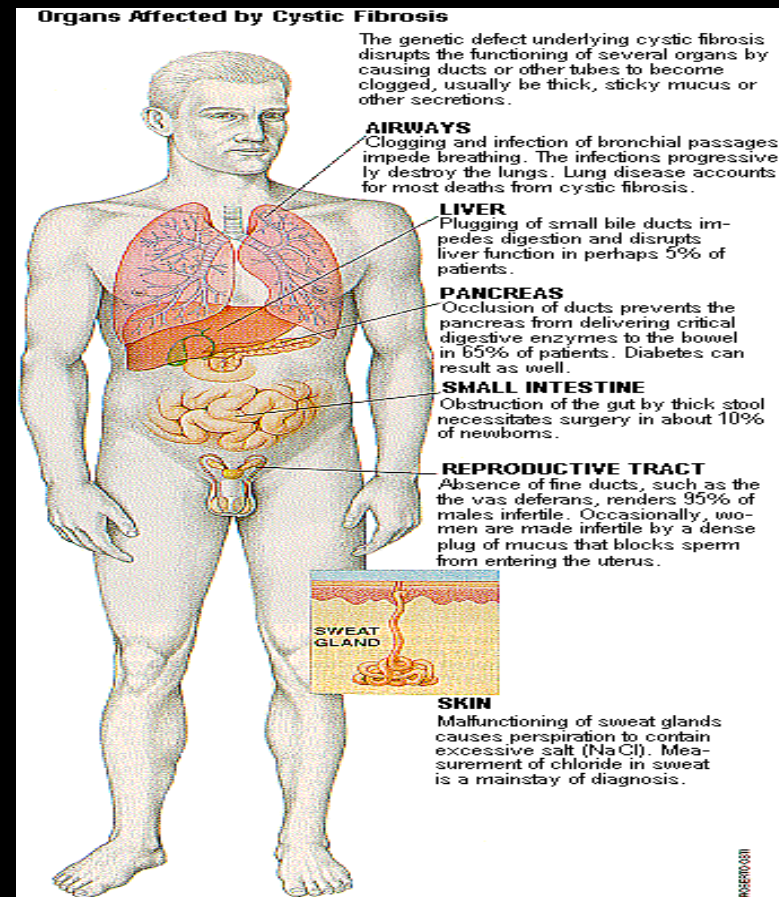
Christopher Penland, Ph.D.
Vice President of BioPharma Programs
Cystic Fibrosis Foundation

The Legal Stuff First

To advance drug development and a search for a cure, Cystic Fibrosis Foundation Therapeutics has contractual agreements with several companies to receive royalties related to drugs that are developed as a result of CFFT funding. Any royalties we receive are used in support of our mission.

Cystic Fibrosis Organ Involvement

- Recessive genetic disease
- Multiorgan involvement (sinus, lungs, pancreas, liver, intestinal tract, skin, reproductive tract, skeletal system)
- Morbidity and mortality today primarily linked to progressive loss of lung function

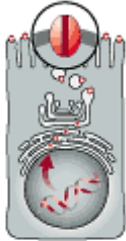


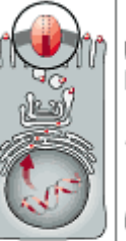
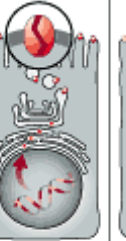



Welsh, MJ and AE Smith. *Scientific American*. 1995

CFTR Gene, Protein and Mutations

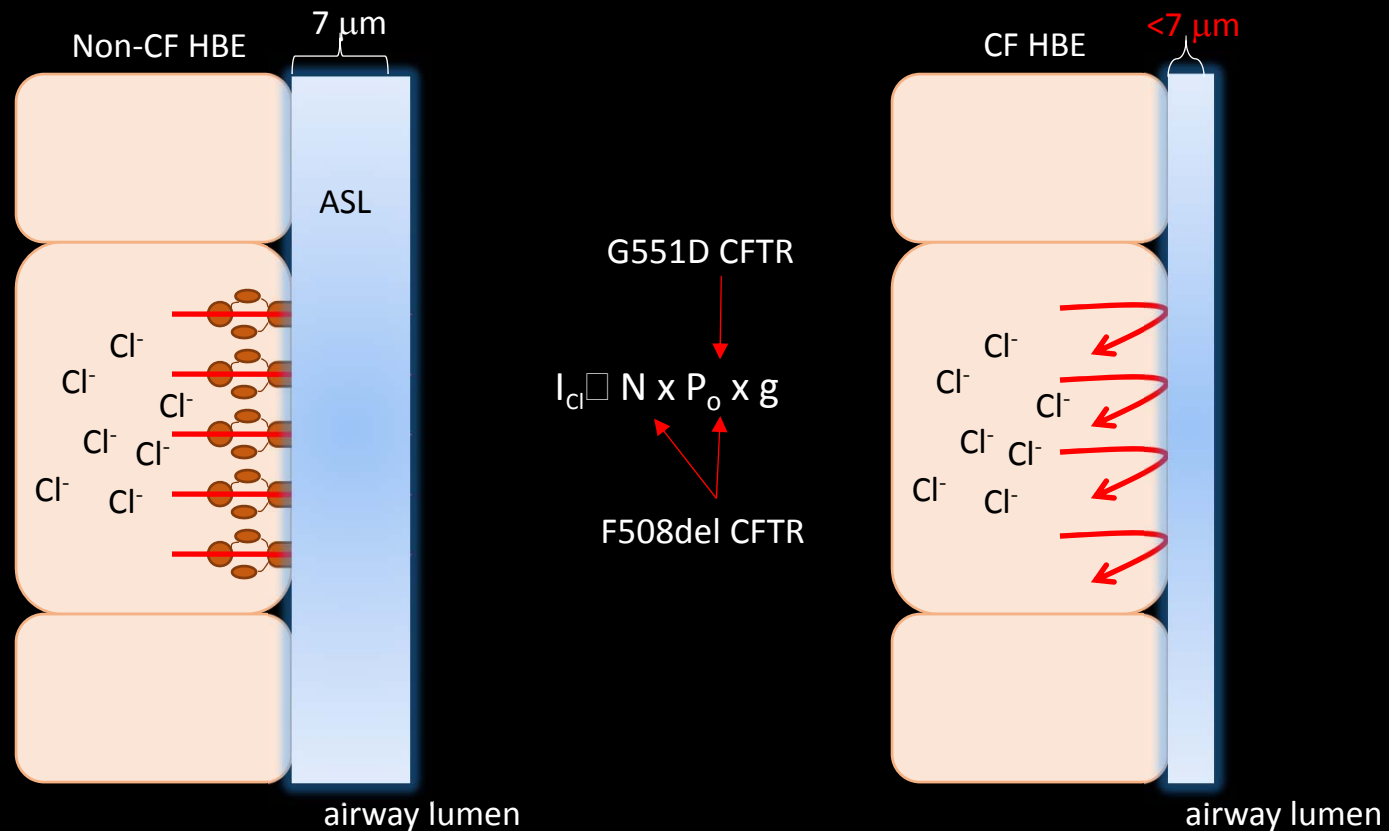
- hCFTR encodes a 1480 aa ATP binding cassette transporter (2 transmembrane domains, 2 nucleotide binding domains) that differs from other members of the ABC family by the presence of a cytosolic regulatory domain.
- CFTR is a ATP, PKA-activated anion channel. Permeability $I^- > Cl^- >> HCO_3^-$.
- >1000 described mutations in hCFTR gene.
- Most prevalent mutation worldwide is loss of phenyalanine at position 508 (F508del CFTR).
- Genotype-phenotype relationship variable among target tissues (vas deferens > pancreas >> lung) suggesting likelihood of environmental and genetic modifiers.

CFTR “Broad” Mutation Classification

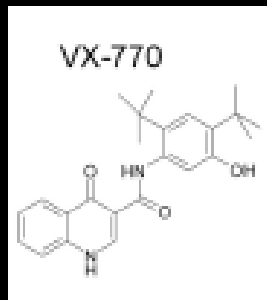
Defect Classification	Normal	I	II	III	IV	V
						
Defect Result		No synthesis	Block in Processing	Block in Regulation	Altered Conductance	Reduced Synthesis
Types of Mutation		Nonsense; Frameshift	Missense; Amino Acid Deletion ($\Delta F508$)	Missense; Amino Acid Change (G551D)	Missense; Amino Acid Change (R117H) (R347P)	Missense; Amino Acid Change (A445E) Alternative Splicing

* Some mutations exert multiple negative effects (e.g., F508del – processing and regulation)

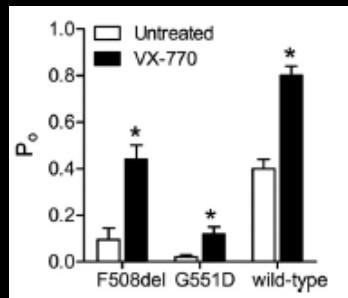
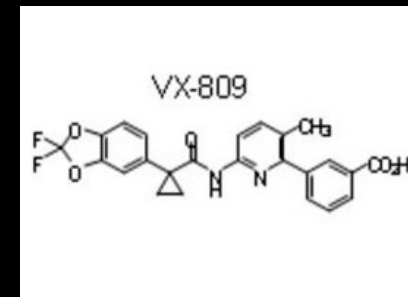
Electrophysiological Impact of Mutations on CFTR Protein Function



Discovery and Development of CFTR Modulators

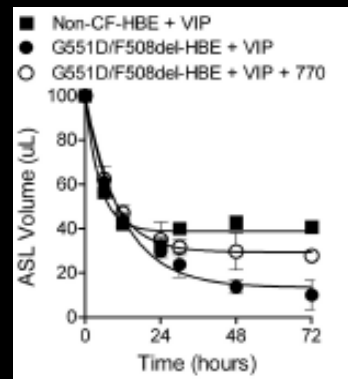
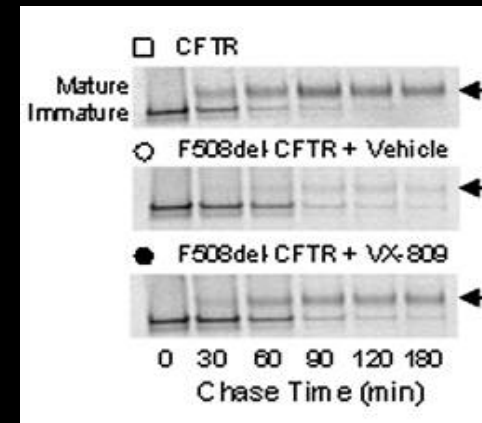


VX-770 and VX-809 structures



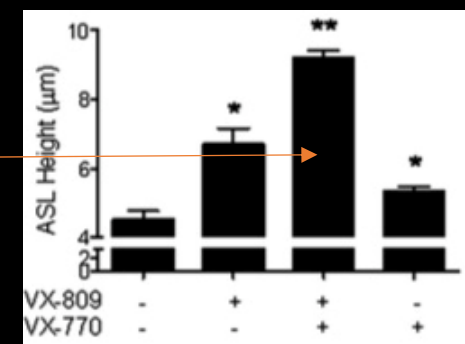
VX-770 augments (G551D, F508del and wt) membrane resident CFTR open channel probability.

VX-809 rescues membrane trafficking of F508del CFTR



Restoration of channel function is reflected in tissue level function.

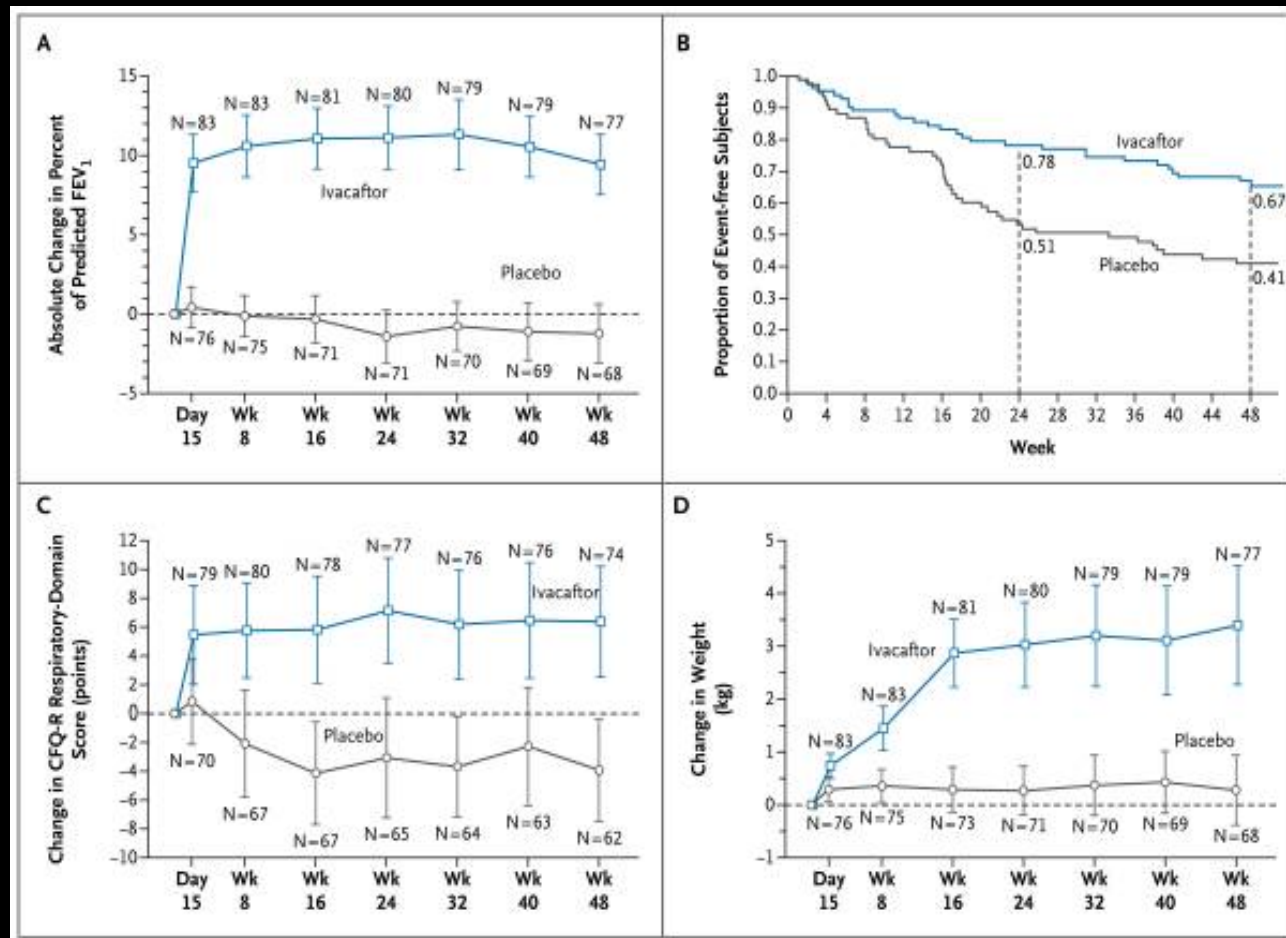
VX-809 effect magnified by VX-770 co-administration.



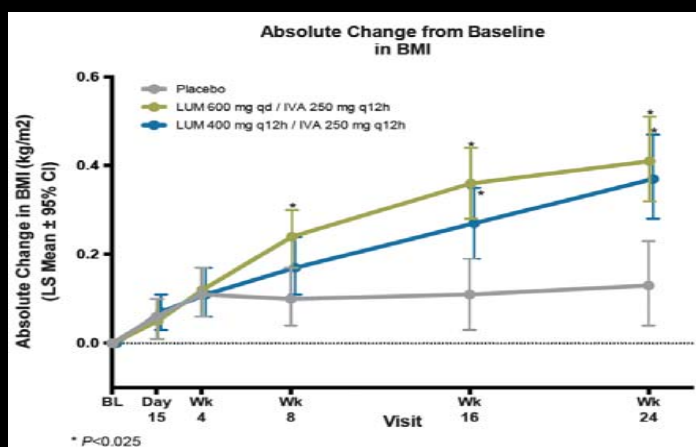
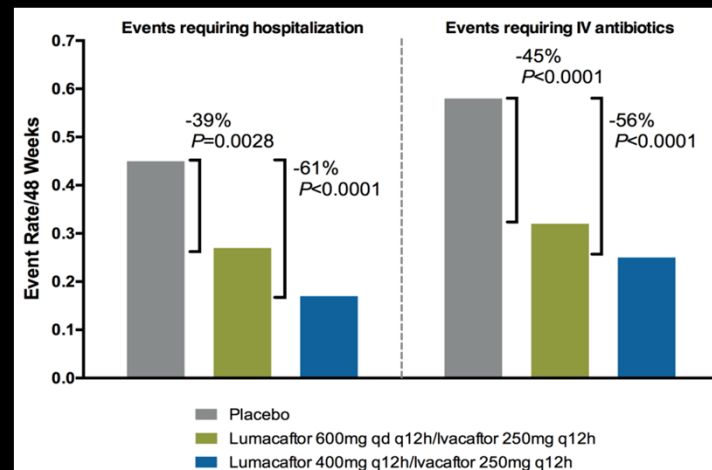
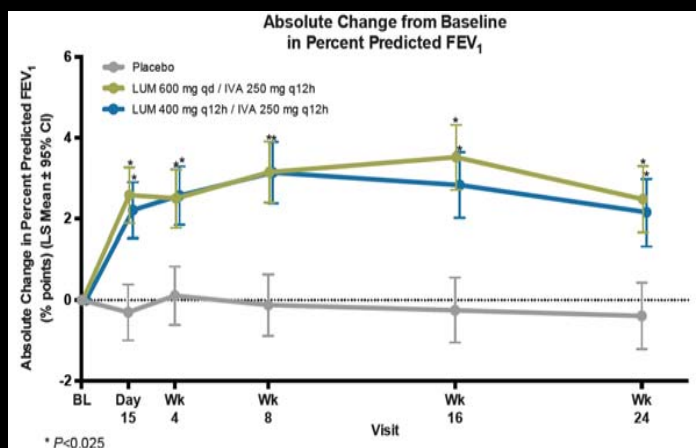
Van Goor F *et al.* PNAS. 2009.
Van Goor F *et al.* PNAS. 2011.

September 27, 2016

Phase 3 Clinical Trial Results of Ivacaftor (VX-770)



Phase 3 Clinical Trial Results of Lumacaftor + Ivacaftor (VX-809 + VX-770)



1. Significant increases in FEV₁ and BMI
2. Decreases in hospitalizations and need for IV antibiotics

Figures courtesy of Michael Boyle, MD

How to derisk pharmaceutical company involvement in an orphan disease?

Basic Tenets of Venture Philanthropy¹:

- Tailored financing
- Multi-year support
- Performance measurement
- Engagement
- *Organizational capacity building*

Additional measures we've chosen to take:

- Non-monetary assistance
- Clinical Trial Infrastructure
- Patient Education

$$\text{Impact} = \text{Innovation} + \text{Scale}^2$$


¹<https://webgate.ec.europa.eu/socialinnovationeurope/en/magazine/finance/articles-reports/venture-philanthropy-defined>

²http://ssir.org/articles/entry/when_innovation_goes_wrong


CFTR Toolbox

- CFTR functional and mechanistic assays
- Access to non-commercial resources
 - CFTR modulator panel
 - CFTR antibodies
 - CF human airway epithelia
- Independent testing
 - CFFTI lab
 - Chantest – a division of Charles River


Documenting Disease Liability of CFTR Variants




Clinical and Functional Translation of CFTR



ADDITION TOMORROWS



JOHNS HOPKINS MEDICINE



Welcome to the CFTR2 website


Our Purpose:

CFTR2 is a website that provides information for patients, researchers, and the general public about specific mutations in what is commonly referred to as the cystic fibrosis (CF) gene.


For each mutation or mutation combination included in the database, the website will provide information about:

1. Whether the mutation or mutation combination is CF-causing, and
2. Information about sweat chloride, lung function, pancreatic status, and Pseudomonas infection rate in patients in the CFTR2 database with this mutation or mutation combination.

Information on the CFTR2 website is being updated as further analysis is completed. The most up-to-date clinical information and results of functional testing are available on individual mutation pages. For a complete list of CFTR2 mutations and their characterizations, please visit CFTR2 Mutation List History.

 this site is intended to do:

- This website provides information for members of the general public, including cystic fibrosis patients and their family members, about what is currently known about specific genetic mutations related to cystic fibrosis.
- Patients and their family members are encouraged to visit the section, "For patients and family members" first.
- This website also provides more in-depth research-related information for health care professionals and researchers.

 this site is NOT intended to do:

This website is not intended to help diagnose anyone with CF.

- The information about groups of patients contained on this website should not be used to predict the clinical course of individual patients.
- This website is not intended to provide medical advice to individual patients.
- This website is not intended to provide information about pancreatitis, diabetes mellitus, or other diseases associated with CF.

For more information about CF, [click here](#).

Note: If you have questions about any of the information contained in this website, please consult your doctor.

Cystic Fibrosis Foundation's Therapeutics Development Network

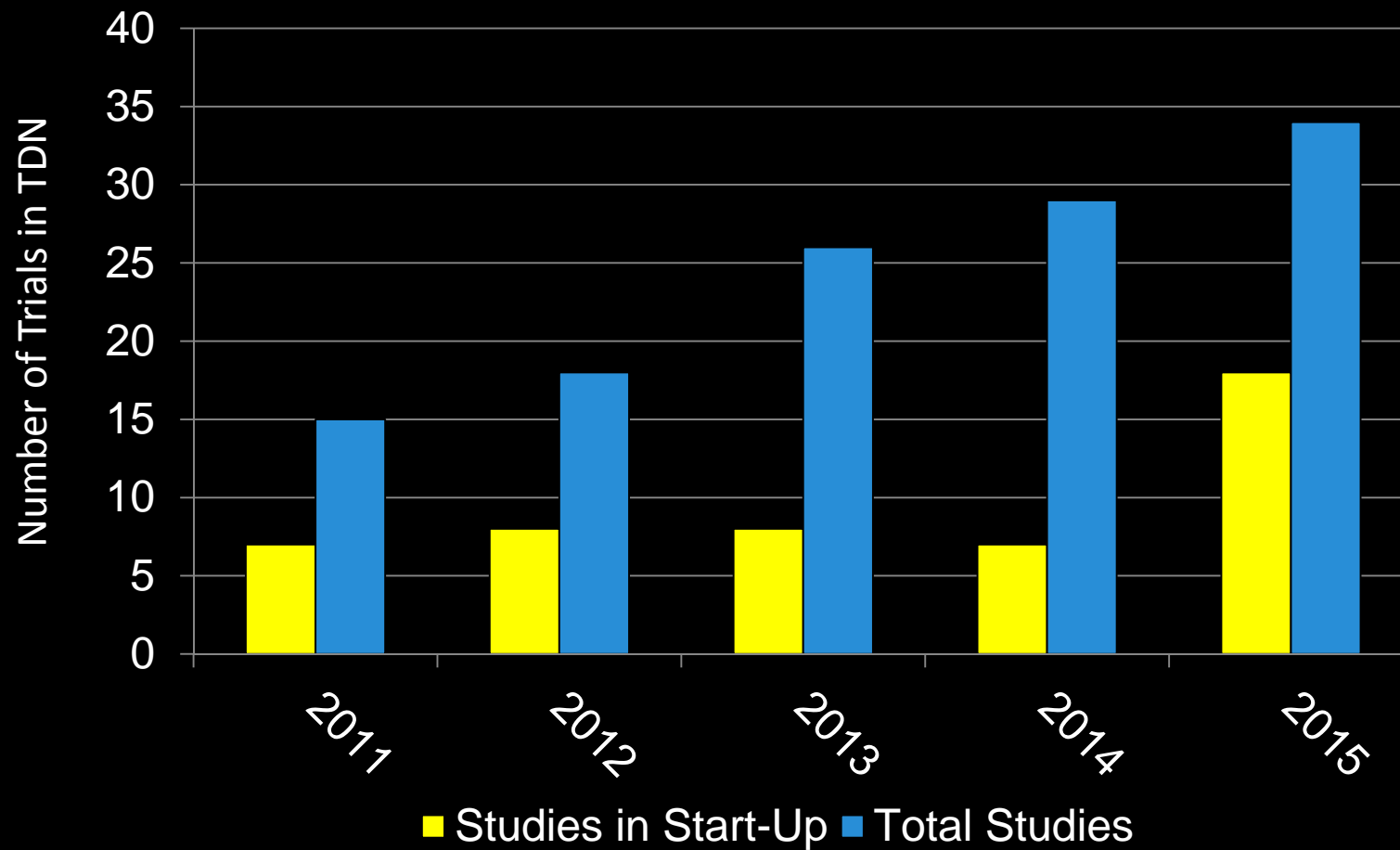
- \$12.8 M in FY2015
- 82 Research Sites
- 150 Investigators
- 330+ Research Coordinators
- Independent DSMB

TDN Leadership Team

- | | |
|----------------------------|--------------------|
| • Mike Boyle, MD | • Nicole Hamblett |
| • George Retsch-Bogart, MD | • Joe Pilewski, MD |
| • Chris Goss, MD | • JP Clancy, MD |
| | • Jill Van Dalfsen |



Expanding Clinical Trial Numbers



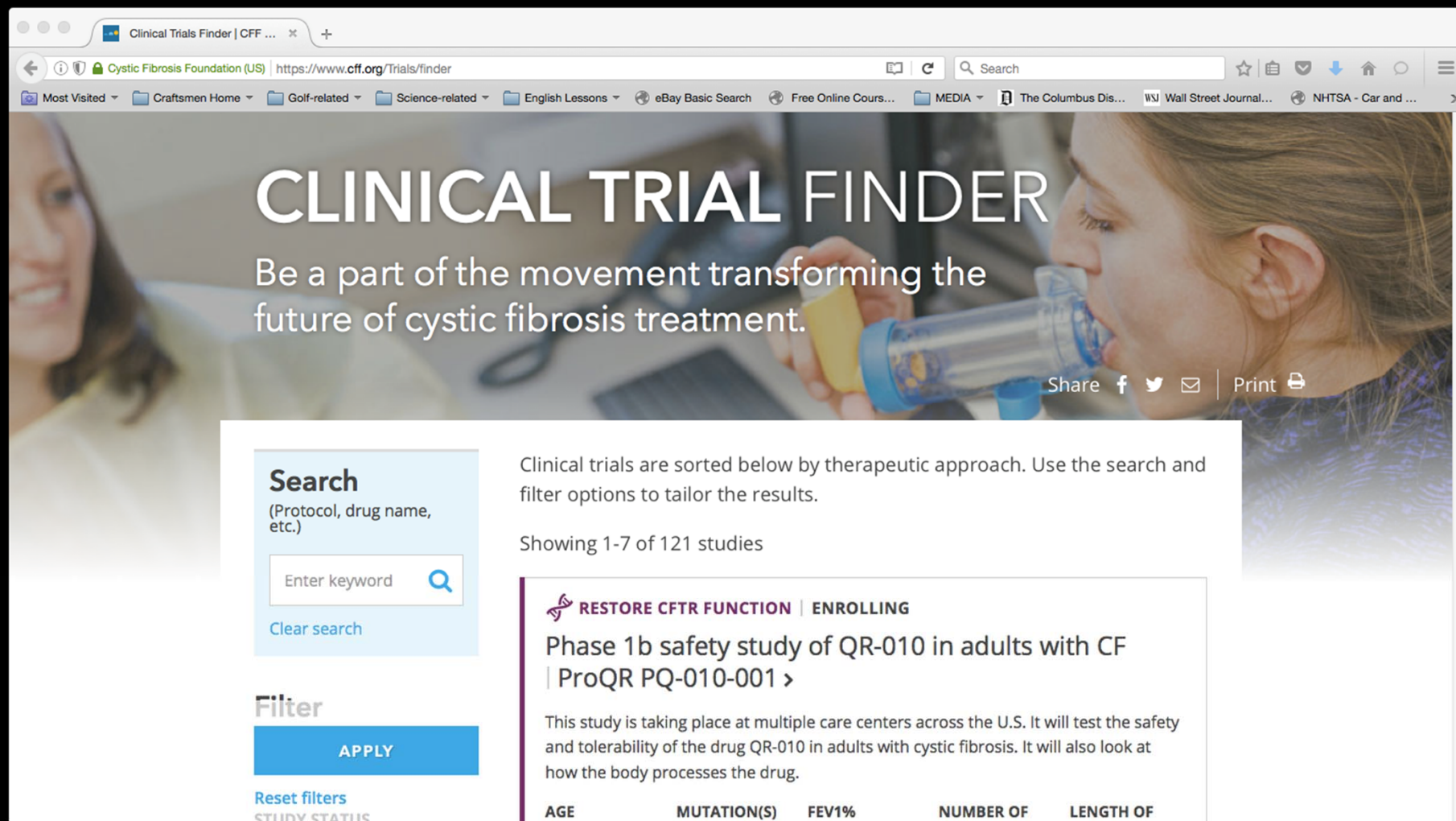
Clinical Trial Participation Requirements

Intentionally Left Blank

Percentage of Center Population Newly Enrolled in Interventional Studies By Trial Site (mid-2016)





Intentionally Left Blank

Clinical Trial Participation: Education and Facilitation




CLINICAL TRIAL FINDER

Be a part of the movement transforming the future of cystic fibrosis treatment.

Share    | Print 

Search
(Protocol, drug name, etc.)

Enter keyword 

Clear search

Filter


APPLY

Reset filters

STUDY STATUS

Clinical trials are sorted below by therapeutic approach. Use the search and filter options to tailor the results.

Showing 1-7 of 121 studies

 **RESTORE CFTR FUNCTION | ENROLLING**

Phase 1b safety study of QR-010 in adults with CF
| ProQR PQ-010-001 >

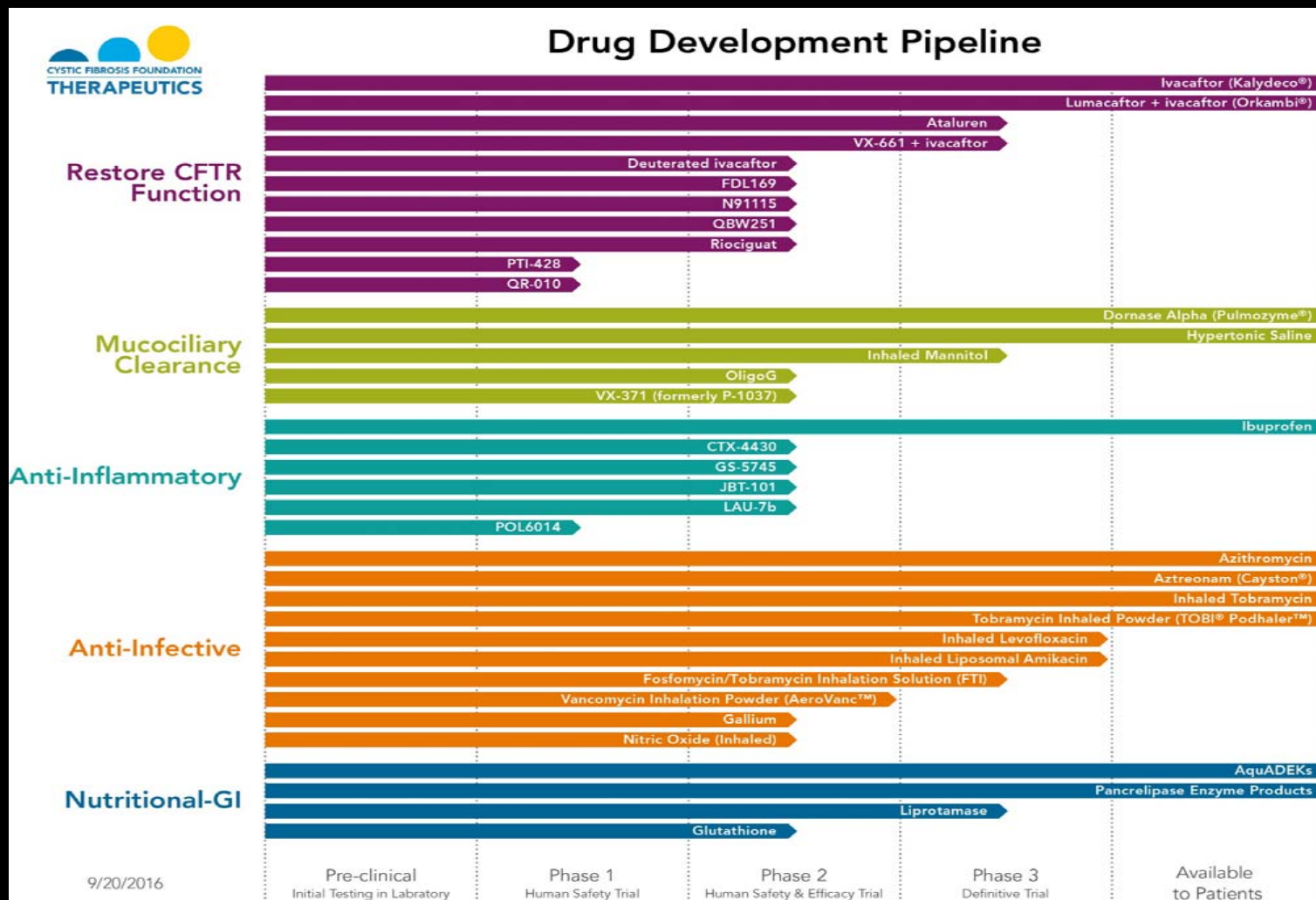
This study is taking place at multiple care centers across the U.S. It will test the safety and tolerability of the drug QR-010 in adults with cystic fibrosis. It will also look at how the body processes the drug.

AGE	MUTATION(S)	FEV1%	NUMBER OF	LENGTH OF
-----	-------------	-------	-----------	-----------

<https://www.cff.org/Trials/finder>

September 27, 2016

17



<https://www.cff.org/Trials/pipeline>

September 27, 2016

18

Thank You