Cystic Fibrosis Drug Discovery and Development: More Than Venture Philanthropy

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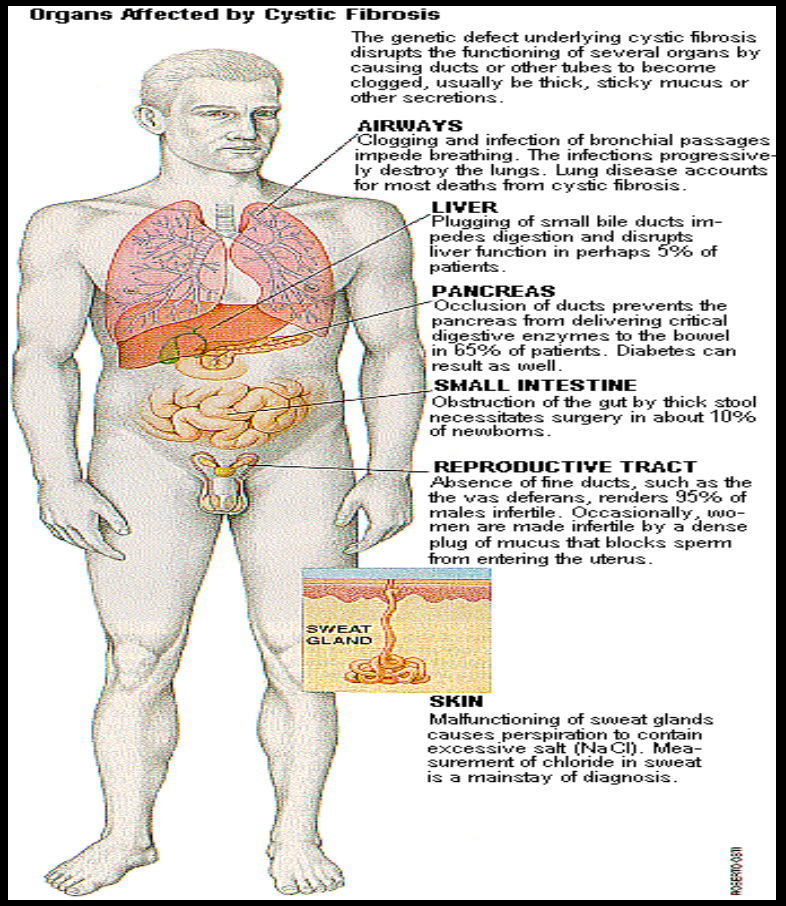
The Legal Stuff First

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

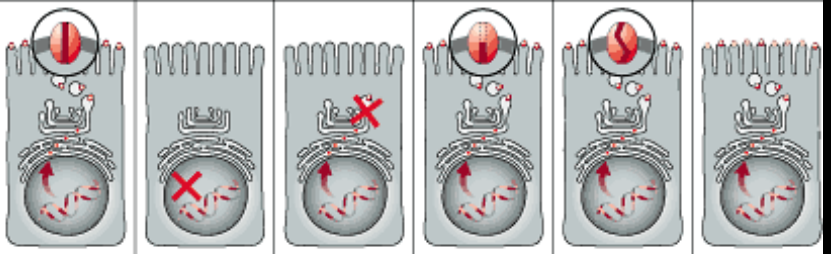


Welsh, MJ and AE Smith. *Scientific American*. 1995

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.

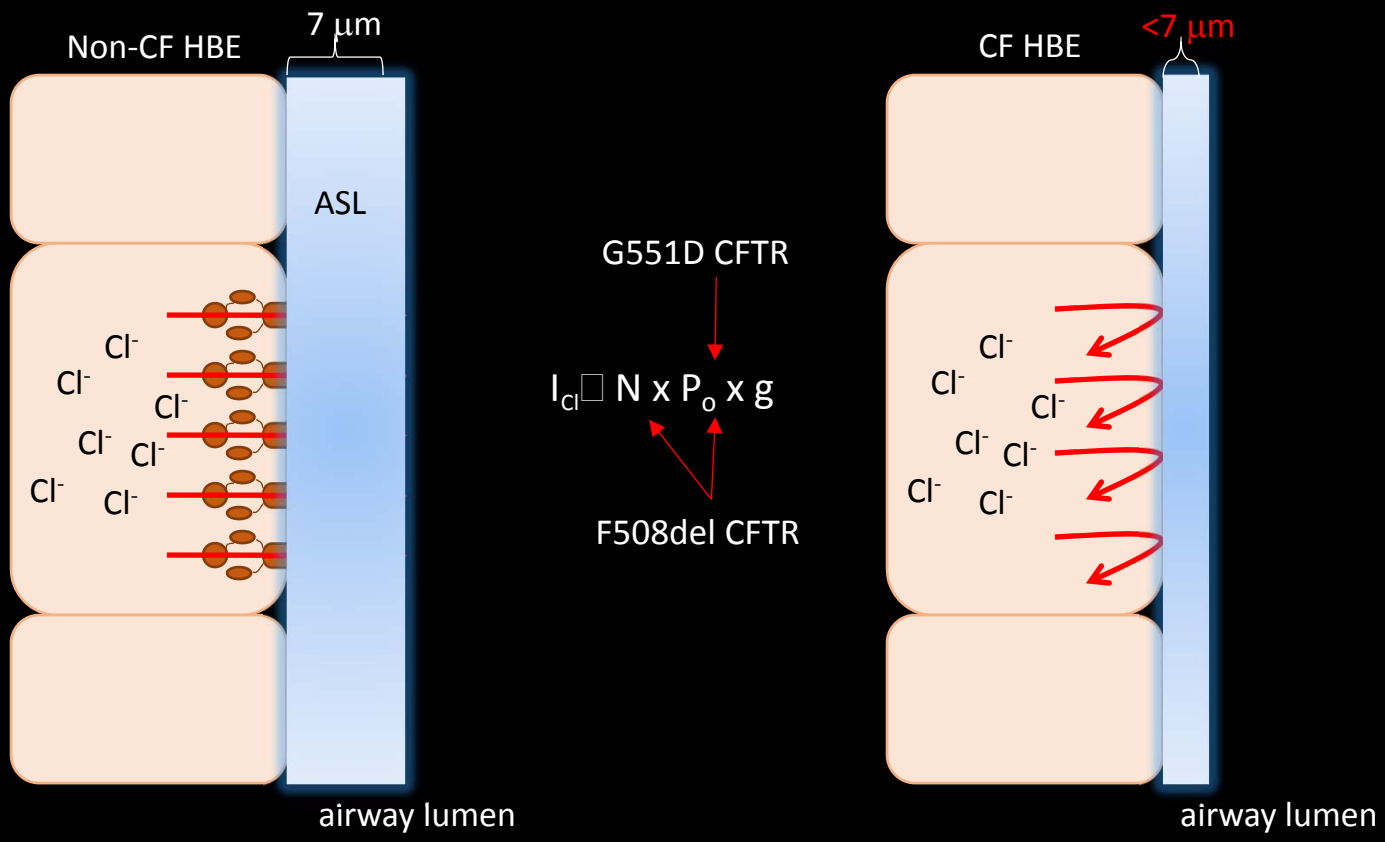
CFTR “Broad” Mutation Classification

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 (ΔF508)	Missense; Amino Acid Change (G551D)	Missense; Amino Acid Change (R117H) (R347P)	Missense; Amino Acid Change (A445E) Alternative Splicing

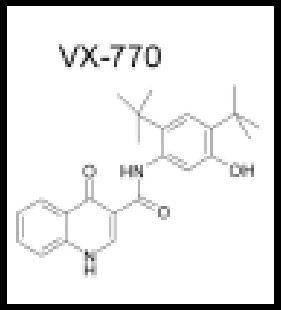
* Some mutations exert multiple negative effects (e.g., F508del – processing and regulation)

Zielenski, J & Tsui LC. *Annu Rev Genet.* 1995.

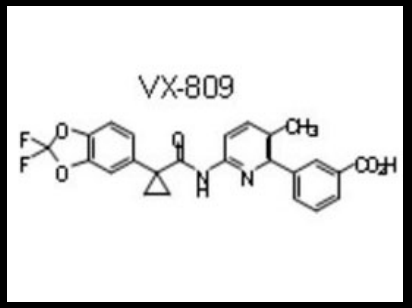
Electrophysiological Impact of Mutations on CFTR Protein Function

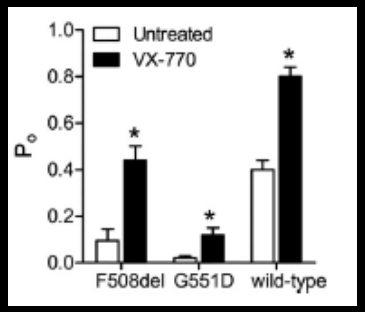


Discovery and Development of CFTR Modulators



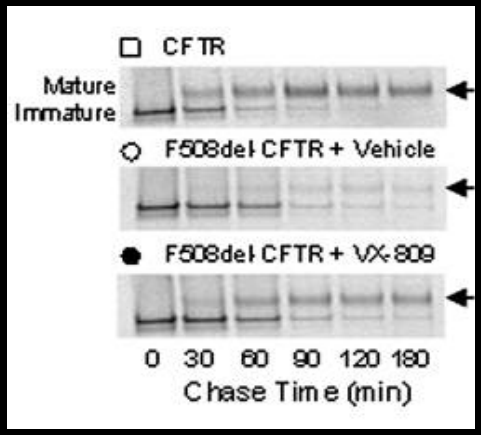
VX-770 and VX-809 structures

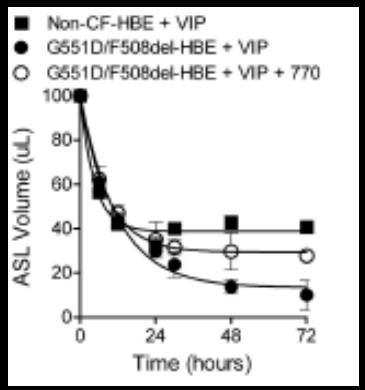




VX-770 augments (G551D, F508del and wt) membrane resident CFTR open channel probability.

VX-809 rescues membrane trafficking of F508del CFTR

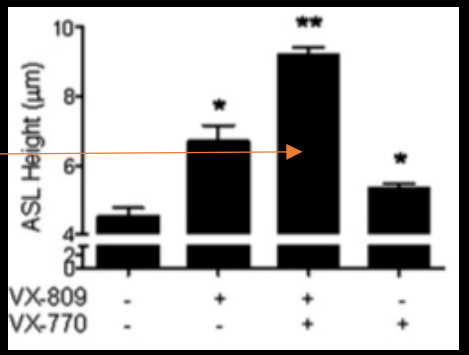




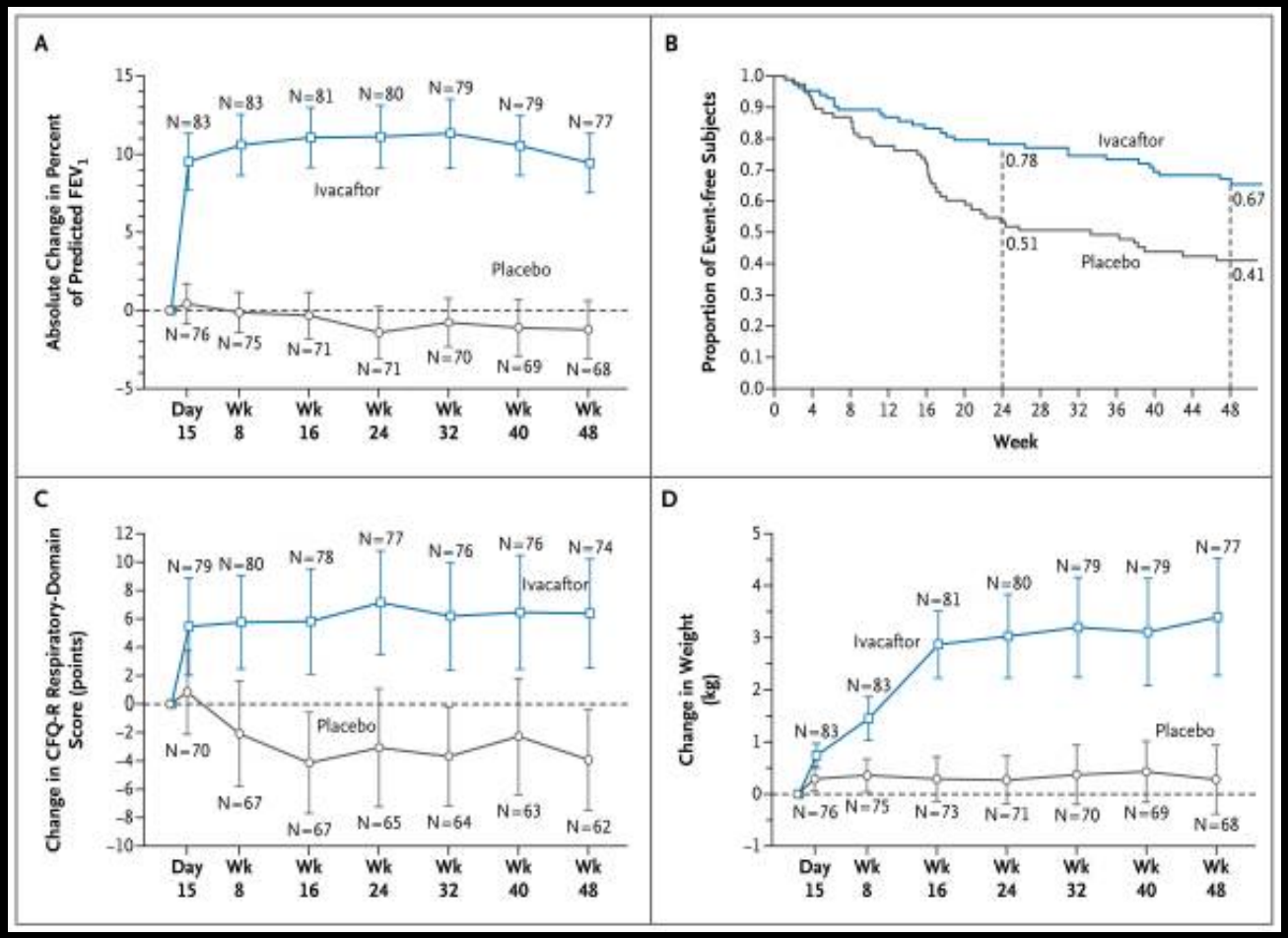
Van Goor F *et al*. *PNAS*. 2009.
Van Goor F *et al*. *PNAS*. 2011.

Restoration of channel function is reflected in tissue level function.

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

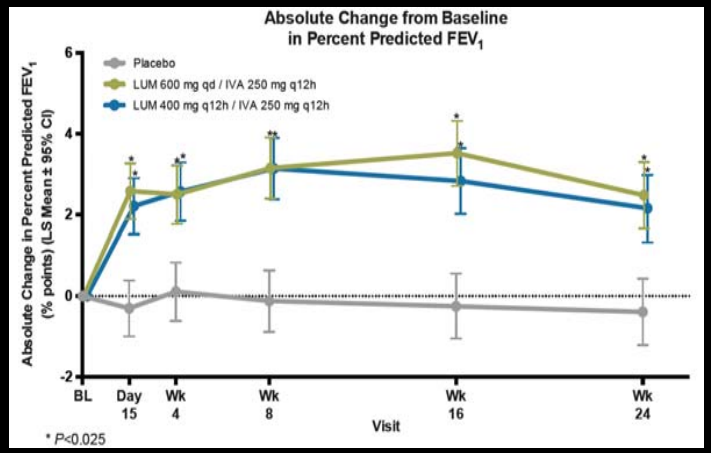


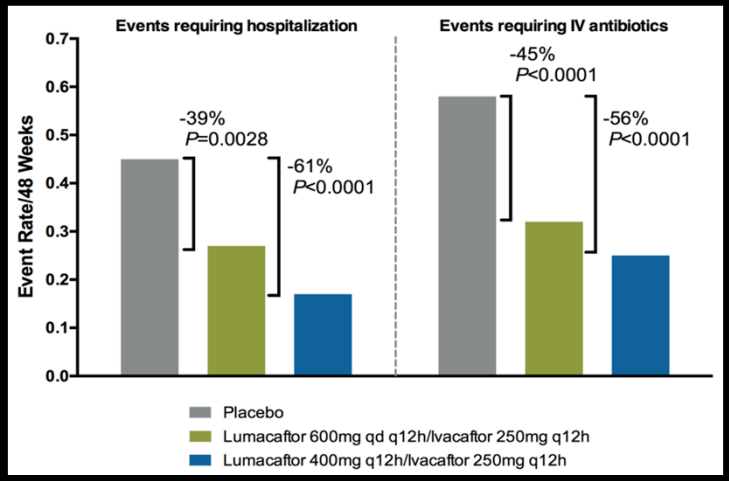
Phase 3 Clinical Trial Results of Ivacaftor (VX-770)

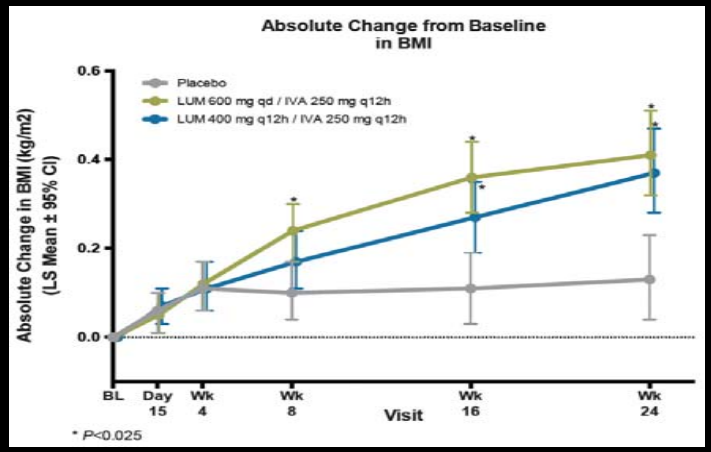


Ramsey, BW *et al*. *N Engl J Med.* 2011

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







1. Significant increases in FEV_1 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 Philanthropy[1]:

- 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

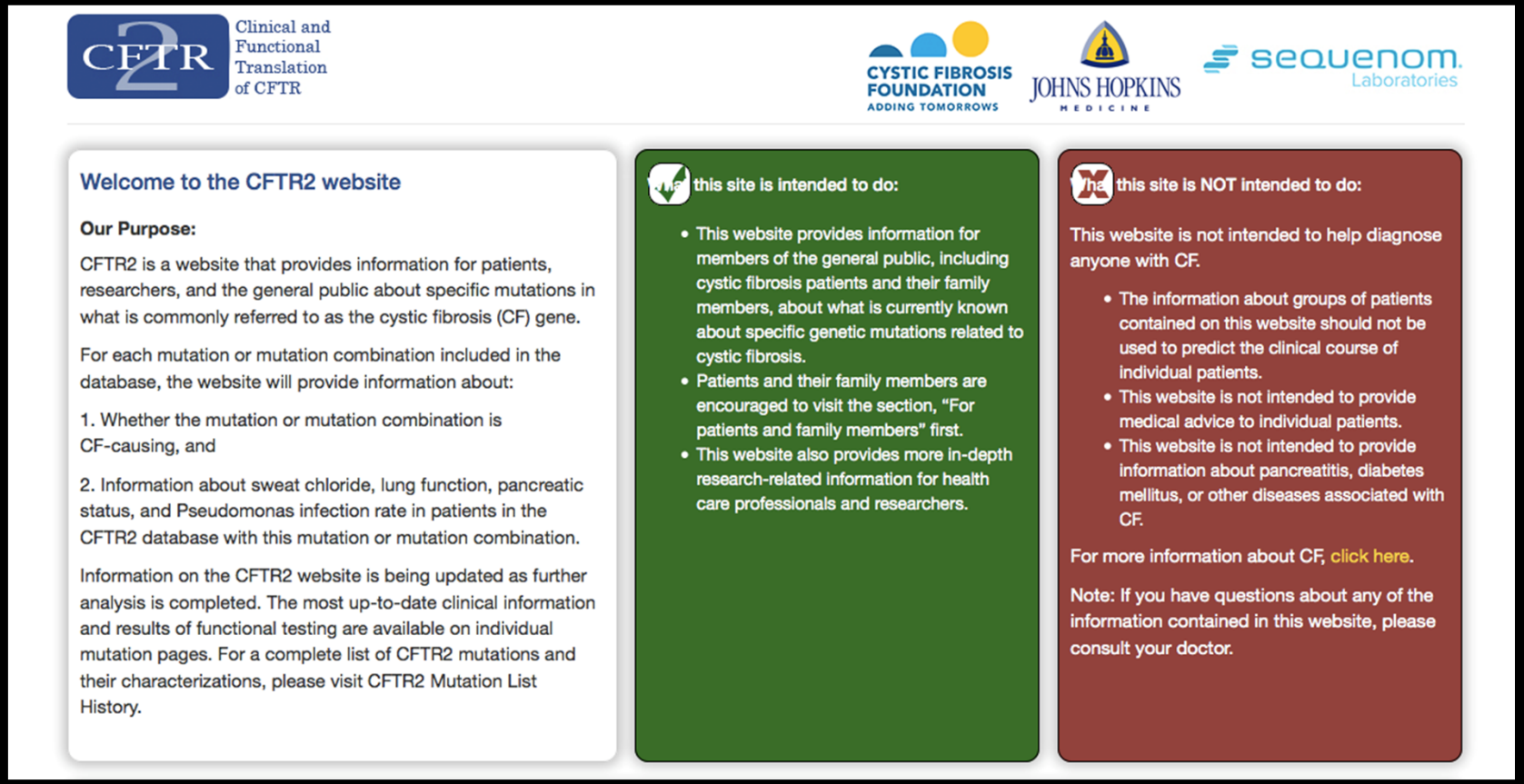
Impact = Innovation + Scale[2]

[1]https://webgate.ec.europa.eu/socialinnovationeurope/en/magazine/finance/articles-reports/venture-philanthropy-defined
[2]*http://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



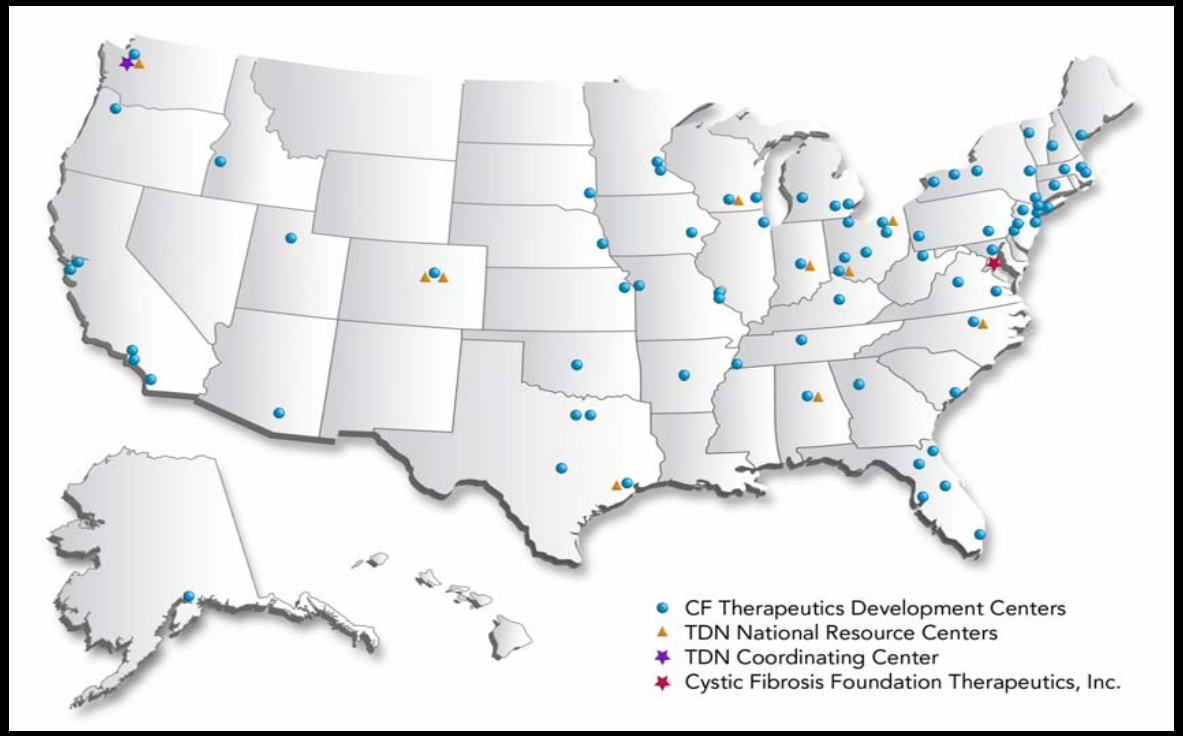
http://cftr2.org/index.php

Cystic Fibrosis Foundation's Therapeutics Development Network

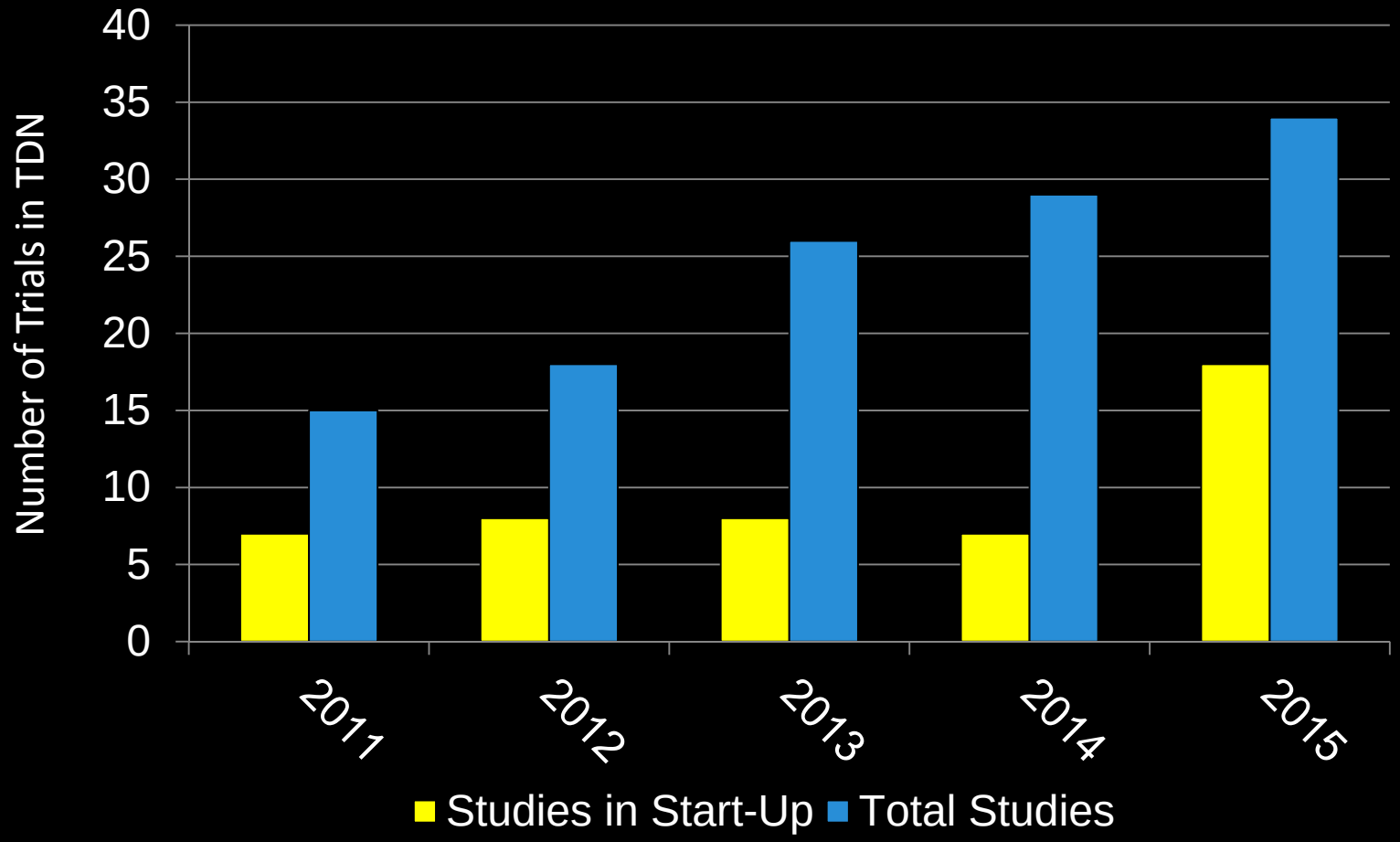
- $12.8 M in FY2015
- 82 Research Sites
- 150 Investigators
- 330+ Research Coordinators
- Independent DSMB

TDN Leadership Team

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



Expanding Clinical Trial Numbers



Clinical Trial Participation Requirements

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

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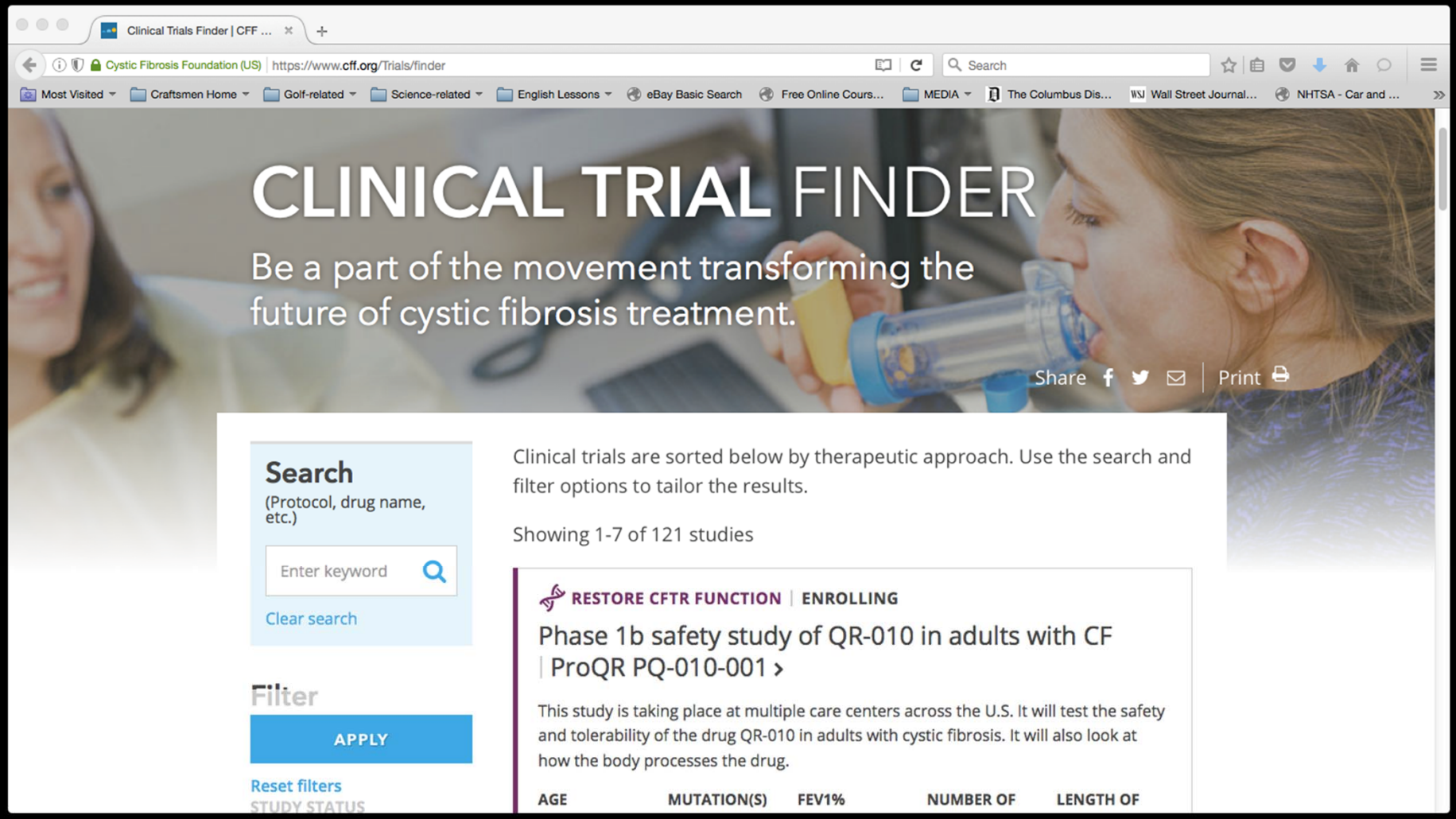
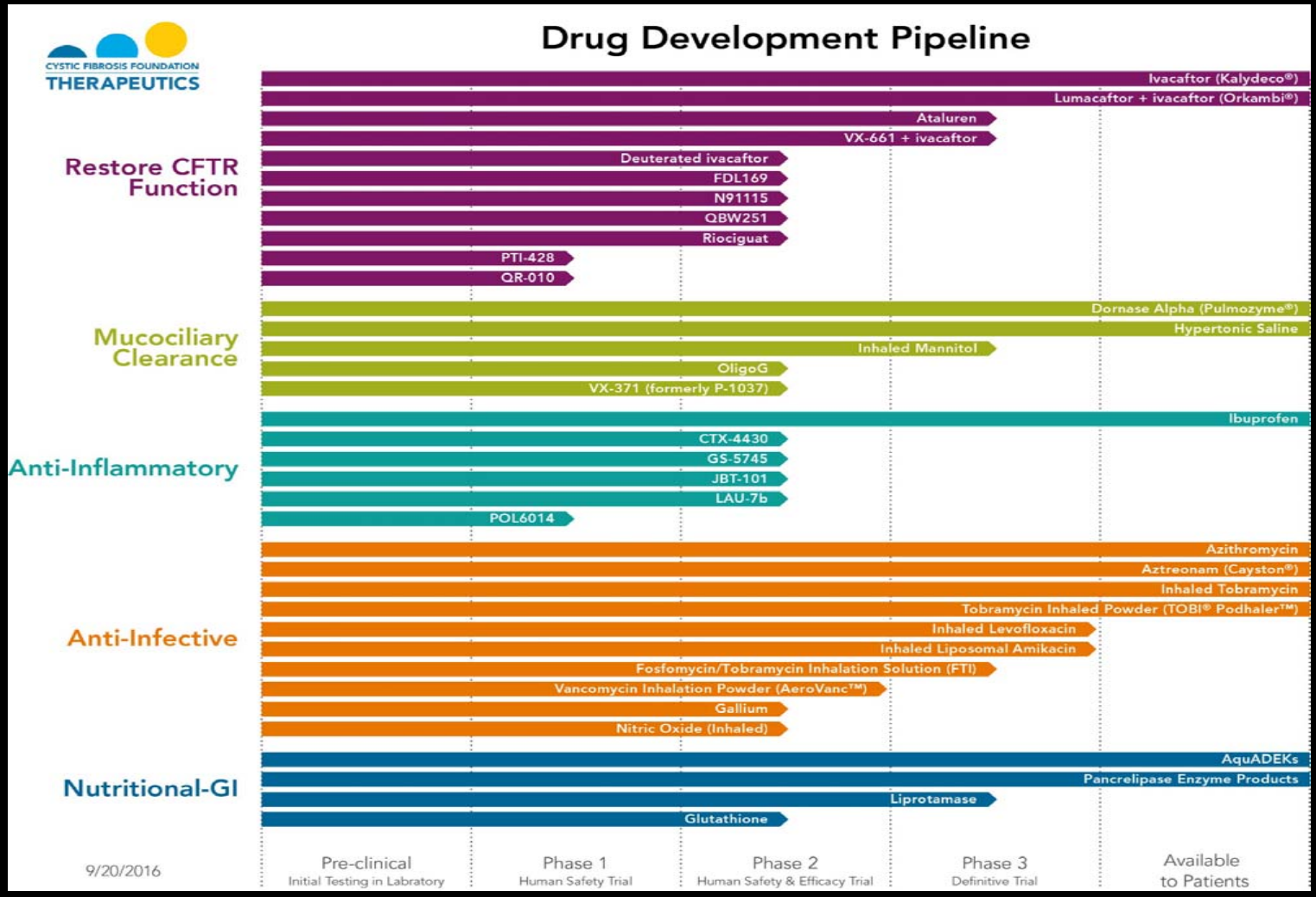
Clinical Trial Participation: Education and Facilitation



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



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

Thank You