Potentiators and Correctors for the Treatment of Rare Diseases: Therapeutic Use of Ivacaftor in Cystic Fibrosis

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Disclosures

Clinical trial contracts

- Vertex
- Novalis
- Bayer
- Parion
- Gilead
- CFFT

Consulting

- Vertex
- Spyryx
- Novalis
- AIT
- Insmed
- ProQR
- Abbvie

Educational presentations

- Vertex
- Genentech
- Nivalis
- Medscape

Grant funding, grant reviews

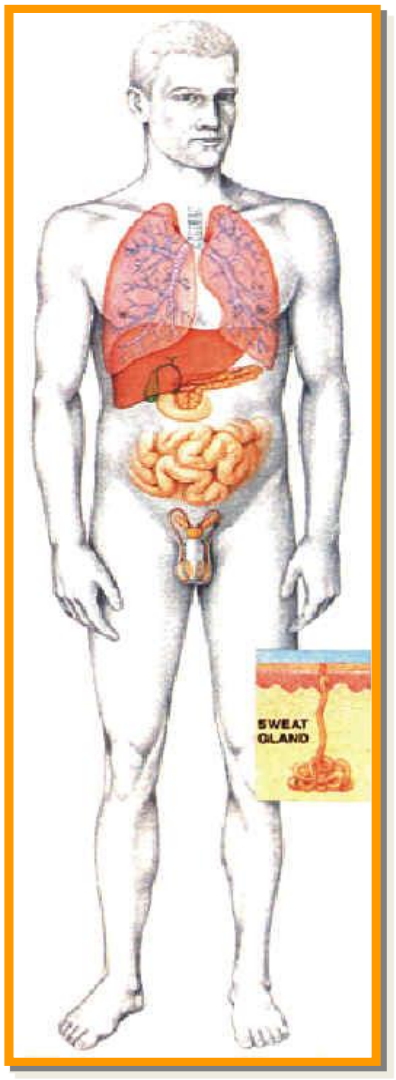
- NIH
- CFFT, US CFF, Canadian CFF
- Gilead

No off label medication use discussed

Cystic Fibrosis

- CFTR = cystic fibrosis transmembrane conductance regulator

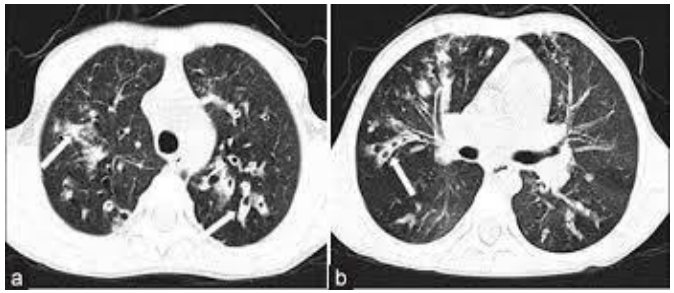
- CFTR doesn't work → cystic fibrosis
  - Genetic, 1:3,000 births
  - Autosomal recessive
  - Lungs, GI tract, pancreas, liver, vas deferens, sweat gland
  - 2,000+ mutations
  - Median predicted survival = 41 yrs



CFTR to CF – numerous targets

Loss of CFTR

Cl- HCO3- Na+

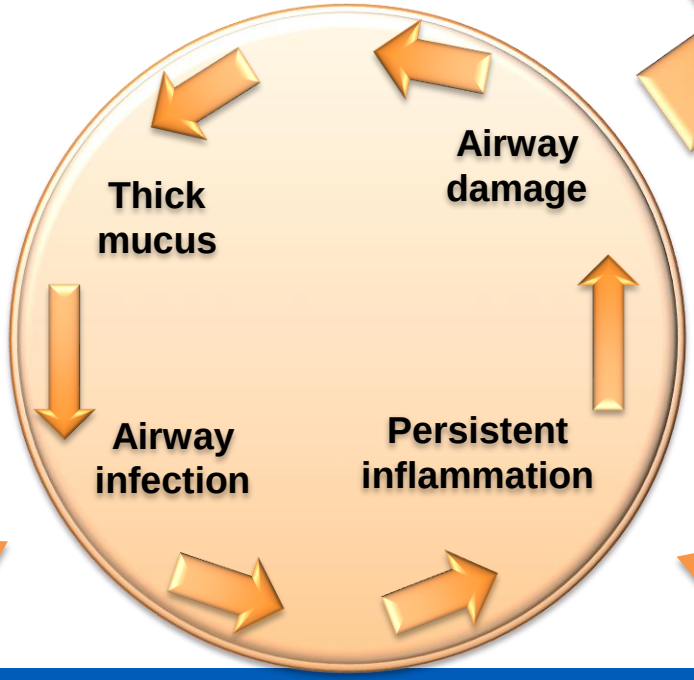


CFTR modulators
Gene transfer
Gene/RNA editing

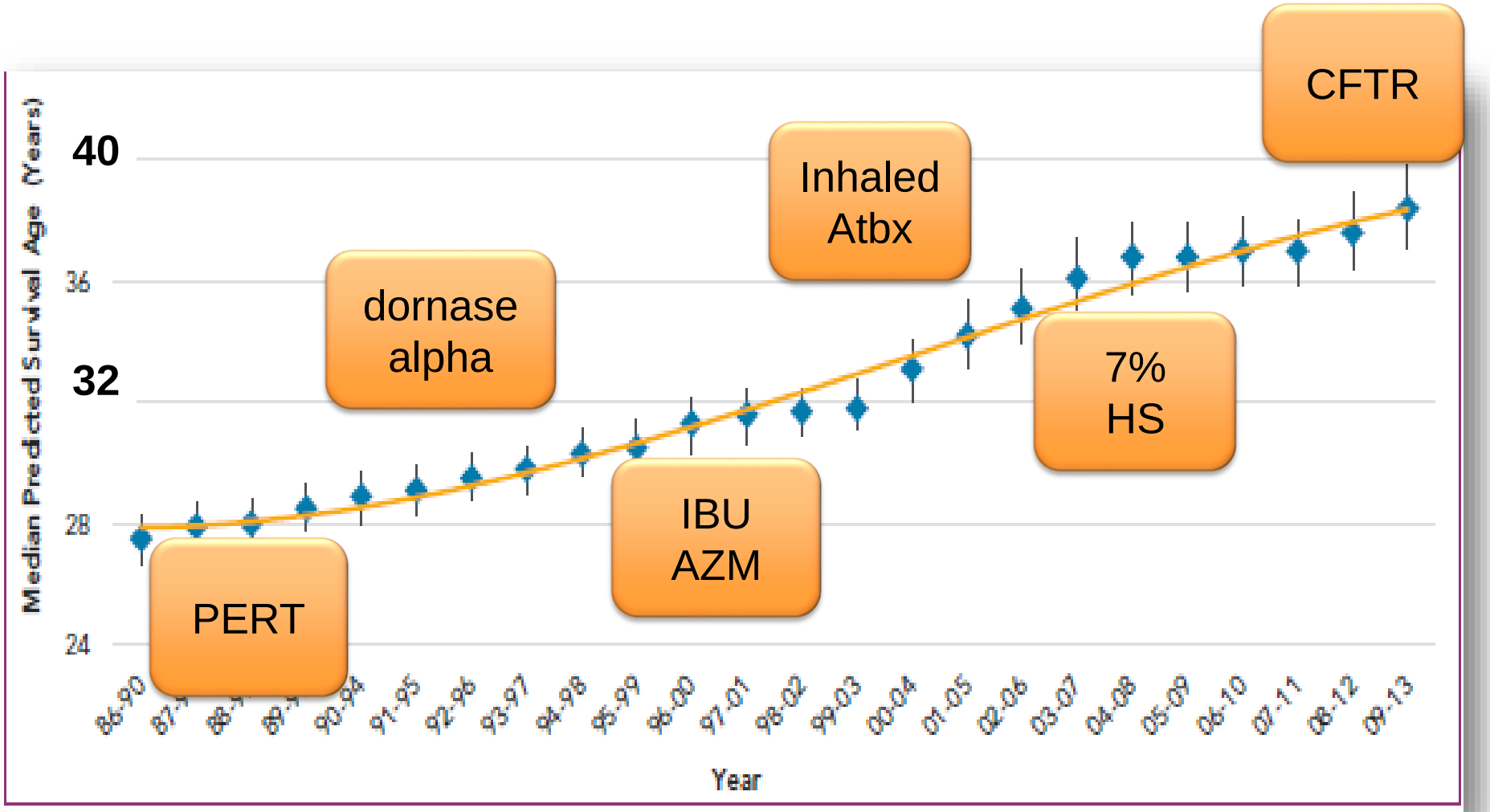
Hydrators
Mucolytics

Antimicrobials

Anti-inflammatories



Evidence-based medicine success



(2013 CFF Annual Report)

Current challenges

Modulators

Azithromycin

Vitamins

High-calorie meals and snacks

Enzymes

School/work

Hypertonic saline

Sports/play

Homework

Nebulized antibiotics

Social life/friends

Albuterol

Family time

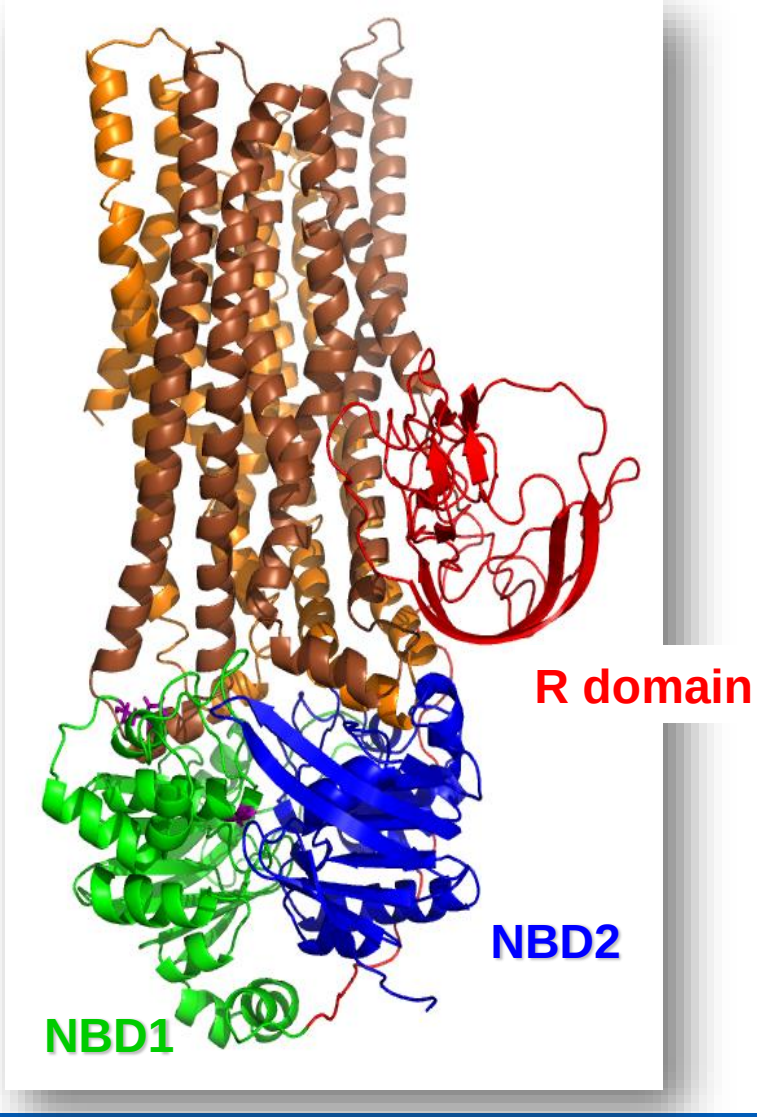
rhDNAse

Rest

Chest PT

Cystic fibrosis and CFTR

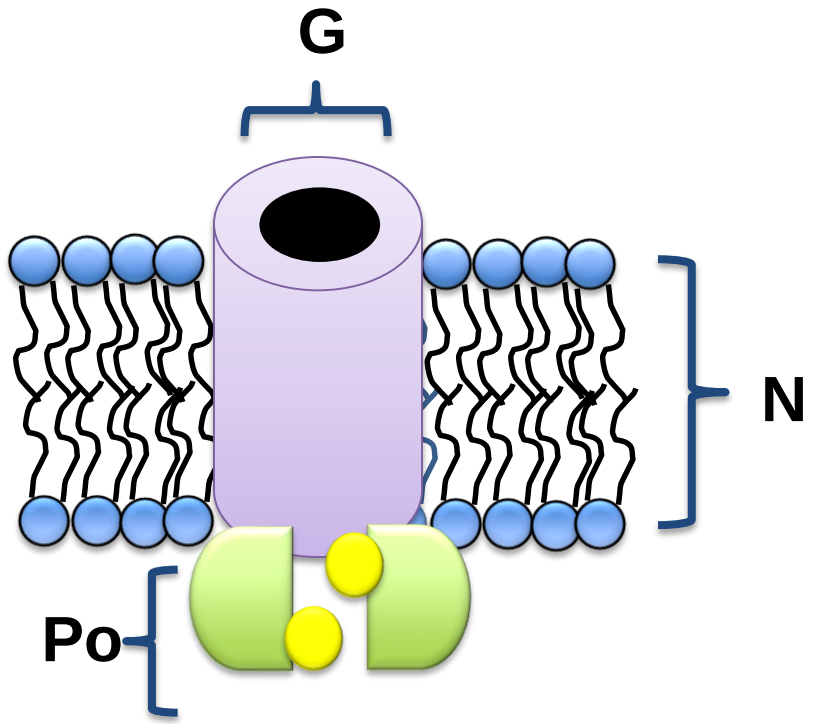
- Traffic ATPase
- Two transmembrane domains (TMDs)
- Two nucleotide binding domains (NBDs)
- One Regulatory domain (R domain)
- Anion channel
  - Cl-
  - HCO3-
  - SCN-, GSH, others?



Serohijos, Adrian W. R. et al. (2008) *Proc. Natl. Acad. Sci. USA* 105, 3256-3261

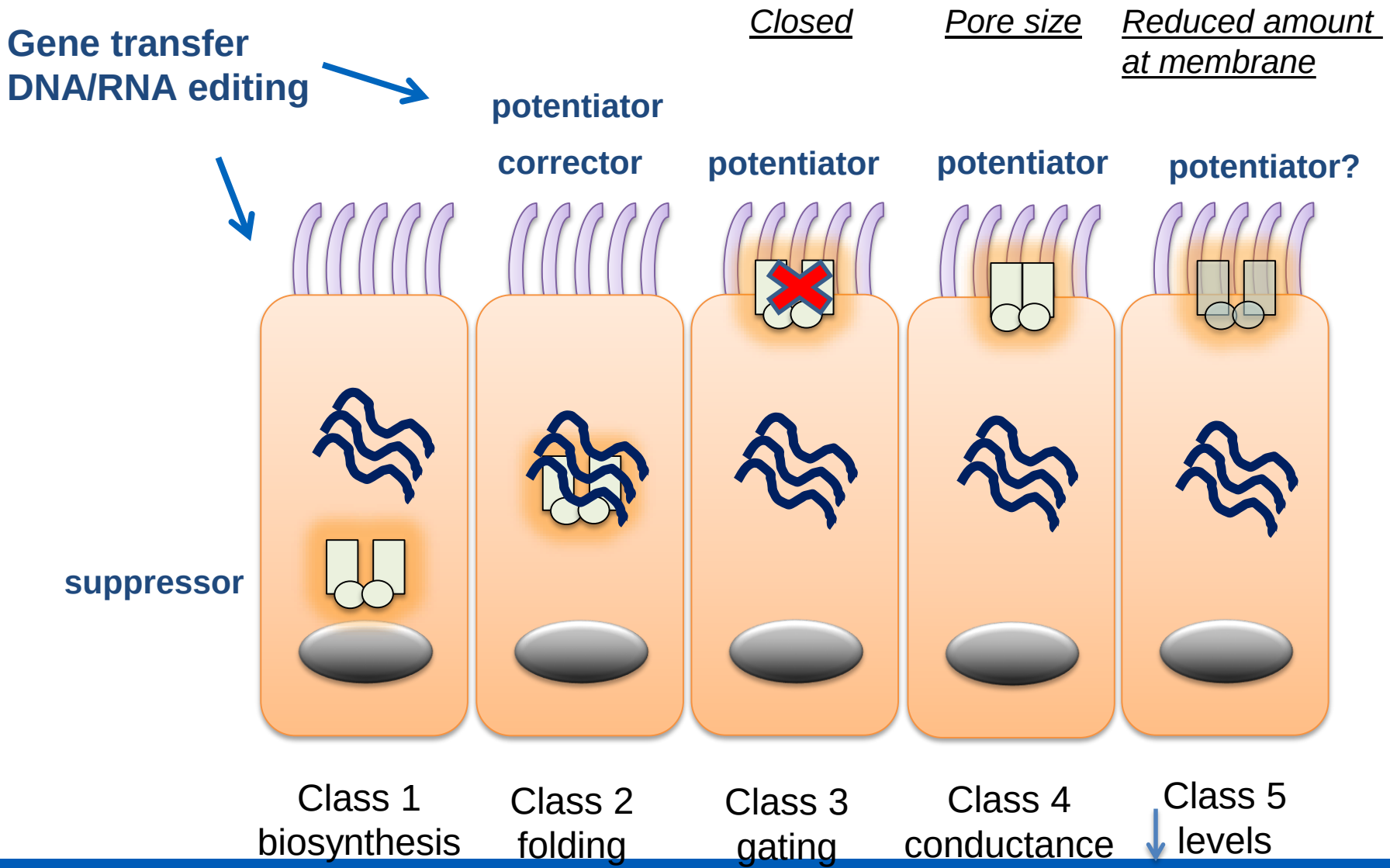
CFTR and ion transport

- How can we modulate CFTR?
  - Number of channels at the plasma membrane (N)
  - How much time each channel spends open vs closed (Po)
  - The size of each chloride channel (G)



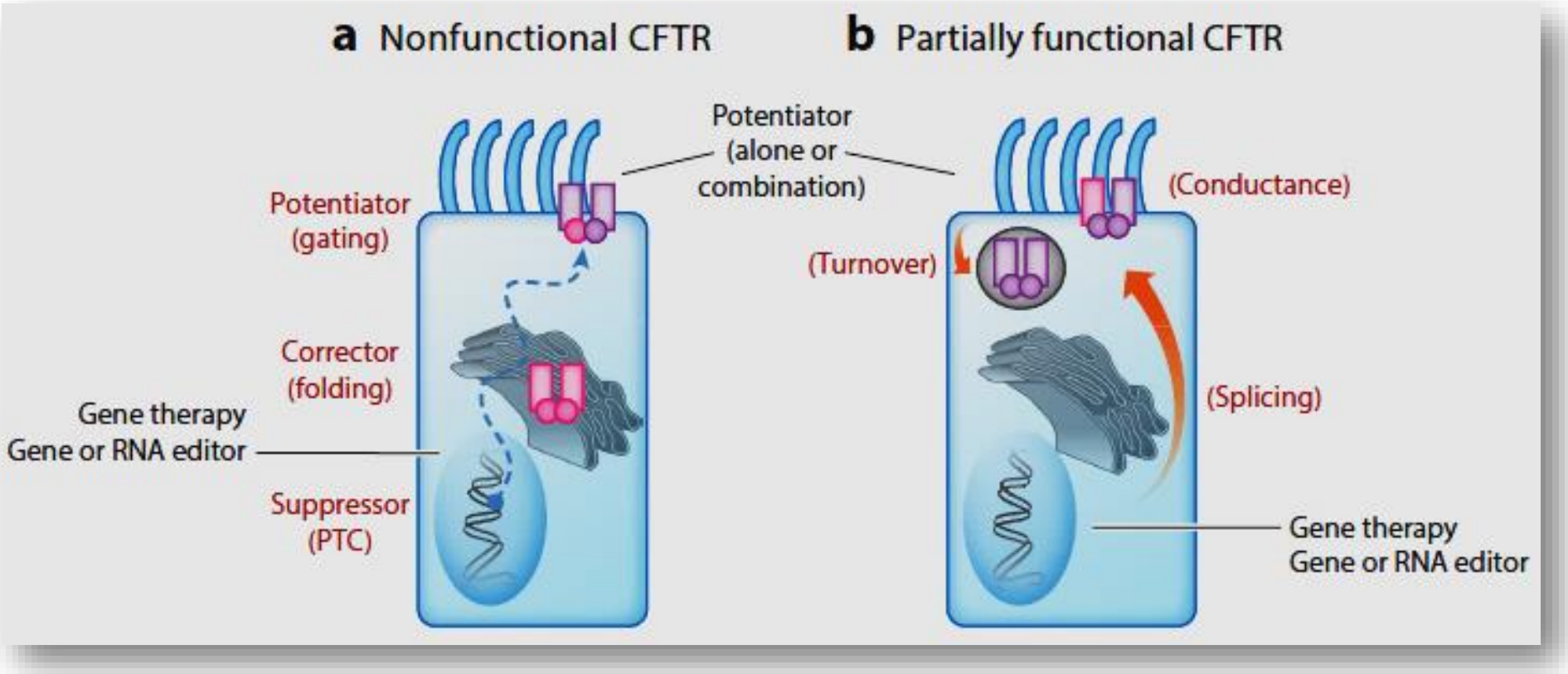
(N x Po x G) = total Cl- transport

Breakdown of CFTR mutations (>2000…)



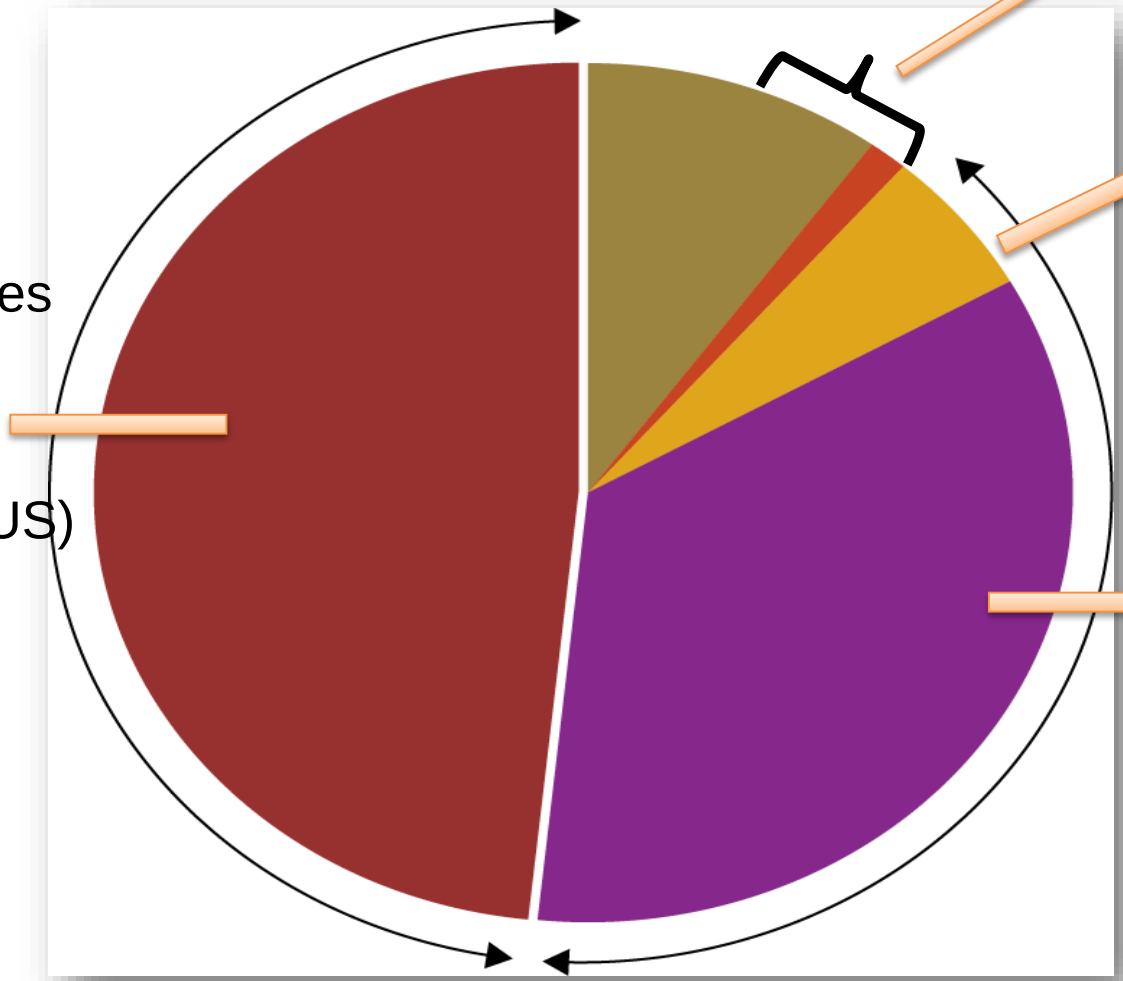
What are CFTR modulators?

- Potentiator – improves gating (Po)
- Corrector – improves trafficking (N)



Spielberg DR and Clancy JP – Cystic fibrosis and it's management through established and emerging therapies
Ann Rev Genomics (2016)

Summary of genotype groupings

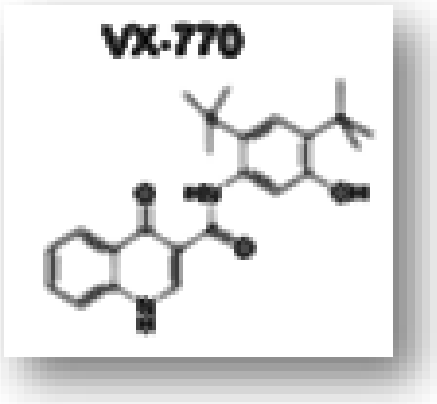


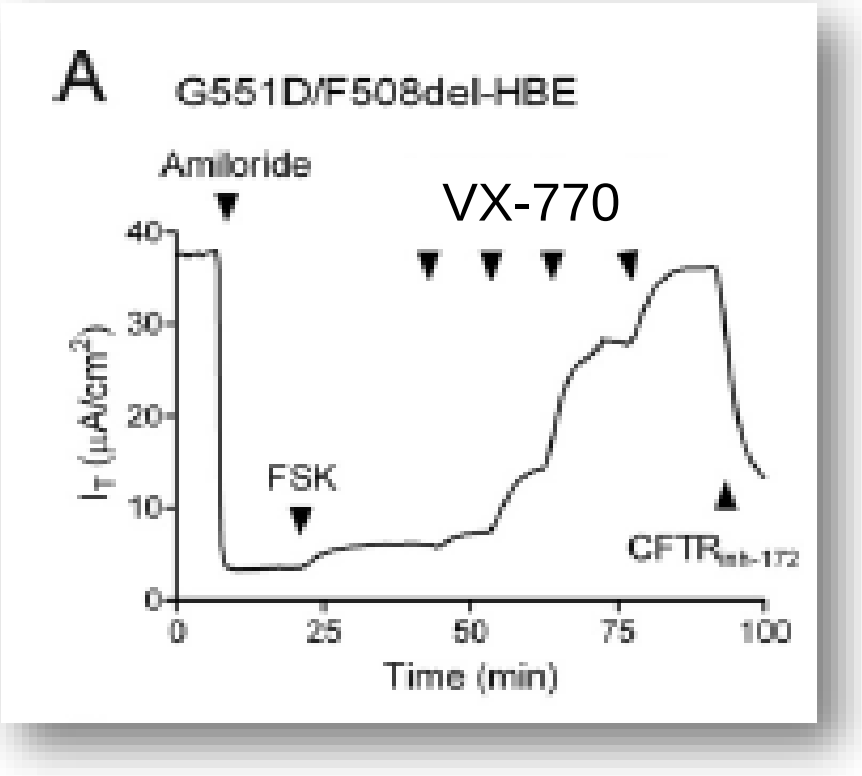
Cystic Fibrosis Foundation Patient Registry. 2014 Annual Data Report. http://www.cff.org.

Potentiating G551D CFTR (VX-770)

- 3rd most common disease-causing mutation (4%)
  - Higher in Ireland (5-10%)
  - Problem with open channel probability (gating)

- Strategy – increase Po
- Development
  - HTS
  - human AECs

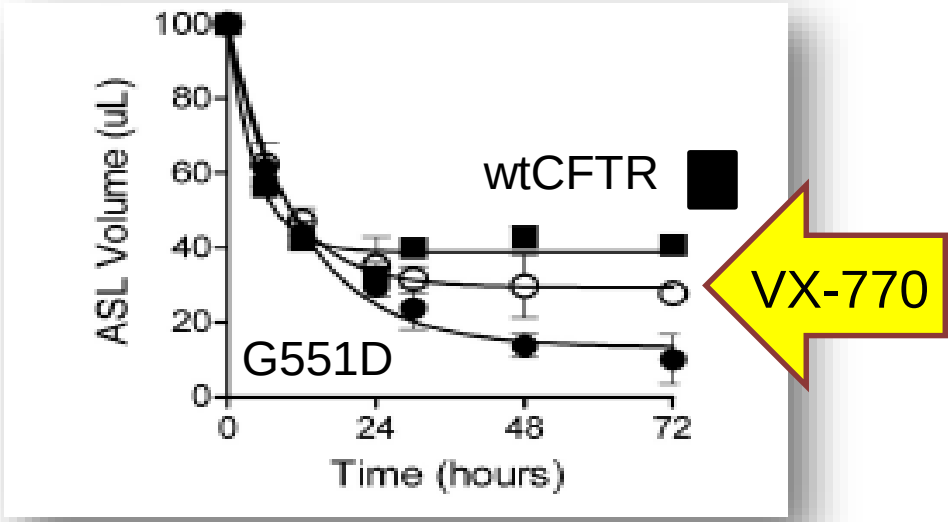




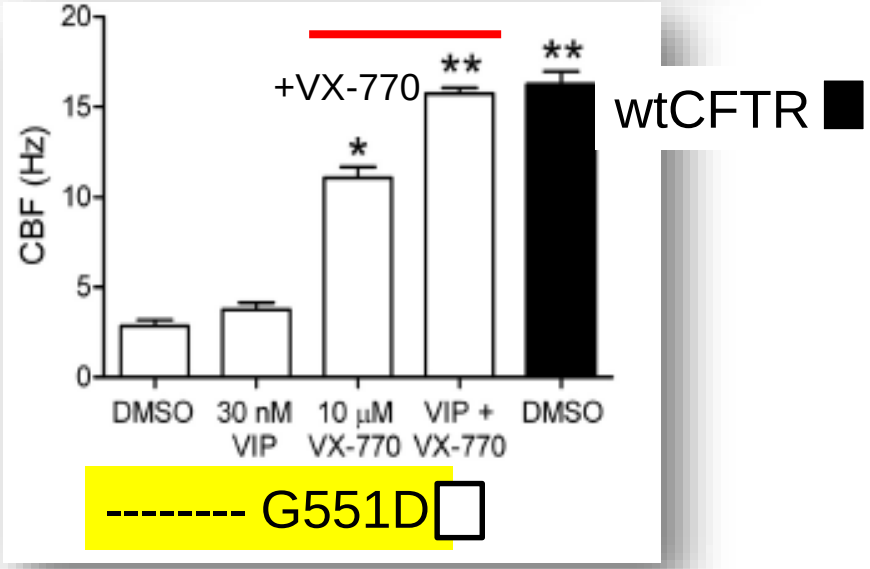
Van Goor, F. et al. *PNAS (11)* 2009;106: 18825-18830.

Restoring AEC functions with VX-770

- Airway surface liquid volume
  - Reduced ~50% in CF
  - Improved with VX-770



- Ciliary beat frequency (CBF)
  - Normalized with VX-770



Van Goor, F. et al. *PNAS (11)* 2009;106: 18825-18830.

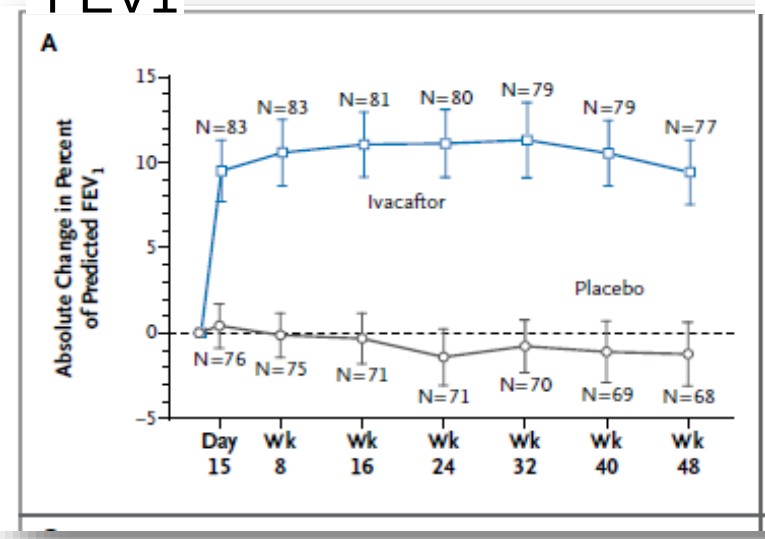
Ivacaftor for gating mutations

G551D patients: STRIVE results: N=161 (>12 yr); FEV_1 = 63.6%; RDBPC

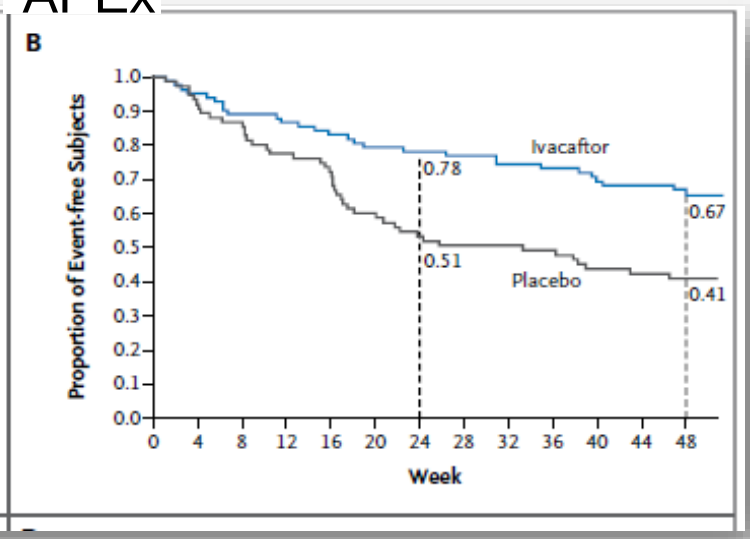
Ivacaftor: 48 weeks
Safety and efficacy

Placebo

FEV1



APEx



A new 'benchmark'

Class 3 gating

Ramsey, B et al. *New Engl J Med* (2011), 365: 1663-1672

Ivacaftor in young children

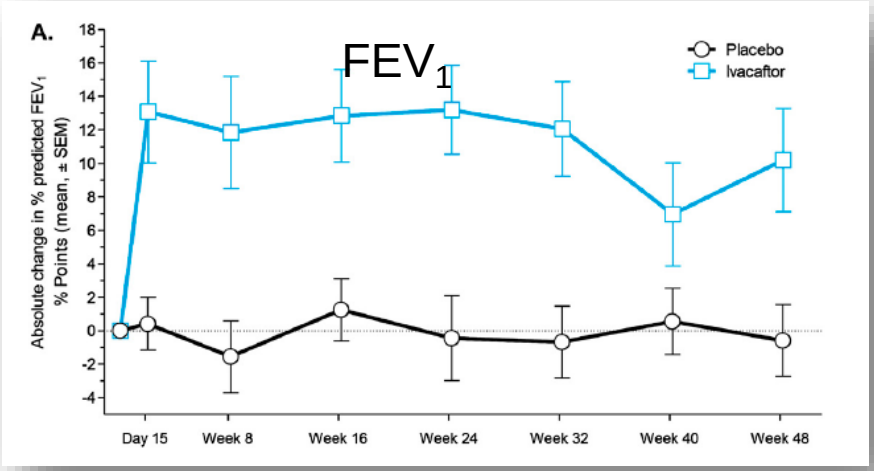
- Children age 6-11 yrs with G551D CFTR mutation (mean age 8.9 yr)
- 150 mg every 12 hr vs placebo

Ivacaftor: 48 weeks
Safety and efficacy

Placebo

52 subjects (26 each group – 4 plac. withdrew)

- FEV_1 % predicted increase 12.5% (p<0.001)
- Weight +2.8 kg (p<0.001)
- SC -53.5 mM (p<0.001)
- Similar AEs



Davies, JC et al. Efficacy and safety of ivacaftor in patients 6 to 11 years with cystic fibrosis with a G551D mutation
Amer Journ Resp Crit Car Med Vol 187, Iss 122, pp 1219-1225, Jun 1, 2013

Ivacaftor in very young children

- Children age 2-5 yrs with gating mutations (KIWI)
- Weight based dosing (50 mg or 75 mg every 12 hrs, 14 kg cutoff)

Part A	**Part B**
4 days	24 weeks
Short term safety	Longer term pharmacodynamics

9 subjects

34 subjects

- 33 completed study
- Similar exposure vs adults
- Common AEs: cough (56%), vomiting (29%)
- LFTs: 15% with 8 X ULN, 4 with study drug interrupted, 1 discontinued study drug
- Reduced SC (-46.9 mM), BMI Z score (+0.4) – $p<0.001$

Davies, JC et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a *CFTR* gating mutation (KIWI): an open-label, single-arm study. *Lancet Resp Med* Vol 4, Issue 2, Feb 2016, p 107-115

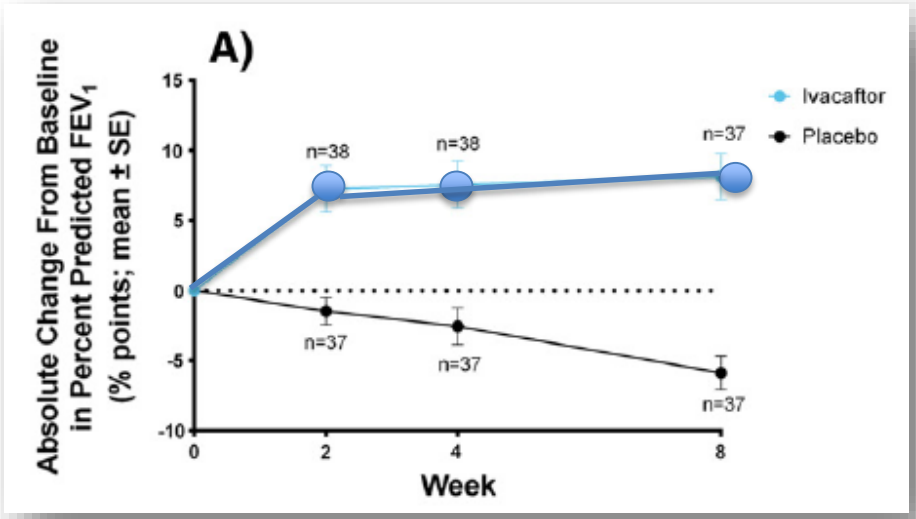
Ivacaftor in non-G551D gating mutations (KONNECTION)

- Patients > age 6 yrs (mean age 22.8 yr)
- 150 mg every 12 hr vs placebo in eight week crossover trial

ivacaftor X placebo → 24 weeks open label extension

39 subjects

- FEV_1 % predicted increase 10.7% (p<0.001)
- BMI +0.7 kg/m^2 (p<0.001)
- SC -49.2 mM (p<0.001)
- CFQ-R +9.6 (p<0.001)
- Similar AEs



De Boeck K et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis with and non-G551D mutations
Amer Journ Resp Crit Car Med Vol 187, Iss 122, pp 1219-1225, Jun 1, 2013

CFTR and R117H

- Age > 6 yrs with R117H mutation (KONDUCT)
- Partial function, gating AND conduction defects

Ivacaftor: 24 weeks
Safety and efficacy

Placebo

Class 3 and 4

Gating and conductance

<u>69 subjects</u>

- Abs. increase FEV1 % pred = 2.1% (p=0.20)
- Rel. increase FEV1 % pred = 5.0% (p=0.06)
- CFQ-R increase = +12.6 (p=0.002)
- Sig. reduction in SC

- <u>>18 yrs (n=50)</u>
  - Abs. FEV1 % pred = +5.0% (p=0.01)
  - Rel. FEV1 % pred = +9.1% (p<0.01)

Vertex Press Release: Dec. 13, 2013

Words from the POTUS

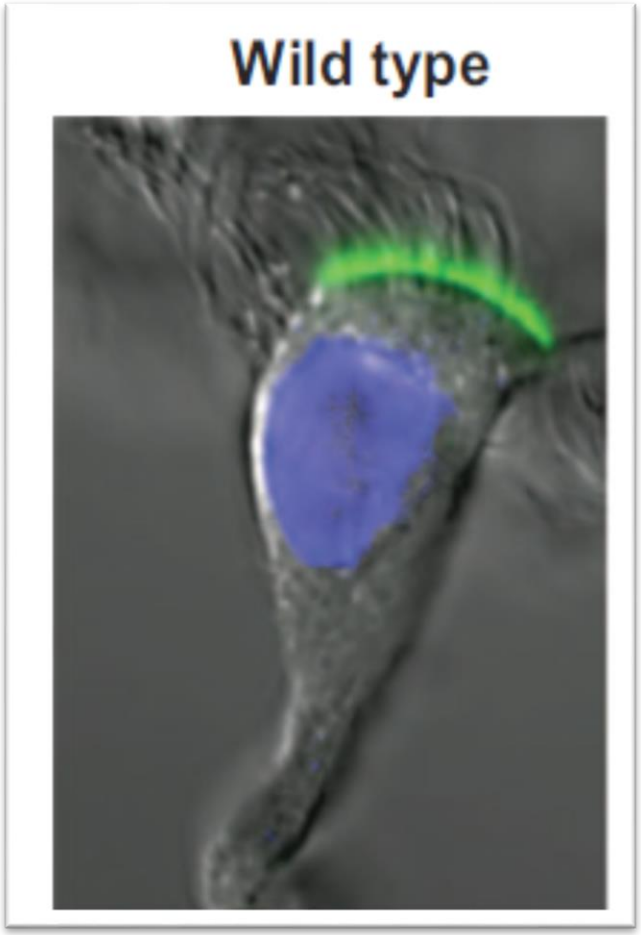
Barack Obama State of the Union Address (January 20, 2015):

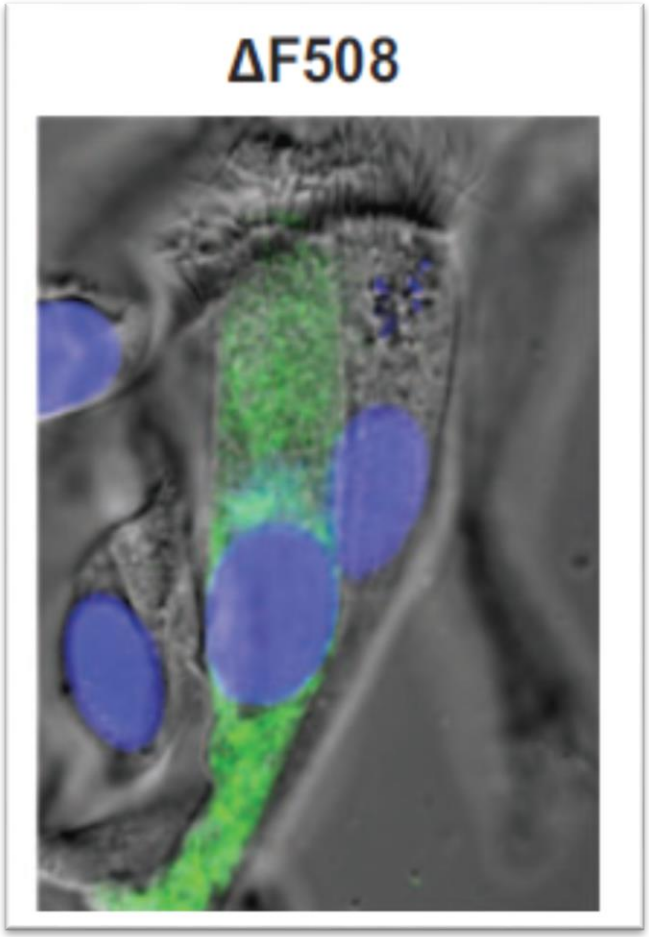
"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine: ***one that delivers the right treatment at the right time."***

"In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable.

Modulating F508del CFTR

- **85% CF patients have one copy**
- **50% have two**



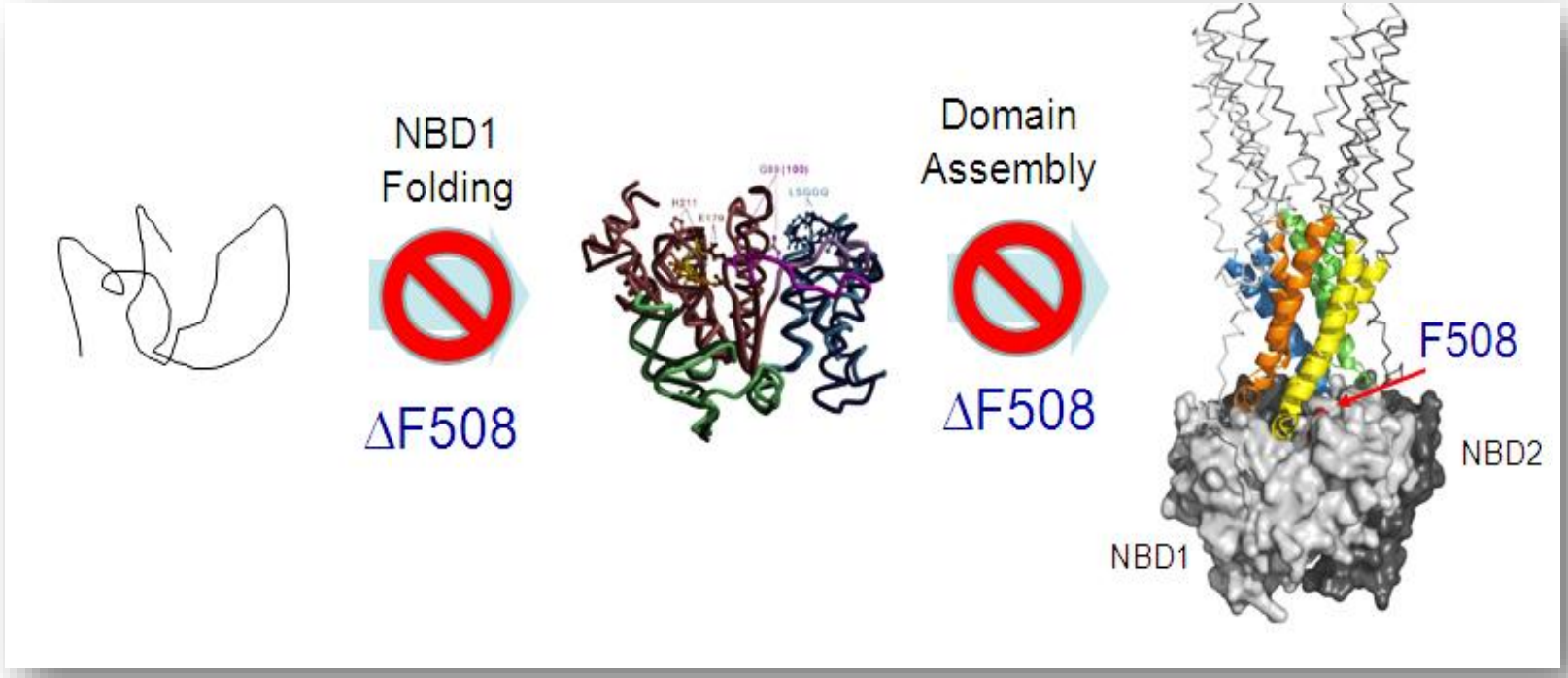


Riordan J. *Ann Rev Biochem*. 2008;77:701-726.

Correcting F508del CFTR – it's complicated

- Two problems identified that contribute to folding defect
  - Co-translational folding of NBD-1
  - Domain assembly (NBD-1 and ICL4 interactions)

…And gating defect when at the plasma membrane

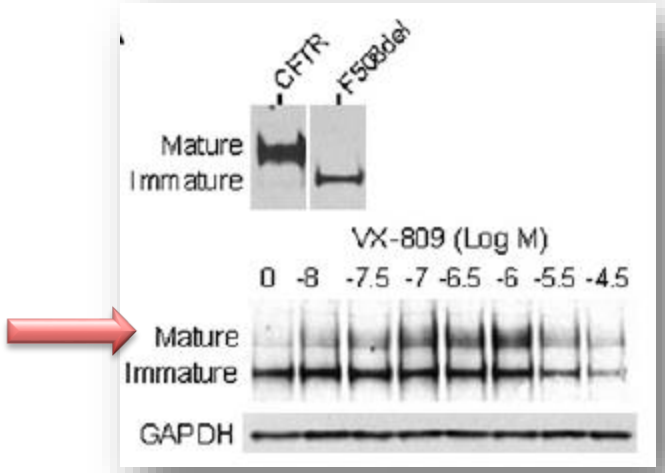


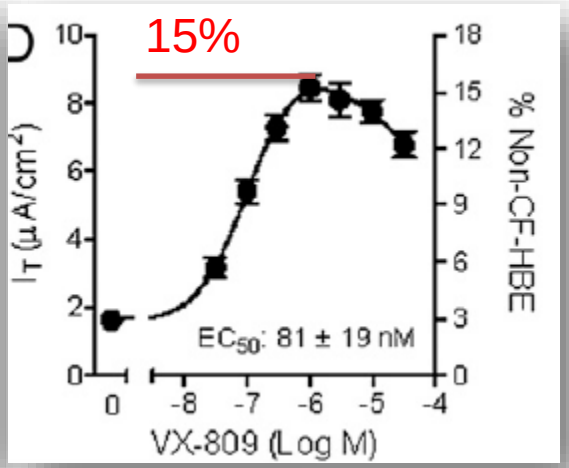
Lukacs, G and Verkman, A. *Trends in Mol Med* (2012) 2:Vol 18

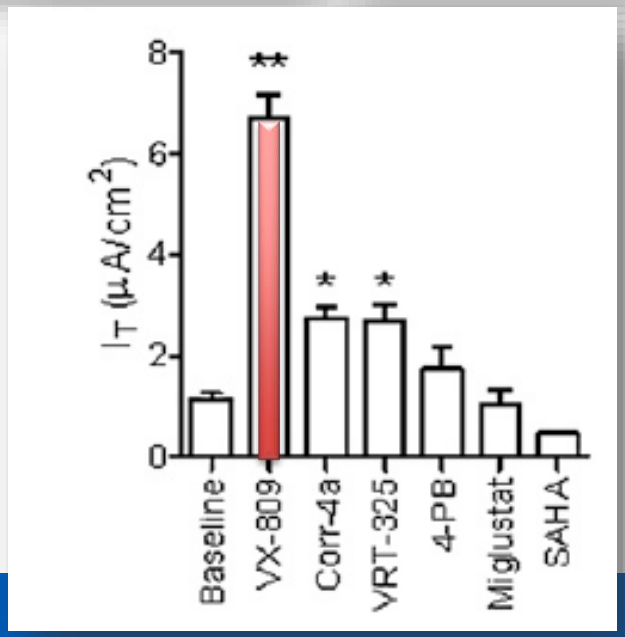
(Courtesy of CFF and M Mall)

Correcting F508del CFTR (AECs) with VX-809

- Strategy
  - Increase N
- TOP (VX-809):
  - Dose/response of F508 correction
    - (C Band, current)
  - ~15% of non-CF
- BOTTOM:
  - VX-809 c/w other correctors





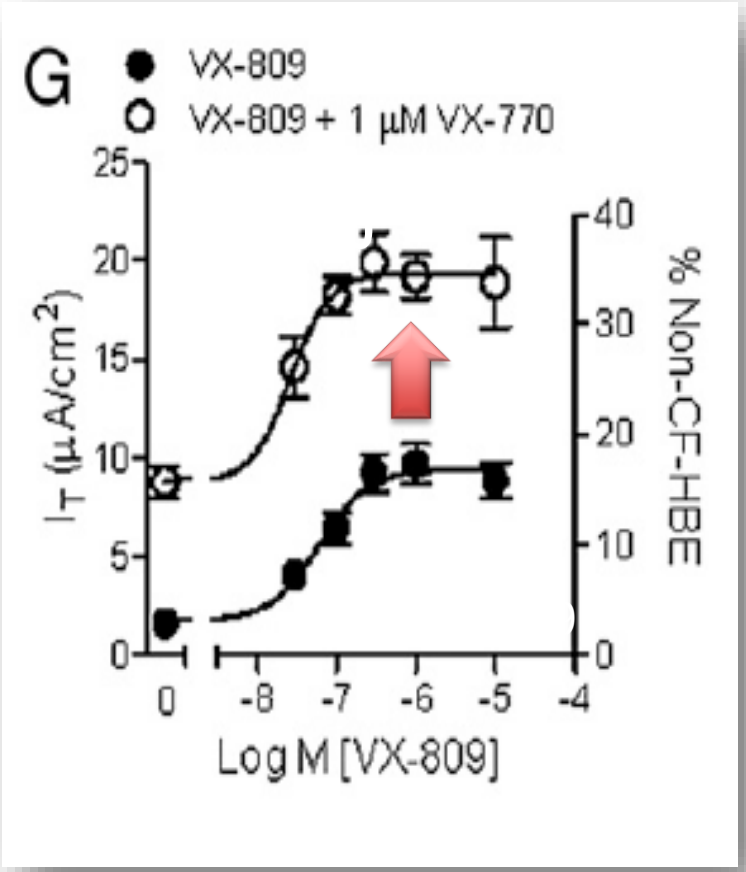


Vangoor, et al. *PNAS (108)* 2011;46:18843-18848

Correcting AND Potentiating F508del

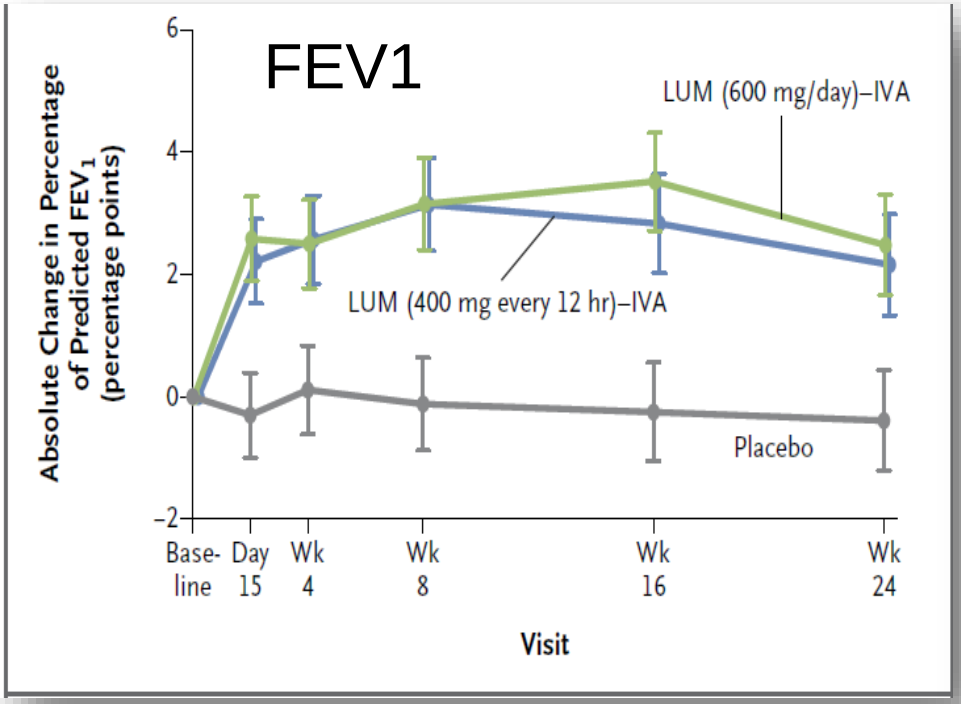
lumacaftor + ivacaftor

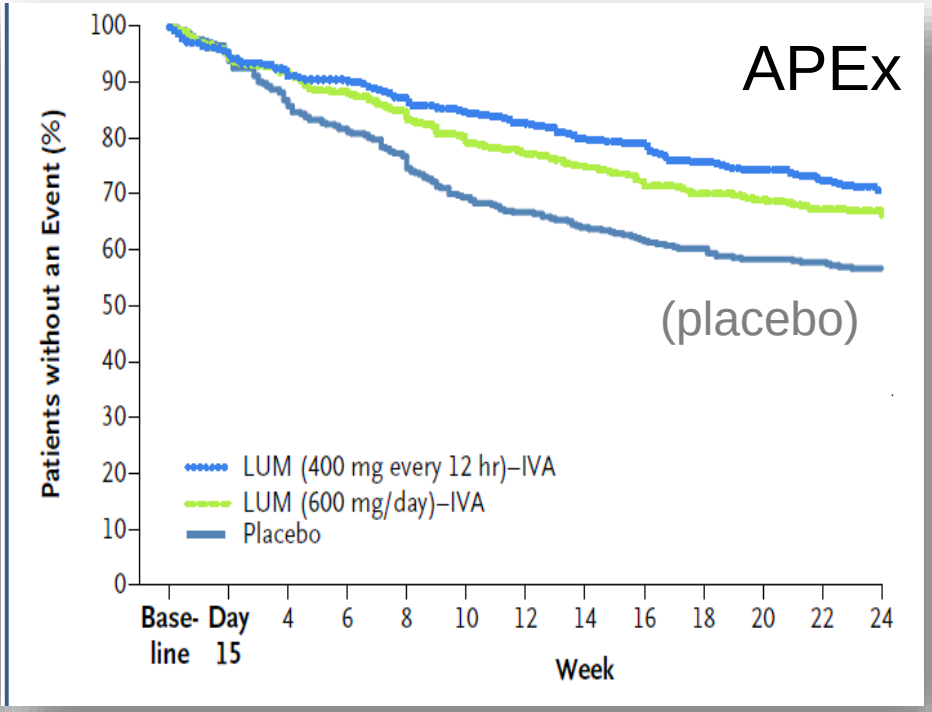
- F508del CFTR
  - Complex problems
  - N AND Po
- <u>Two Phase II studies</u>
  - Lumacaftor + ivacaftor
  - Safety, dose-ranging, PK and PD



TRAFFIC and TRANSPORT

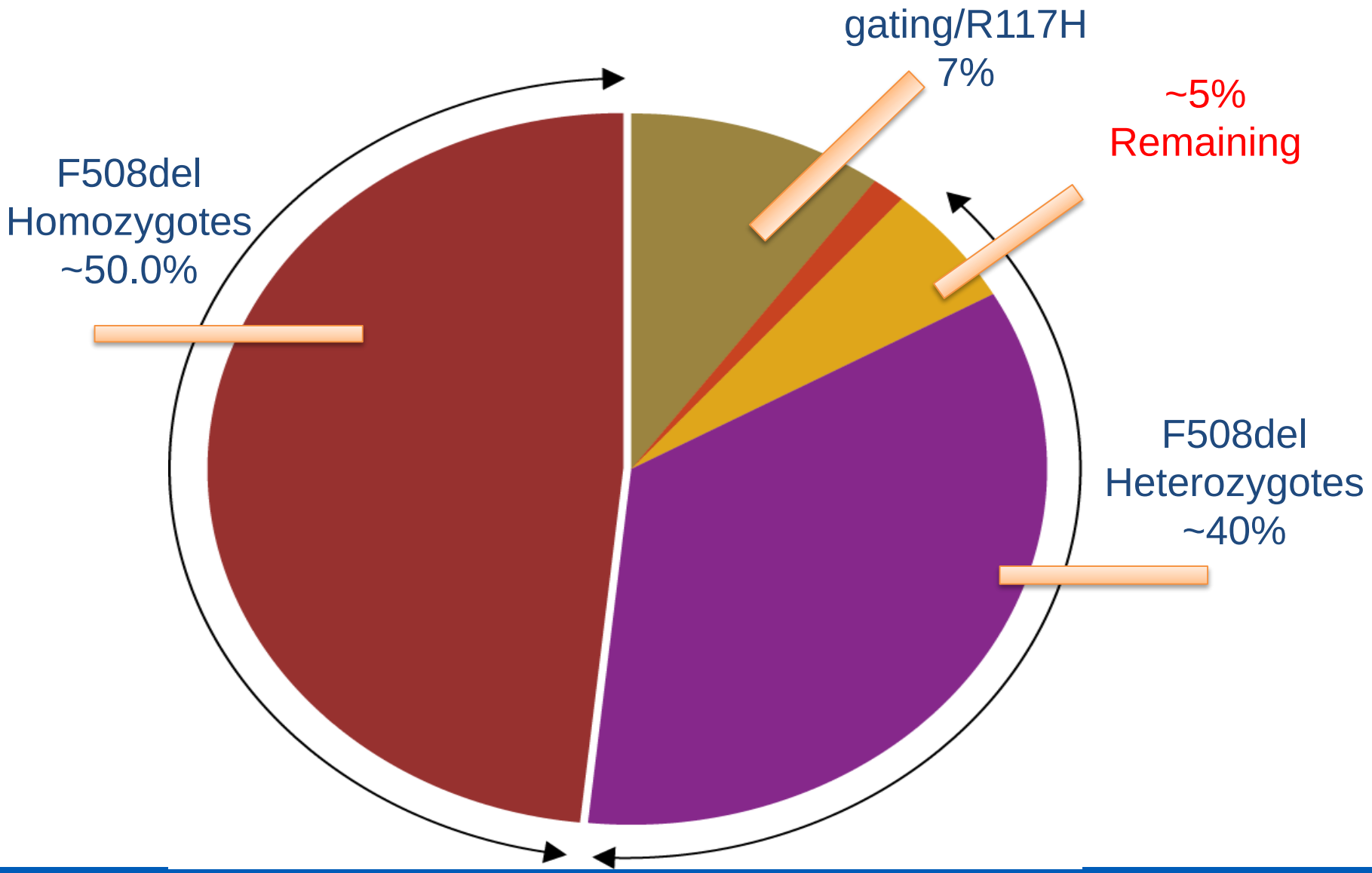
- RDBPC trial (24 week) 1122 F508del/F508del randomized
- Lumacaftor (2 doses) + ivacaftor vs placebo
- FEV_1 improvement (p<0.001); APEx improvement (p<0.001)





Wainwright, C et al *New Engl J Med*. Jul. 16;373(3) 220-31 (2015)

Summary: genotype-based coverage



Cystic Fibrosis Foundation Patient Registry. 2012 Annual Data Report. http://www.cff.org.

Summary

- Evidence based medicine has steadily advanced CF outcomes
  - Escalating burden of care
- HTS can successfully identify CFTR modulators
- CFTR is a valid target
  - Gating mutations
  - F508del CFTR
- Emergence of CFTR modulators offers potential to transform CF care and outcomes

Thanks to:

- **Clancy Lab and Coordinators**
  - Beth Decker, RN
  - Dee Terrill, RRT
  - Kelly Thornton, CCRC
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  - Jenny Jeffries, RN
  - Megan Meyer, RN
  - Drs. Gary McPhail, John Brewington and Beth Kramer
  - Alicia Ostmann, Erin Filbrandt, Lauren Strecker, Kristina Ray