Νέες Θεραπευτικές Εξελίξεις στη Κυστική ίνωση

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Σισμανόγλειο ΓΝΑ

Περιεχόμενο παρουσίασης

- Σύνοψη παθοφυσιολογίας
- Νεώτερα δεδομένα στην συμπτωματική θεραπεία
- Στοχευμένες θεραπείες – CFTR μεταλλάξεις / CFTR ρυθμιστές
- Νεώτερα δεδομένα στην γονιδιακή θεραπεία
- Μέθοδοι αξιολόγησης νέων θεραπειών

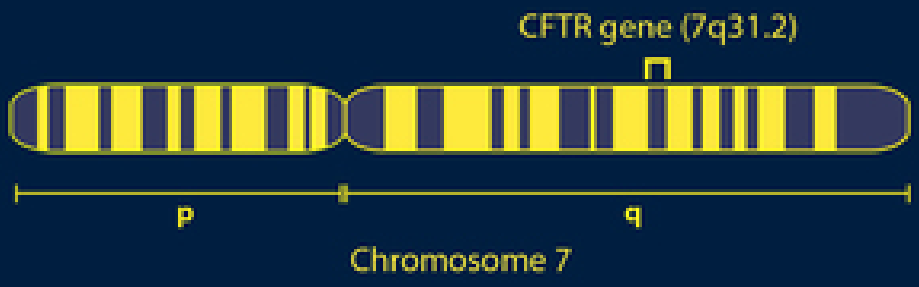
Cystic Fibrosis

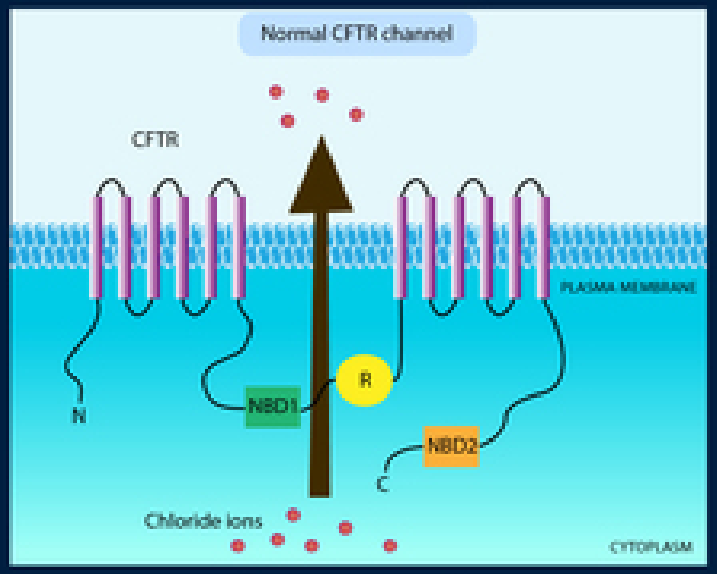
Burden of CF

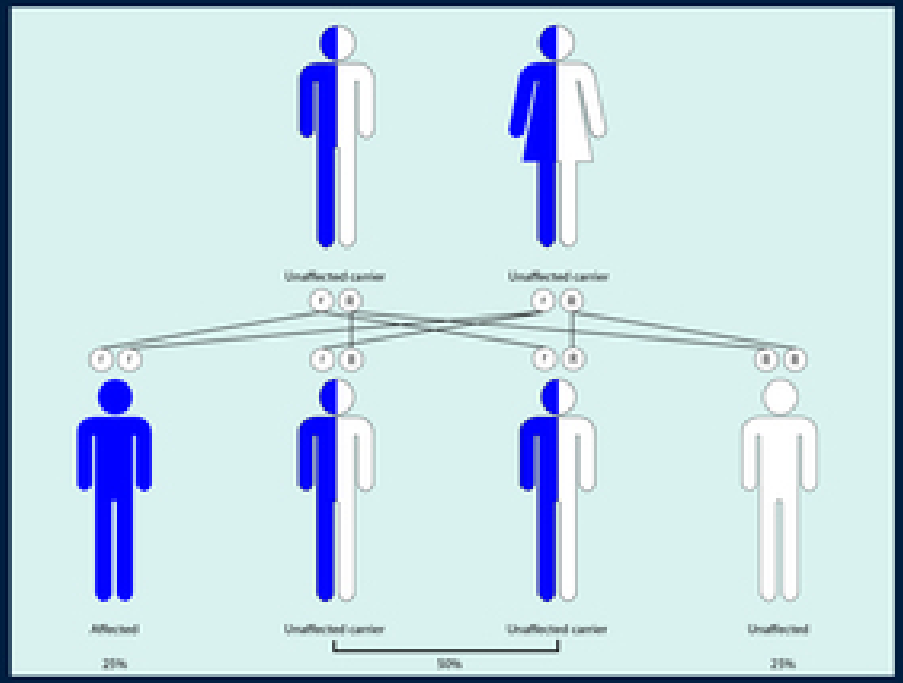
- Most common "life-shortening" recessive disease in Caucasians
  - 1:3,200 in the northern Europian US
  - 1:15,000 population in blacks
  - 1 :10,500 Native Americans
  - 1 :9,200 Hispanics
  - 1 :31,000 Asian Americans
  - 1 :90,000 Asians

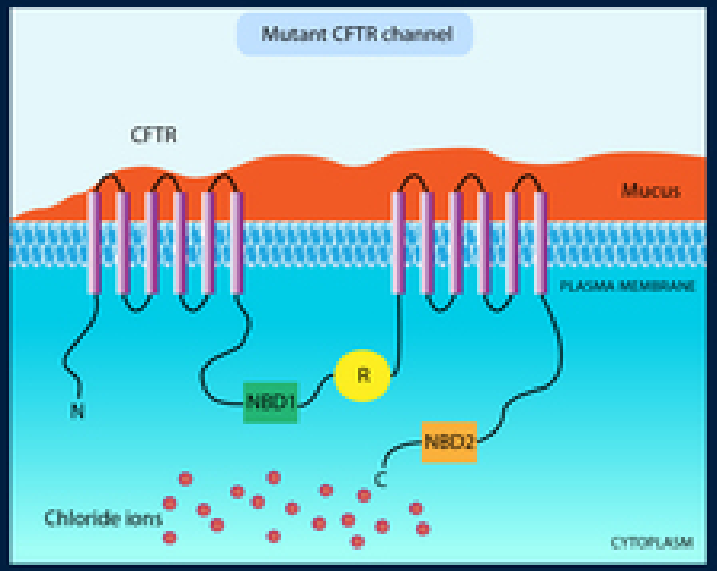
  (Ref : emedicine medscape)
- 1,000 new cases diagnosed / year.
- More than 70% diagnosed by age two.
- More than 45% of CF population is 18 Y or older.
- predicted median age of survival is more than 36.9 years.M>

Cystic fibrosis





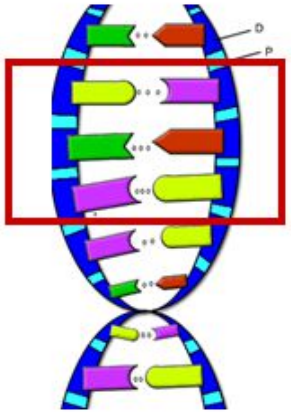




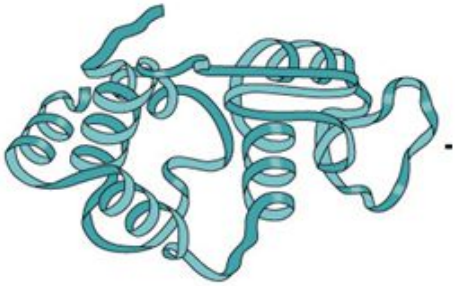
Autosomal Recessive Inheritance

Cause of Cystic Fibrosis (CF)

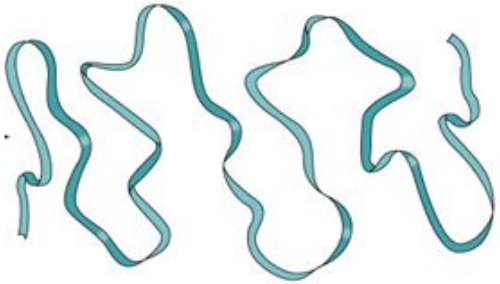
- The "CFTR" gene is mutated
  - 3 base pairs are **deleted**



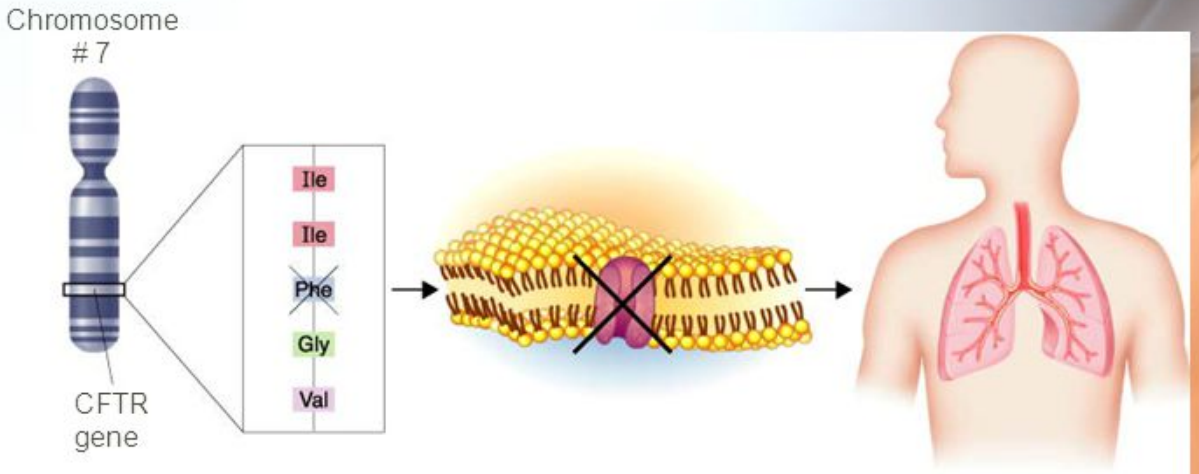
- Mutant protein is missing an amino acid and cannot fold correctly



vs



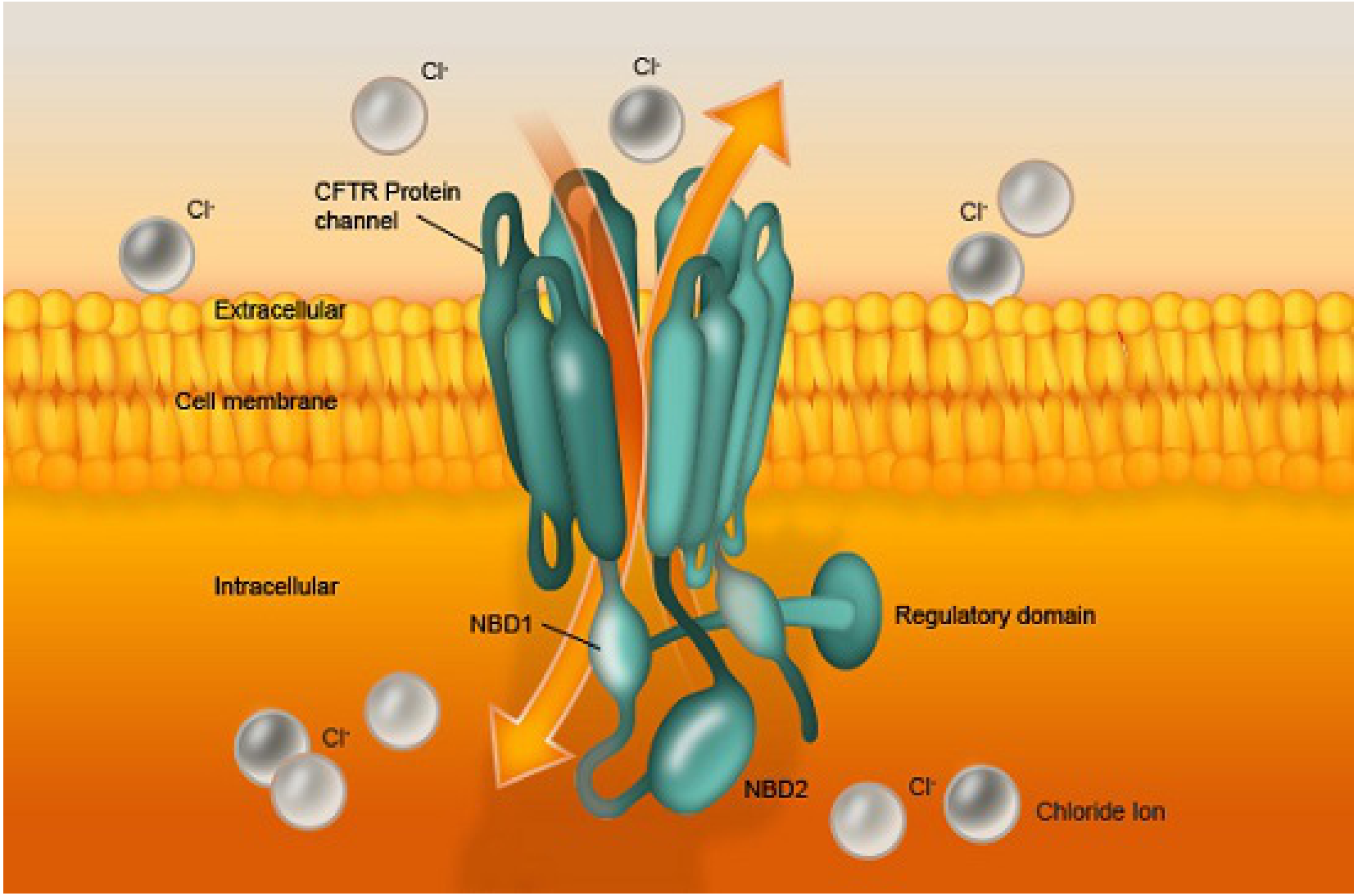
Cystic Fibrosis



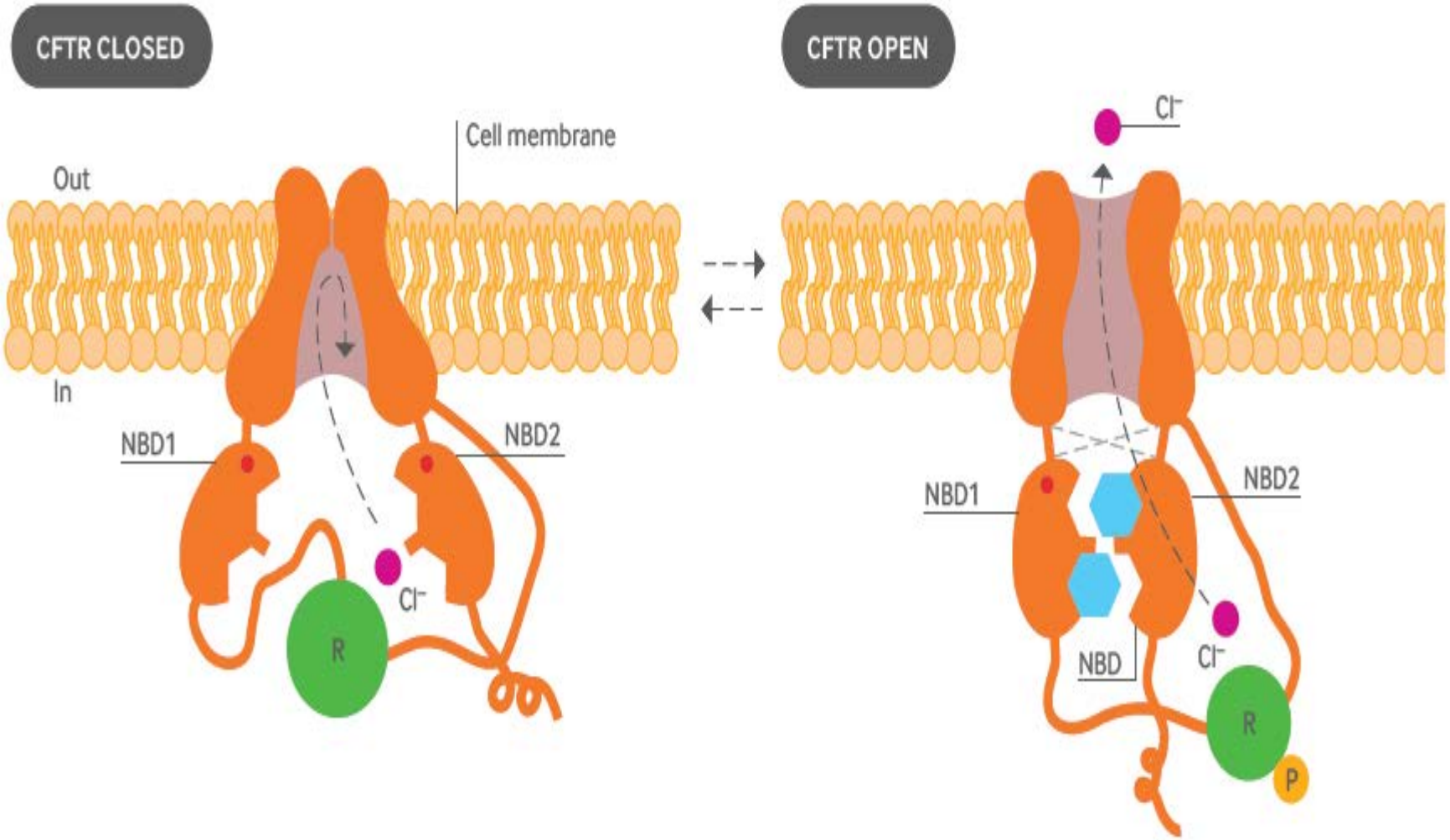
A The most common allele that causes cystic fibrosis is missing 3 DNA bases. As a result, the amino acid phenylalanine is missing from the CFTR protein.

B Normal CFTR is a chloride ion channel in cell membranes. Abnormal CFTR cannot be transported to the cell membrane.

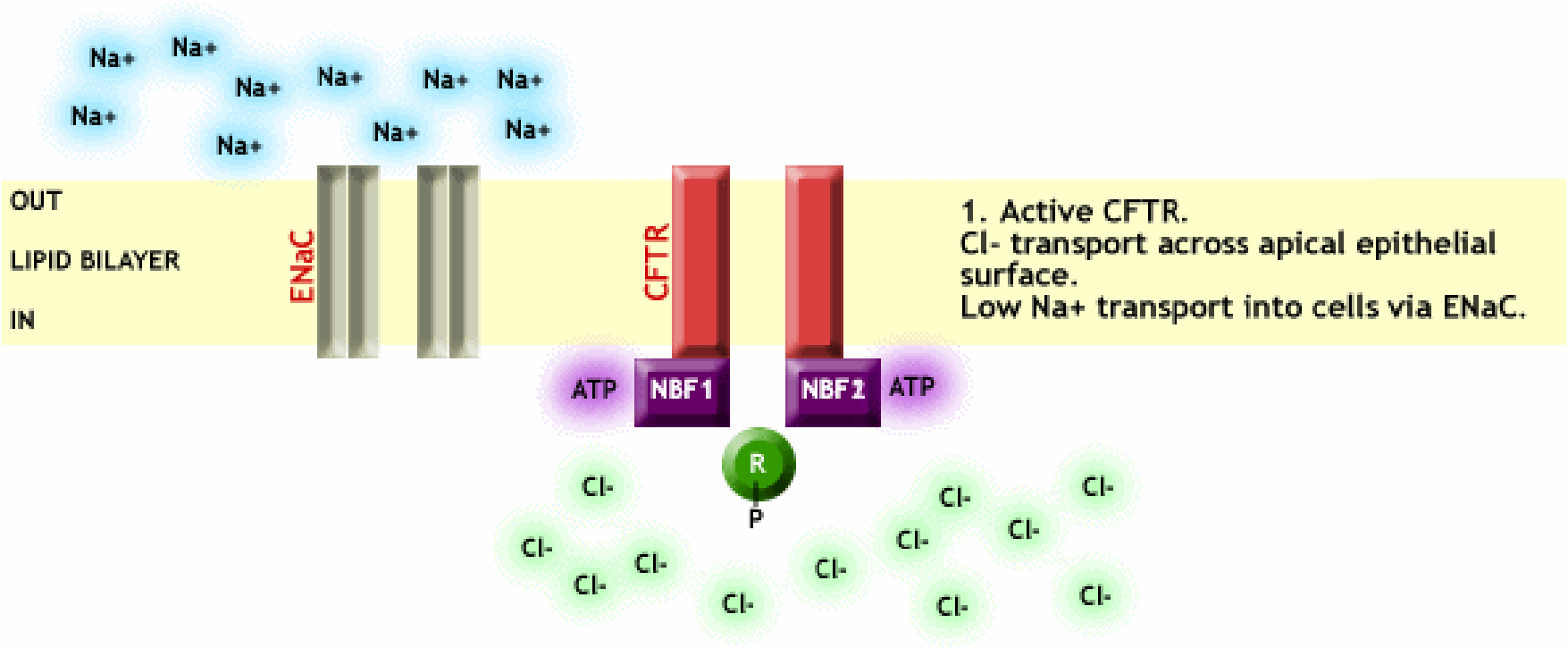
C The cells in the person's airways are unable to transport chloride ions. As a result, the airways become clogged with a thick mucus.



www.healthcare innovations.org, 2015

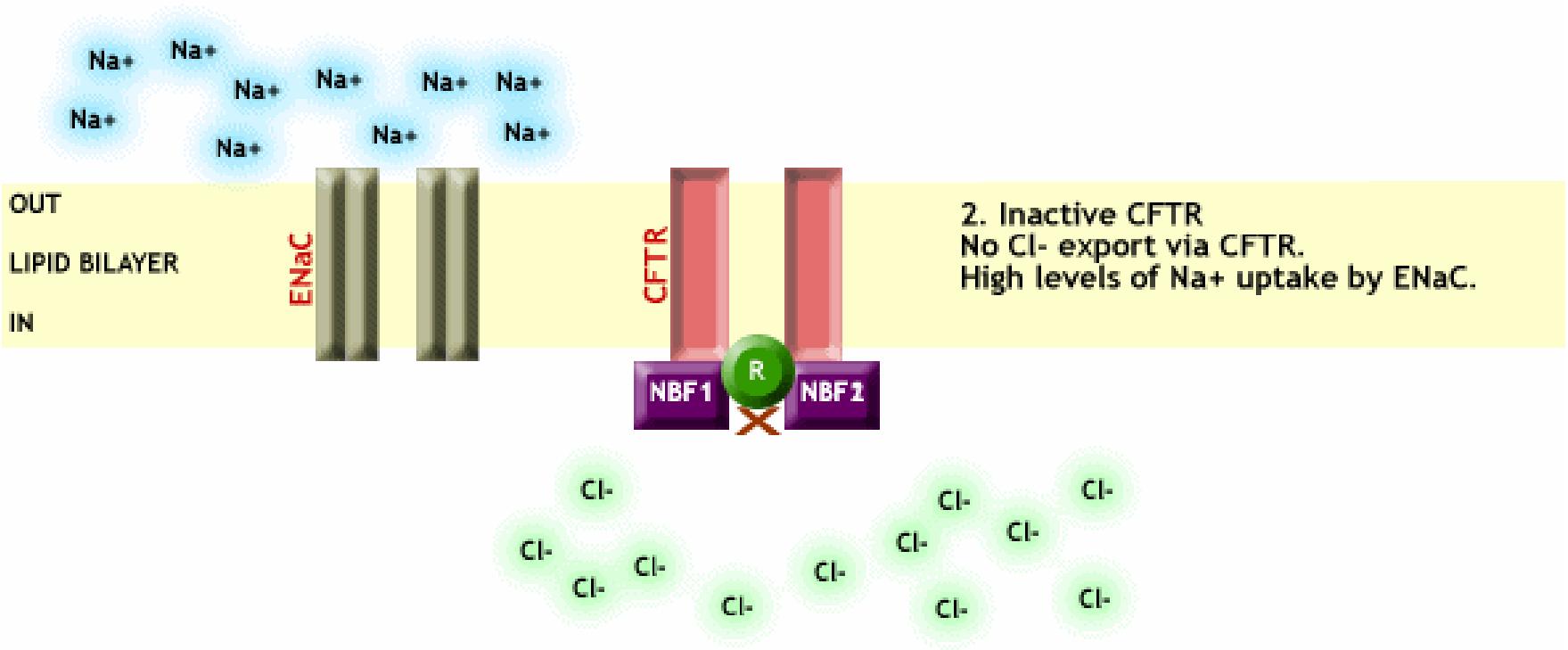

CFTR CLOSED
Cell membrane
Out
In
NBD1
NBD2
Cl⁻
R
CFTR OPEN
Cl⁻
NBD1
NBD2
NBD
Cl⁻
R
P

Normal CFTR function



http://www.cfgenetherapy.org.uk/cysticfibrosis/article/What_causes_Cystic_Fibrosis

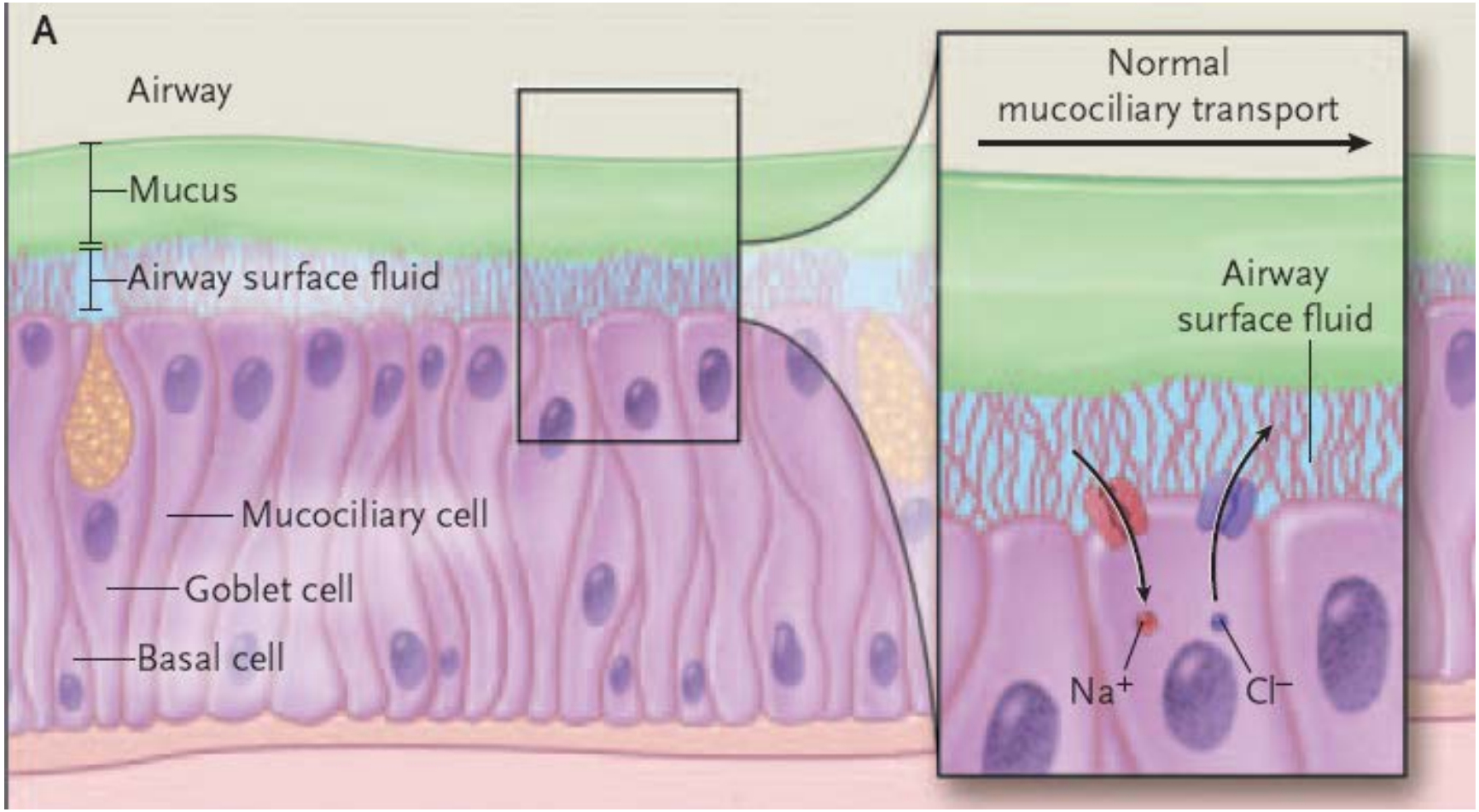
Abnormal CFTR function



http://www.cfgenetherapy.org.uk/cysticfibrosis/article/What_causes_Cystic_Fibrosis

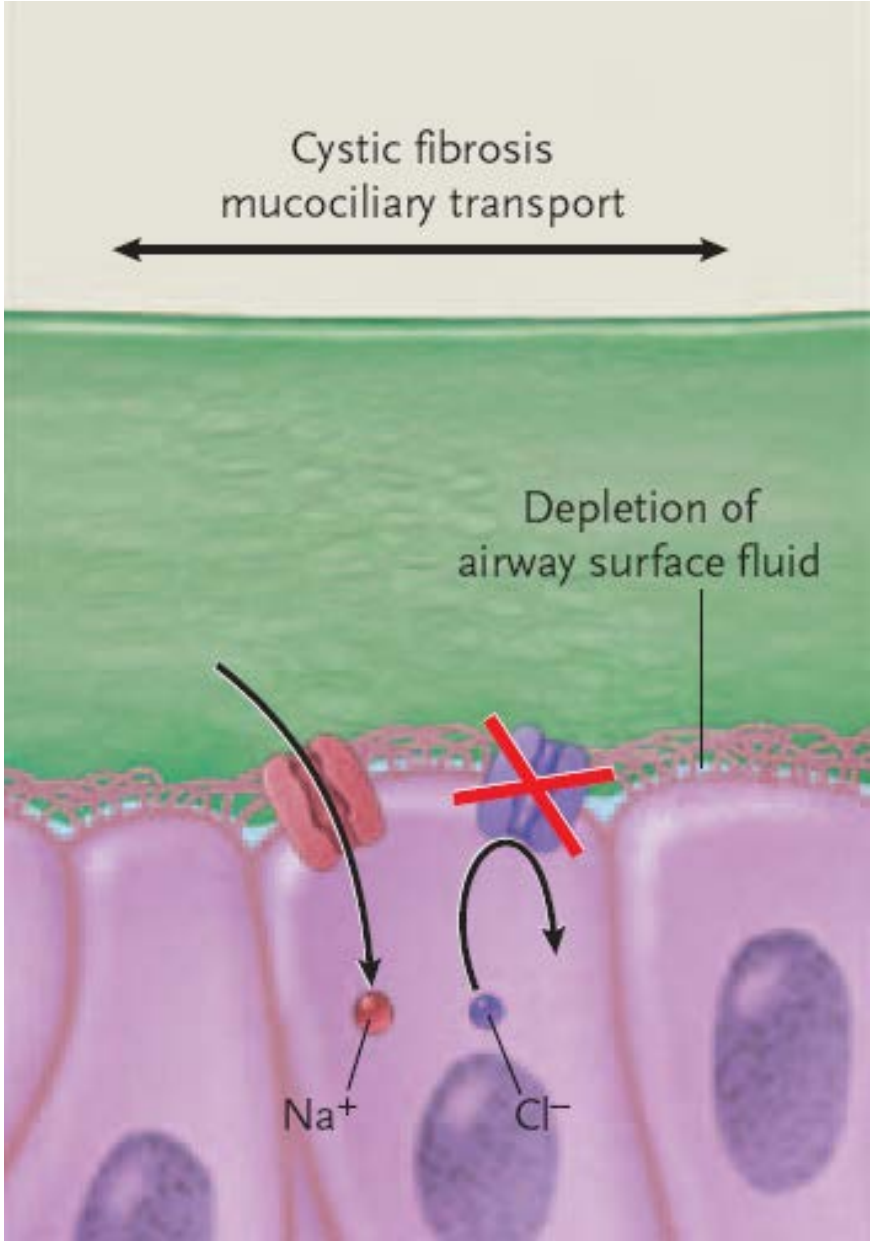
Mucociliary clearance

The importance of airway hydration



Ratjen F *NEJM* 2006

Airway surface liquid depletion in CF



Ratjen F *NEJM* 2006

CF Pathophysiology

CFTR gene defect

↓

Defective ion transport

↓

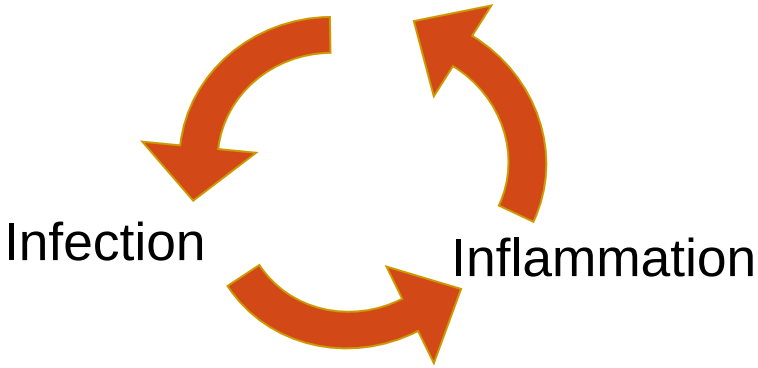
Airway surface liquid depletion

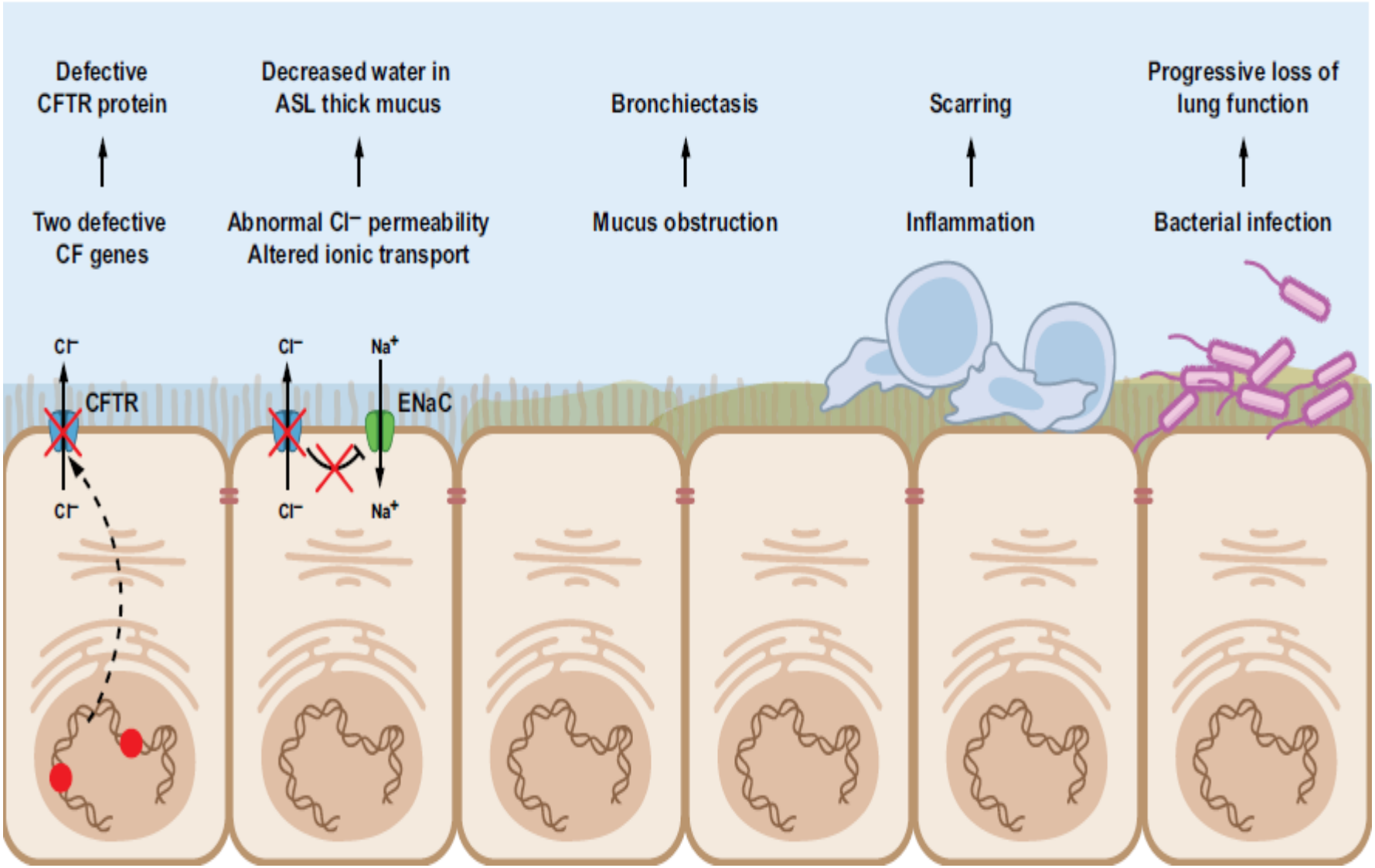
↓

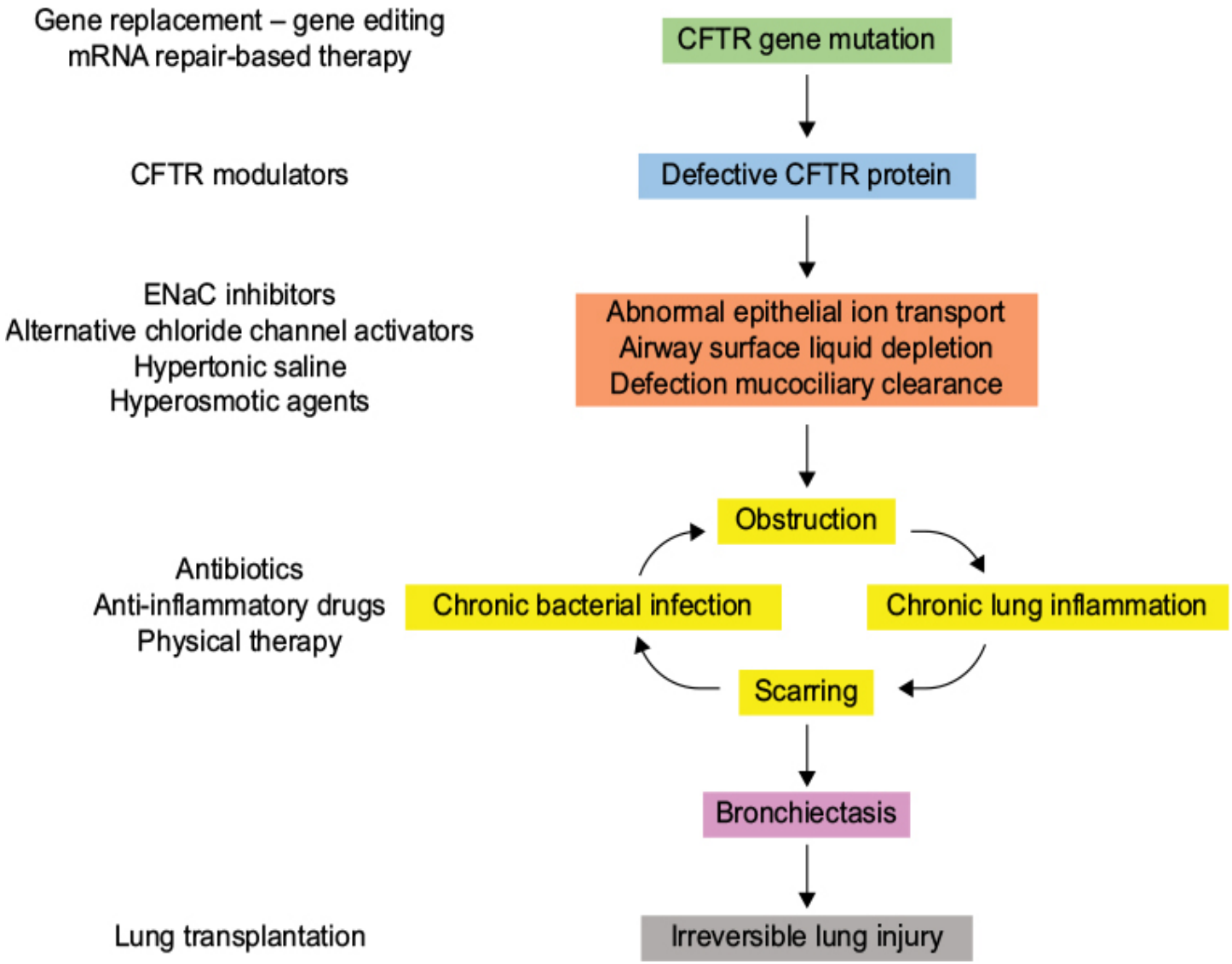
Defective mucociliary clearance

↓

Mucus obstruction




Defective CFTR protein
Decreased water in ASL thick mucus
Bronchiectasis
Scarring
Progressive loss of lung function
Two defective CF genes
Abnormal Cl⁻ permeability Altered ionic transport
Mucus obstruction
Inflammation
Bacterial infection
Cl⁻
CFTR
Cl⁻
Cl⁻
Na⁺
ENaC
Cl⁻
Na⁺

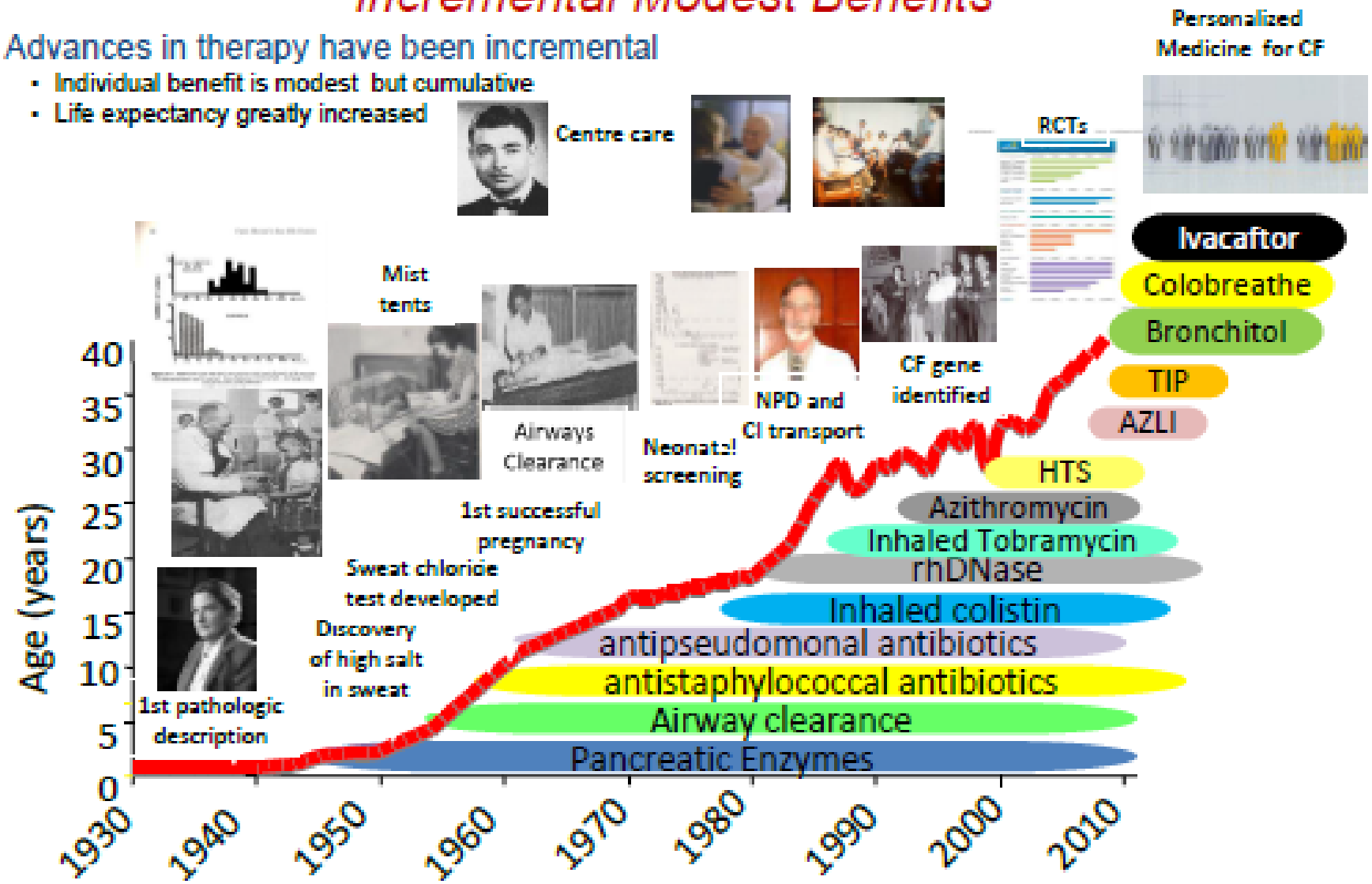

Gene replacement – gene editing
mRNA repair-based therapy
CFTR gene mutation
CFTR modulators
Defective CFTR protein
ENaC inhibitors
Alternative chloride channel activators
Hypertonic saline
Hyperosmotic agents
Abnormal epithelial ion transport
Airway surface liquid depletion
Defection mucociliary clearance
Obstruction
Antibiotics
Anti-inflammatory drugs
Physical therapy
Chronic bacterial infection
Chronic lung inflammation
Scarring
Bronchiectasis
Lung transplantation
Irreversible lung injury

Improved Survival with Treatment Innovation

Incremental Modest Benefits

Advances in therapy have been incremental

- Individual benefit is modest but cumulative
- Life expectancy greatly increased



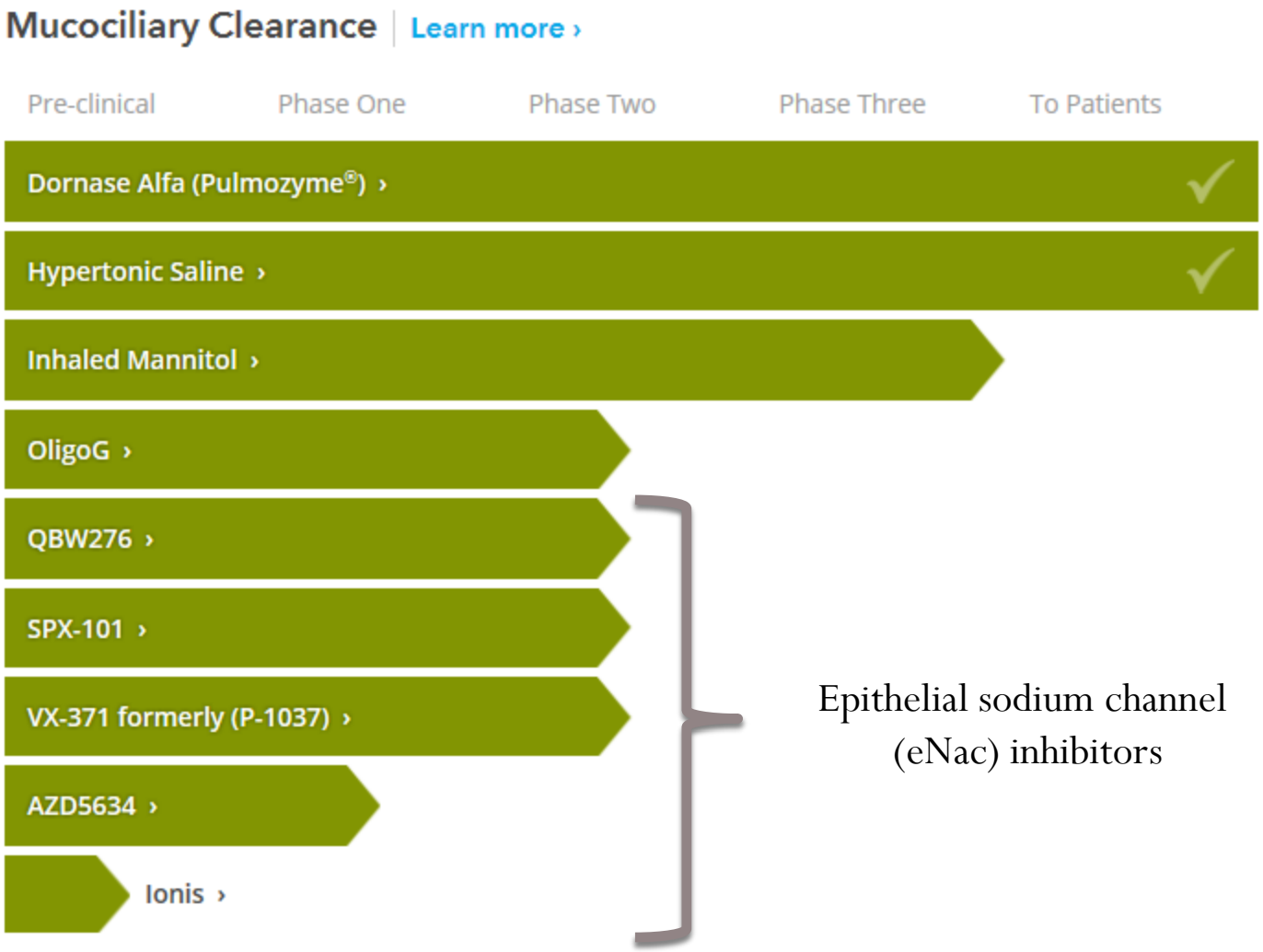
Antimicrobials

Anti-Infective | Learn more ›

Pre-clinical | Phase One | Phase Two | Phase Three | To Patients

- Vancomycin Inhalation Powder (AeroVanc™) › — For treatment of MRSA
- Fosfomycin/Tobramycin Inhalation Solution (FTI) › — Equivalence to nebulised aztreonam in phase 2 studies
- Gallium (IV) ›
- Nitric Oxide (Inhaled) ›
- ALX-009 › — Combination of hypothiocyanite and lactoferrin
- Gallium (Inhaled) ›

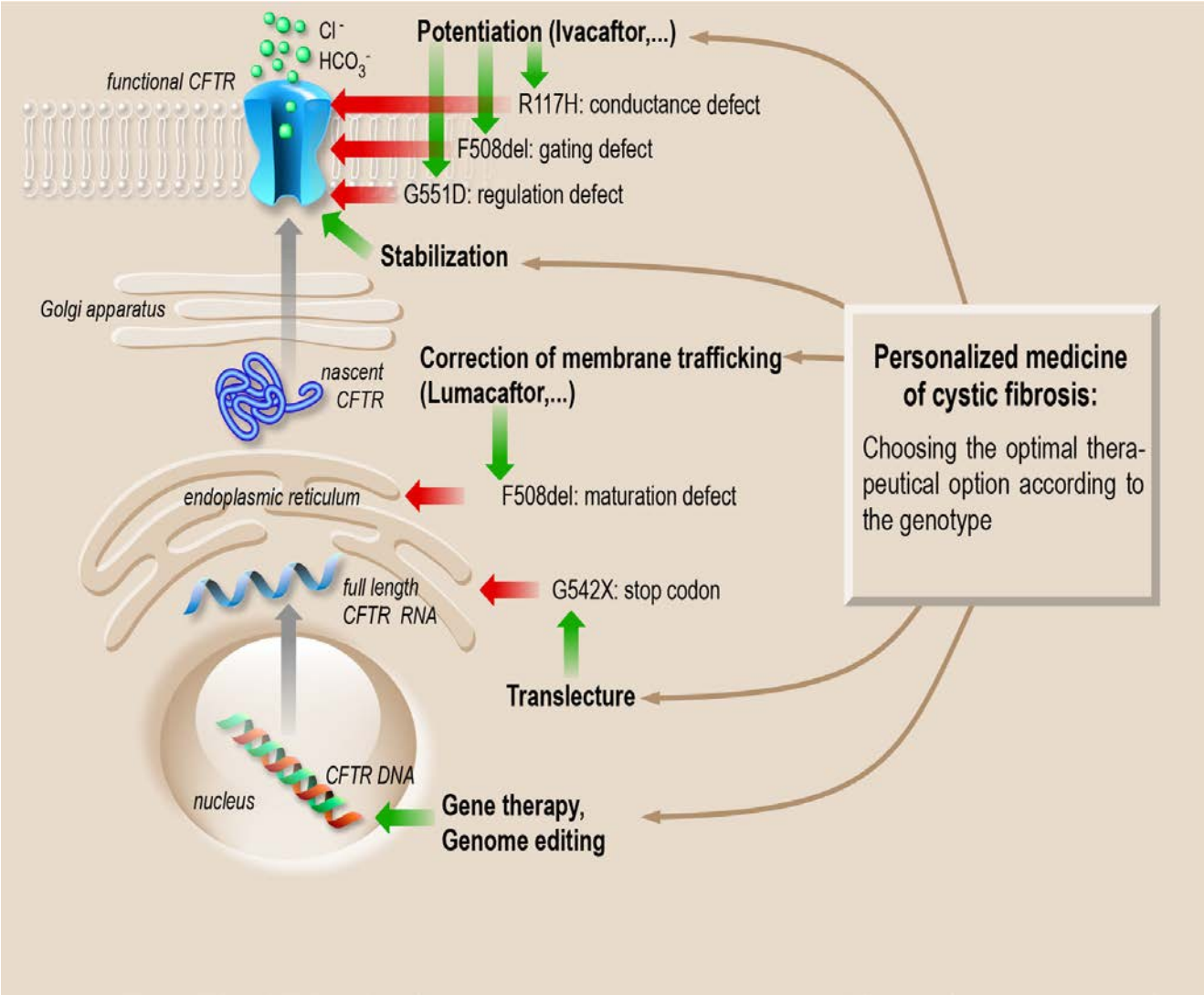
Mucociliary clearance



Anti-inflammatory

Anti-Inflammatory | Learn more ›

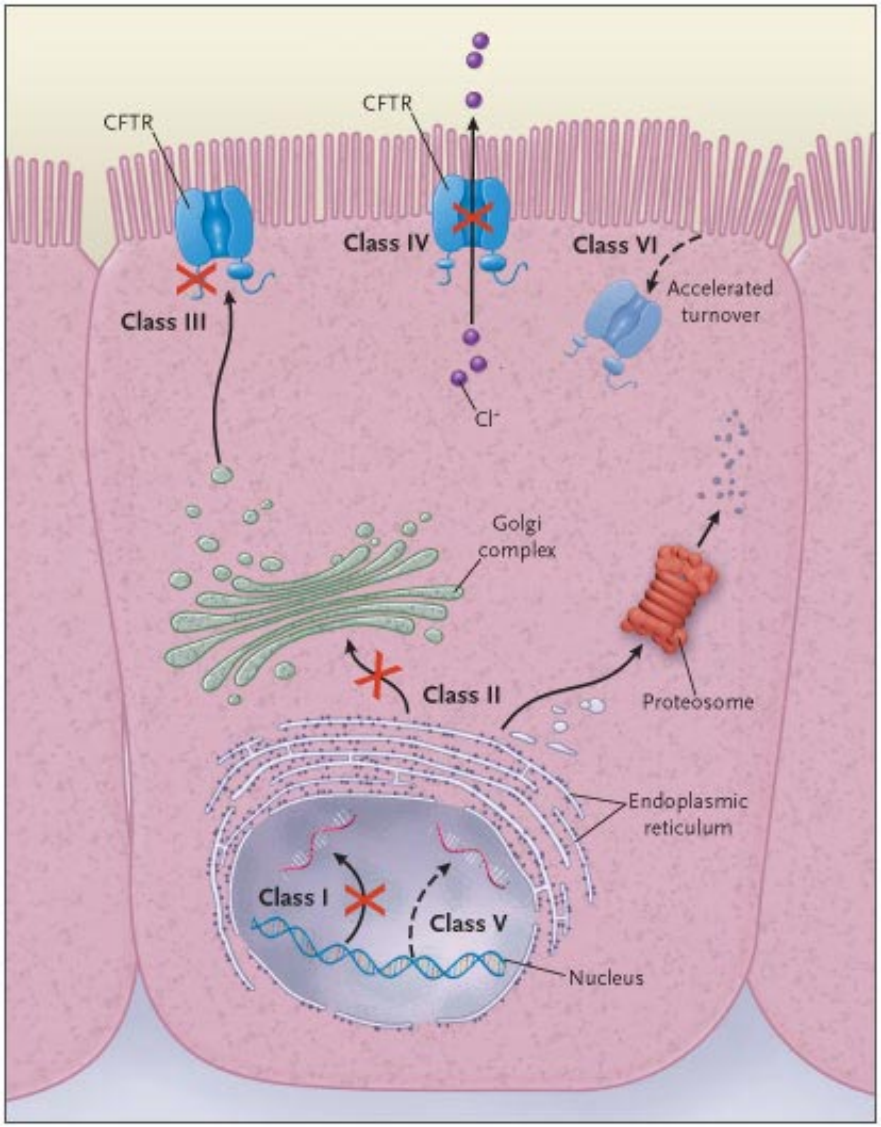
Pre-clinical	Phase One	Phase Two	Phase Three	To Patients	
Anabasum (JBT-101) ›					Enhances resolution of inflammation
Acebilustat (CTX-4430) ›					Reduces sputum neutrophil elastase and serum CRP
LAU-7b ›					Enhances resolution of inflammation
POL6014 ›					Inhaled neutrophil elastase inhibitor



https://news.cnrs.fr/articles/new-strategies-to-fight-cystic-fibrosis

OVER 2,000
DIFFERENT
MUTATIONS
OF THE
CF
GENE

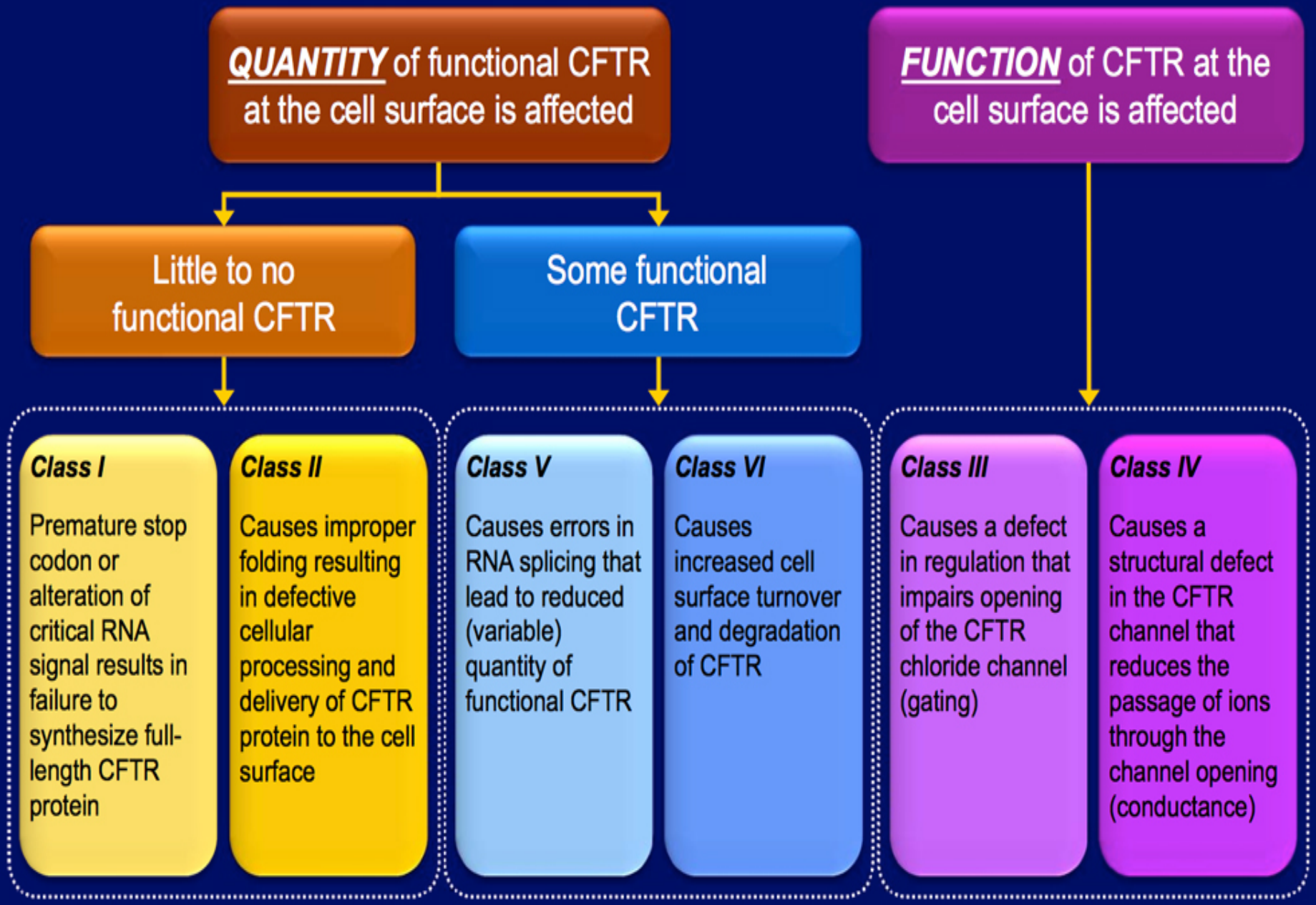
Classes of CFTR Mutation



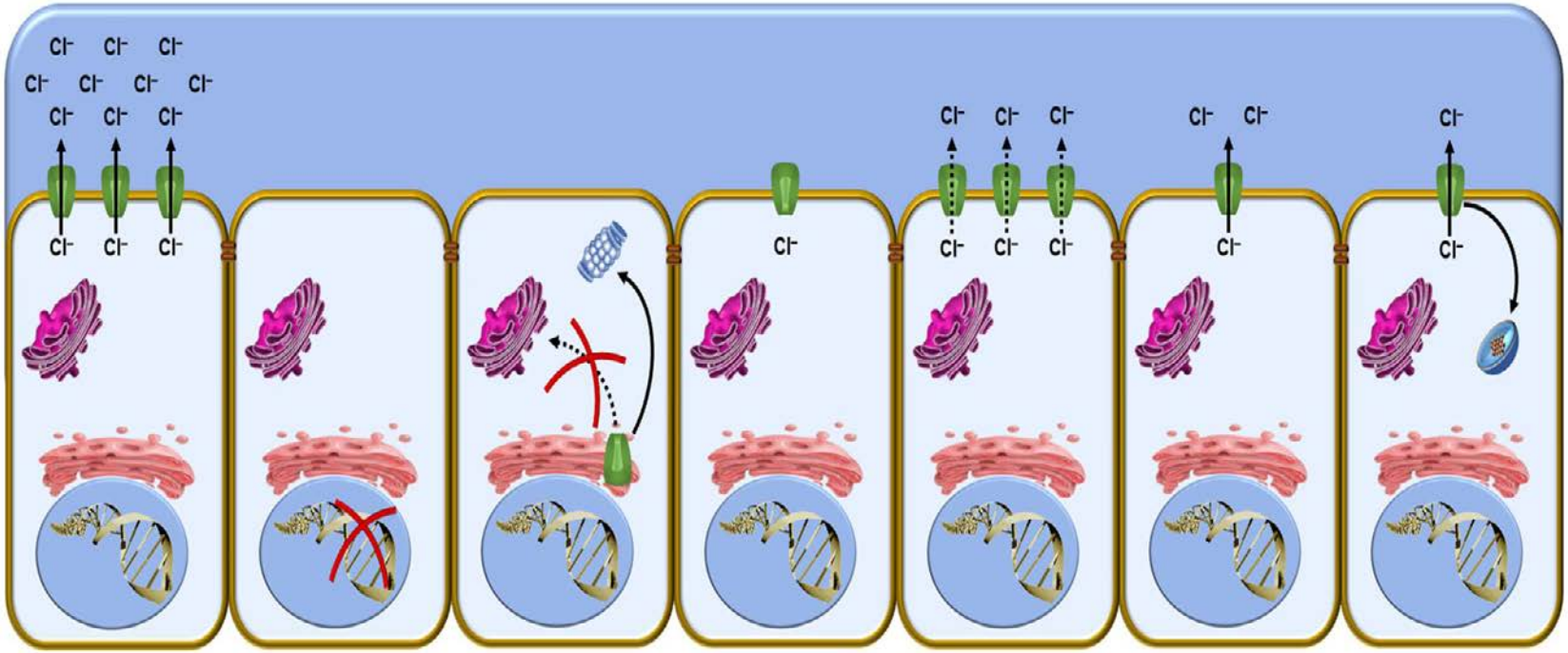
>2000 mutations identified

Class I	Defective synthesis
Class II	Defective processing
Class III	Defective regulation
Class IV	Defective conductance
Class V	Reduced quantity
Class VI	Increased turnover

Rowe SM et al., *NEJM* 2005

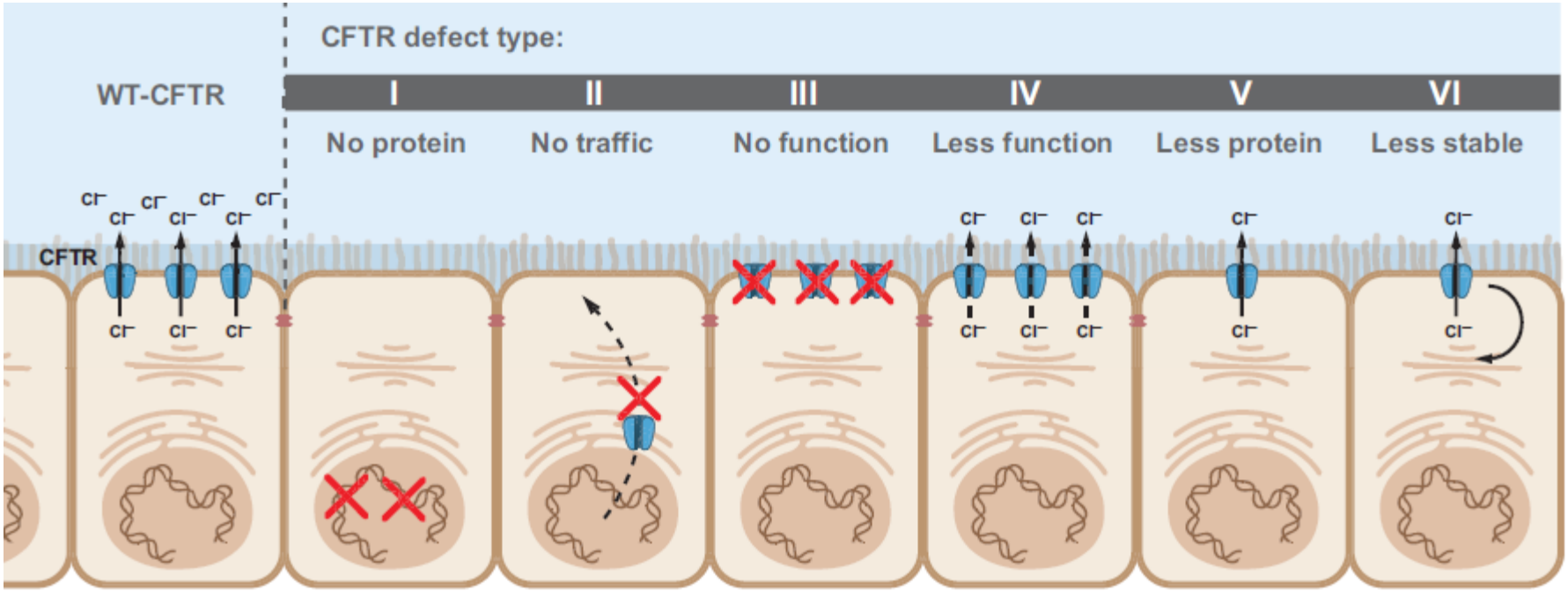


Rowe SM, Miller S, Sorscher EJ. *N Engl J Med*. 2005;352:1992-2001.
Welsh MJ, Smith AE. *Cell*. 1993;73:1251-1254.
Zielenski J. *Respiration*. 2000;67:117-133.



	wt-CFTR	I	II	III	IV	V	VI
Defect types		**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples		G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability

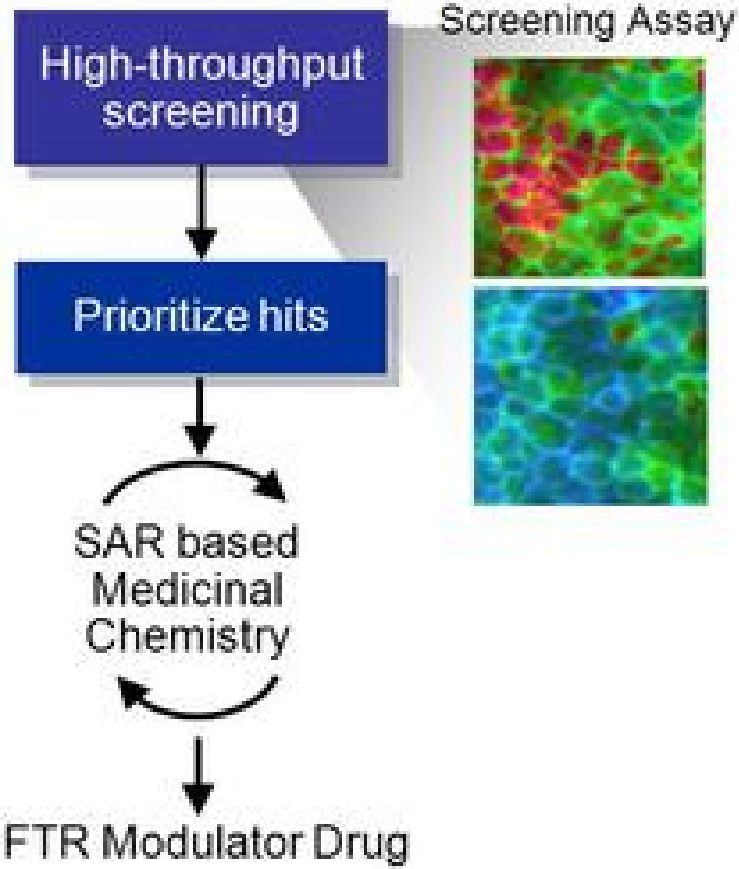
Frontiers in Pharmacology, Sep 2016



	I	II	III	IV	V	VI
Mutation examples	G542X (a) W1282X (a) 1717-1G (b)	F508del N1303K A561E	G551D S549R G1349D	R117H R334W A455E	A455E 3272-26A>G 3849+10 kb C>T	c.120del23 rF508del
Corrective therapy	Rescue synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability
Drug	Read-through compounds	Correctors	Potentiators	Potentiators	AONs Correctors Potentiators	Stabilizers

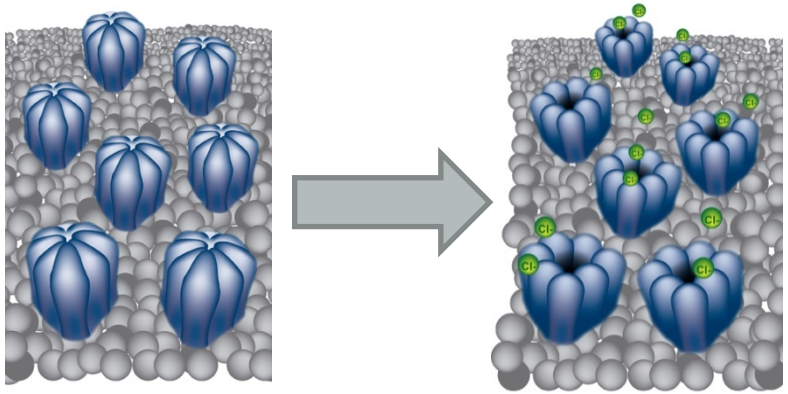
High-Throughput Screening Speeding Up CF Drug Discovery

>10,000 Primary assays/day



Courtesy of Vertex Pharmaceuticals

CFTR Modulators: Different Mechanisms of Action

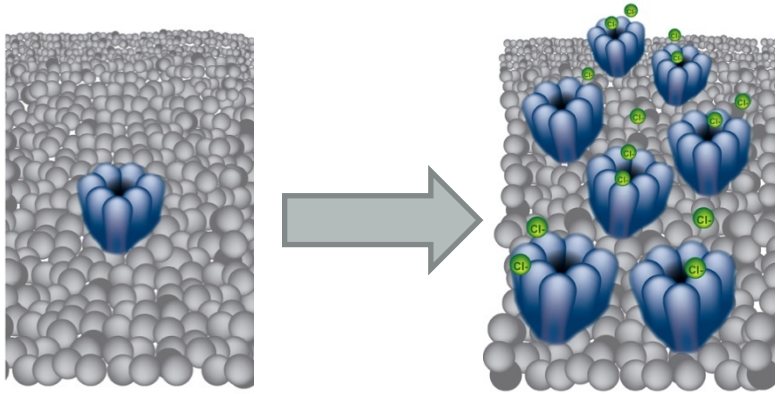


(e.g., G551D)

CFTR Potentiators

Increase chloride transport by potentiating the channel-open probability (or gating) of CFTR protein at the cell surface

e.g., ivacaftor (VX-770)



(e.g., F508del)

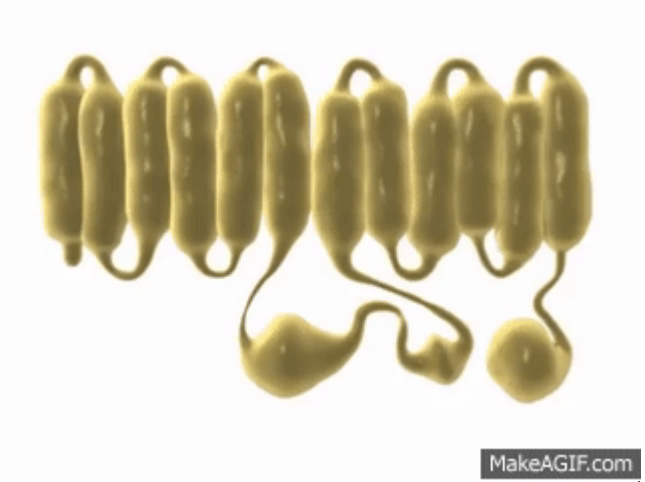
CFTR Correctors

Increase chloride transport by increasing the quantity of functional CFTR delivered to the cell surface

e.g., first generation (lumacaftor, tezacaftor); next generation (VX-440, VX-152, VX-659, VX-445)

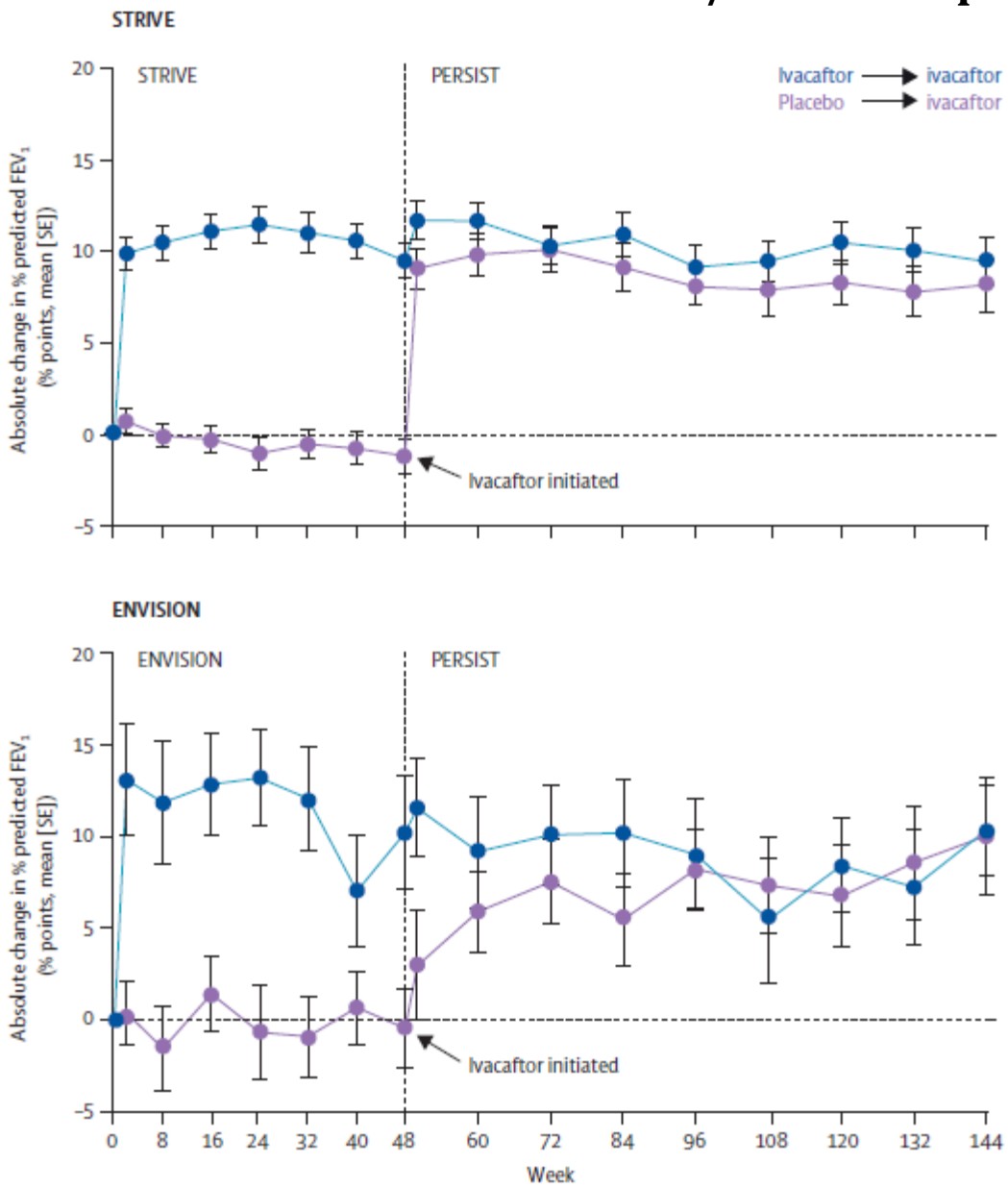
Restore CFTR Function | Learn more ›

	Pre-clinical	Phase One	Phase Two	Phase Three	To Patients	
Ivacaftor (Kalydeco®) ›						✓
Lumacaftor + ivacaftor (Orkambi®) ›						✓
Tezacaftor (VX-661) + ivacaftor ›						
CTP-656 (Deuterated ivacaftor) ›						potentiator
FDL169 ›						corrector
GLPG2222 ›						corrector
QBW251 ›						potentiator
Riociguat ›						enhances CFTR function
VX-152 + tezacaftor + ivacaftor ›						corrector
VX-440 + tezacaftor + ivacaftor ›						corrector
VX-445 + tezacaftor + ivacaftor ›						corrector
VX-659 + tezacaftor + ivacaftor ›						corrector
PTI-428 ›						amplifier
PTI-801 ›						corrector
QR-010 ›						repairs CFTR mRNA

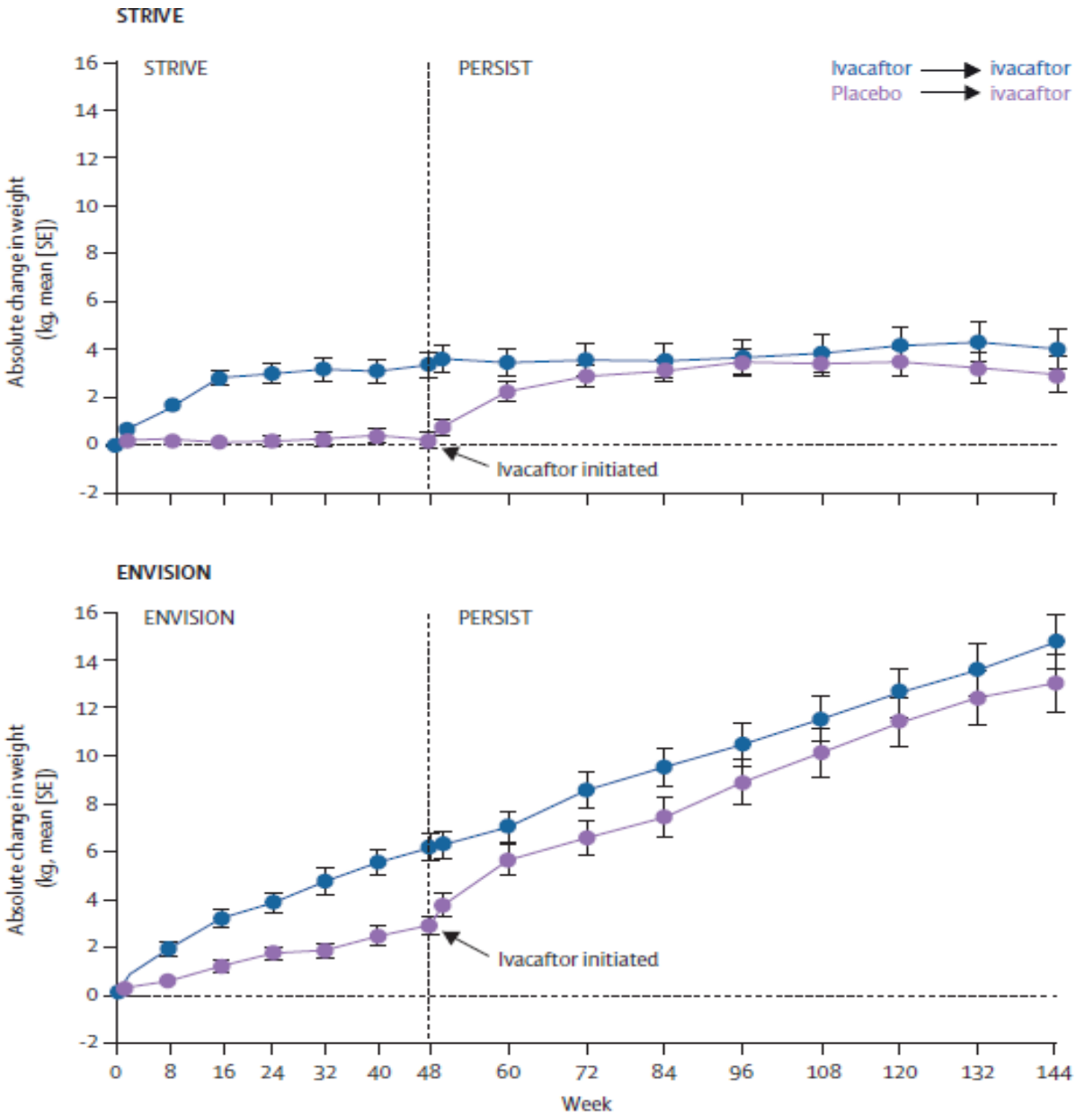


CFTR modulator development pipeline

Ivacaftor vs Placebo / G551D CF patients

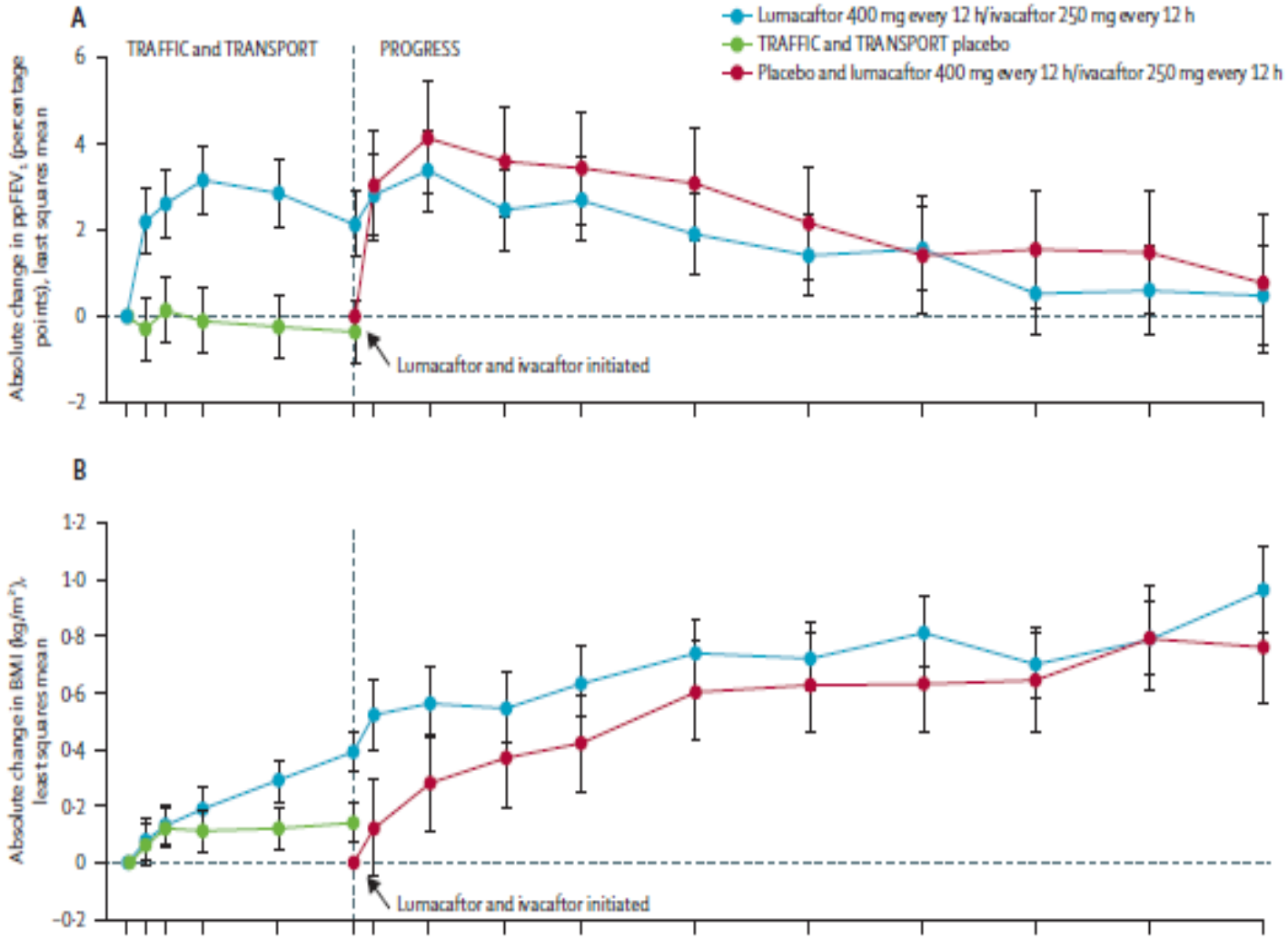


Lancet Respiratory Medicine 2014



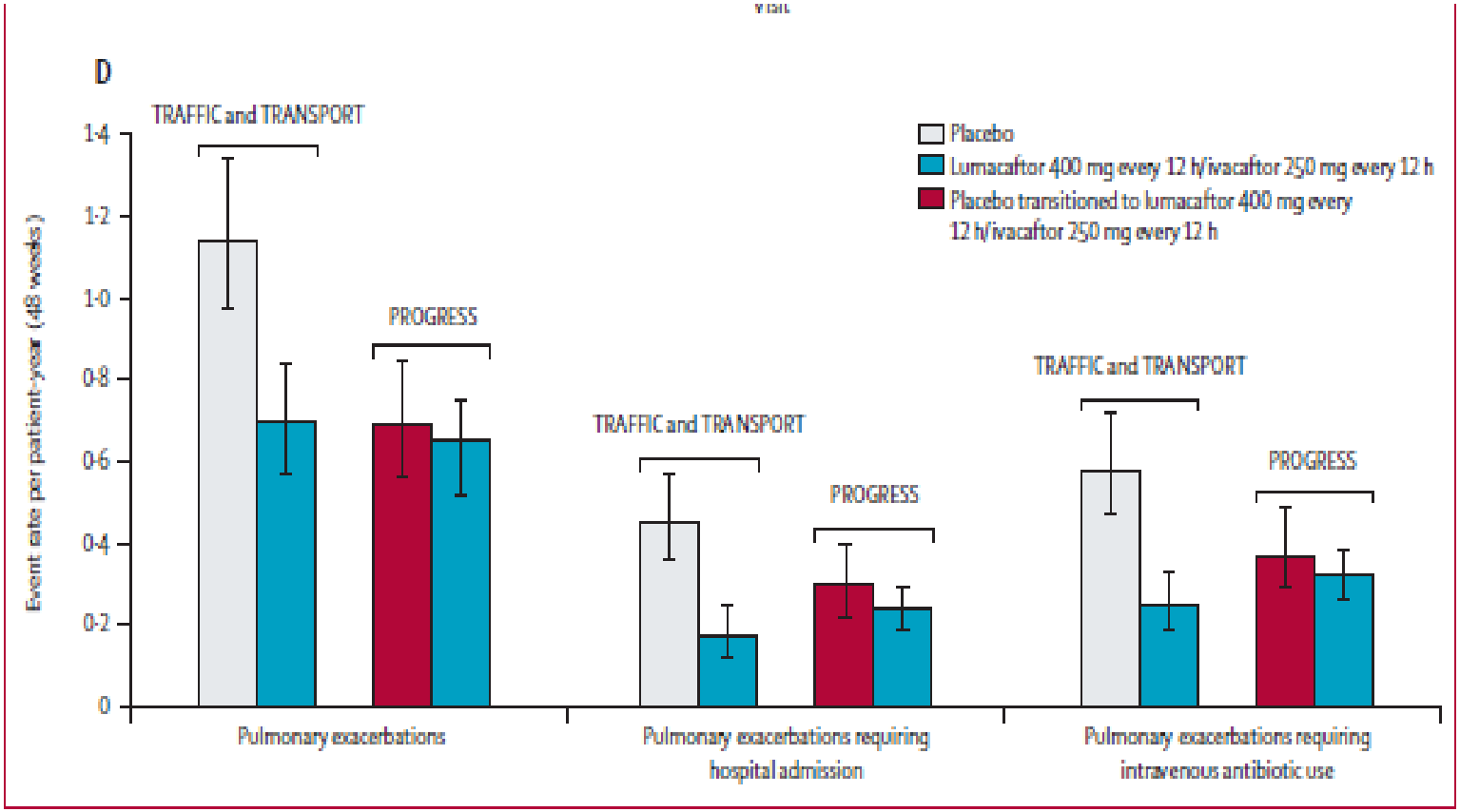
Lancet Respiratory Medicine 2014

Lumacaftor / Ivacaftor in delF508 Homozygous CF patients



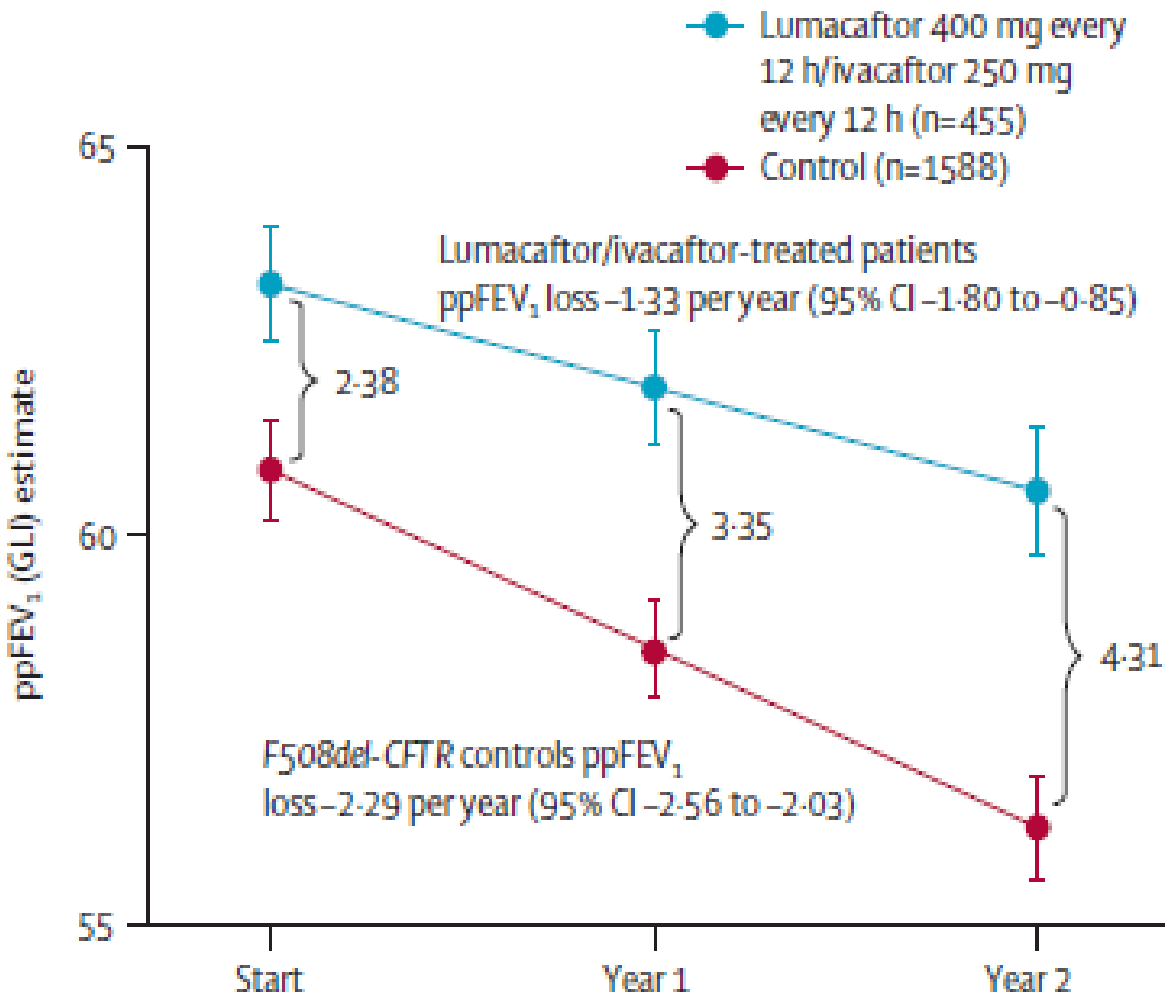
Lancet Respir Medicine 2016

Lumacaftor / Ivacaftor in delF508 Homozygous CF patients



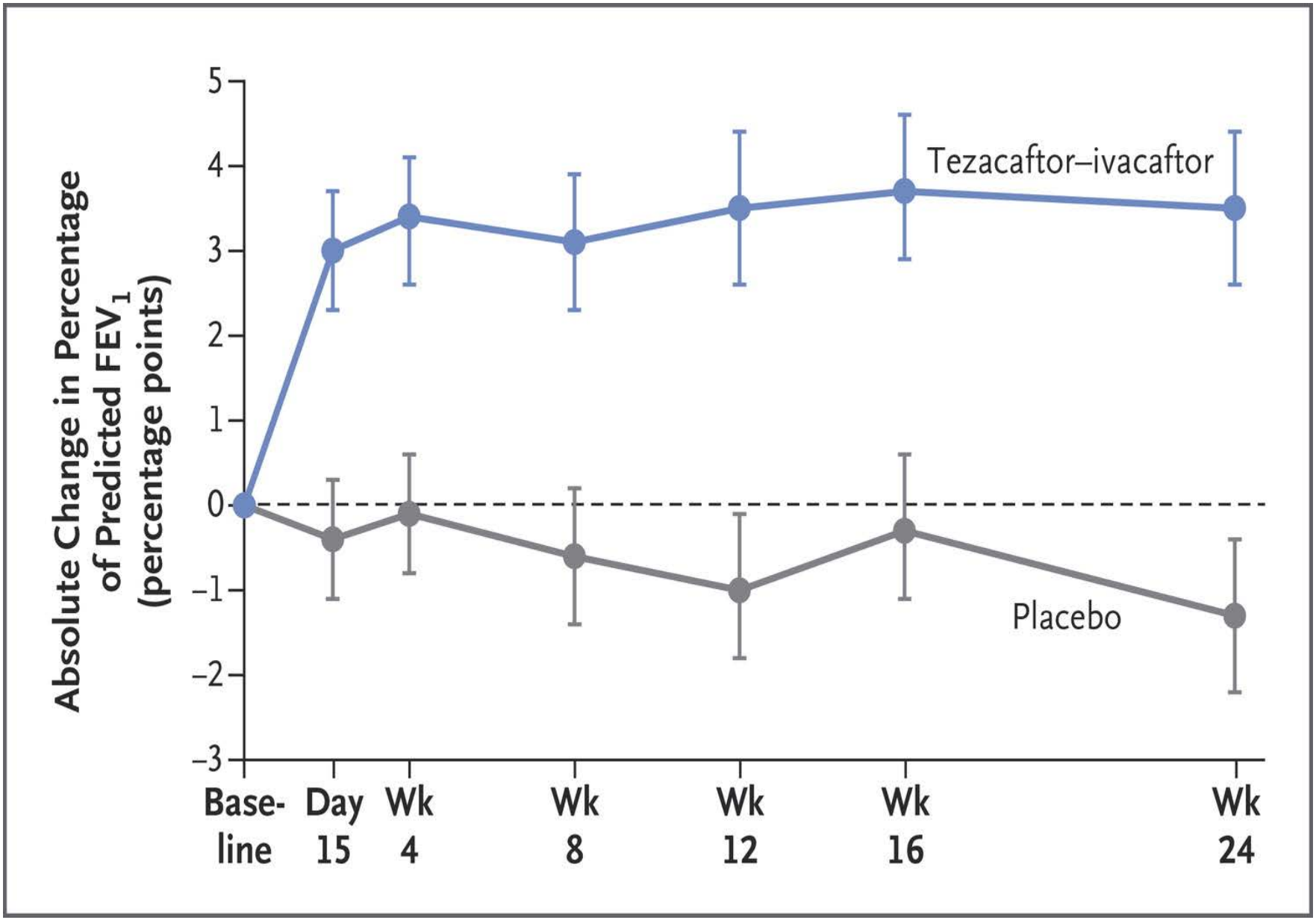
Lancet Respiratory Medicine 2016

Lumacaftor /Ivacaftor in delF508 Homozygous CF patients

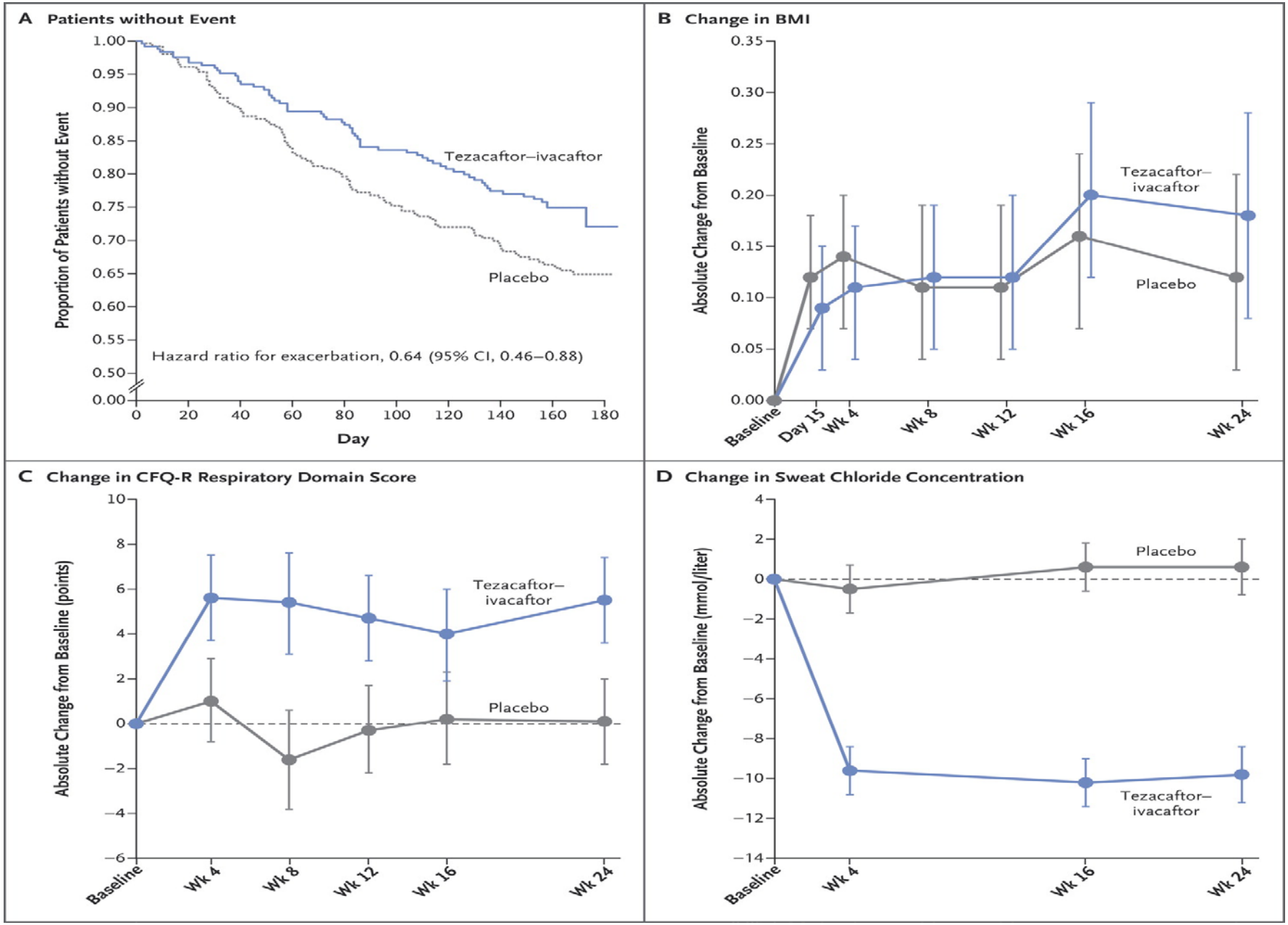


Lancet Respiratory Medicine 2016

Tezacaftor Ivacaftor in delF508 Homozygous CF patients

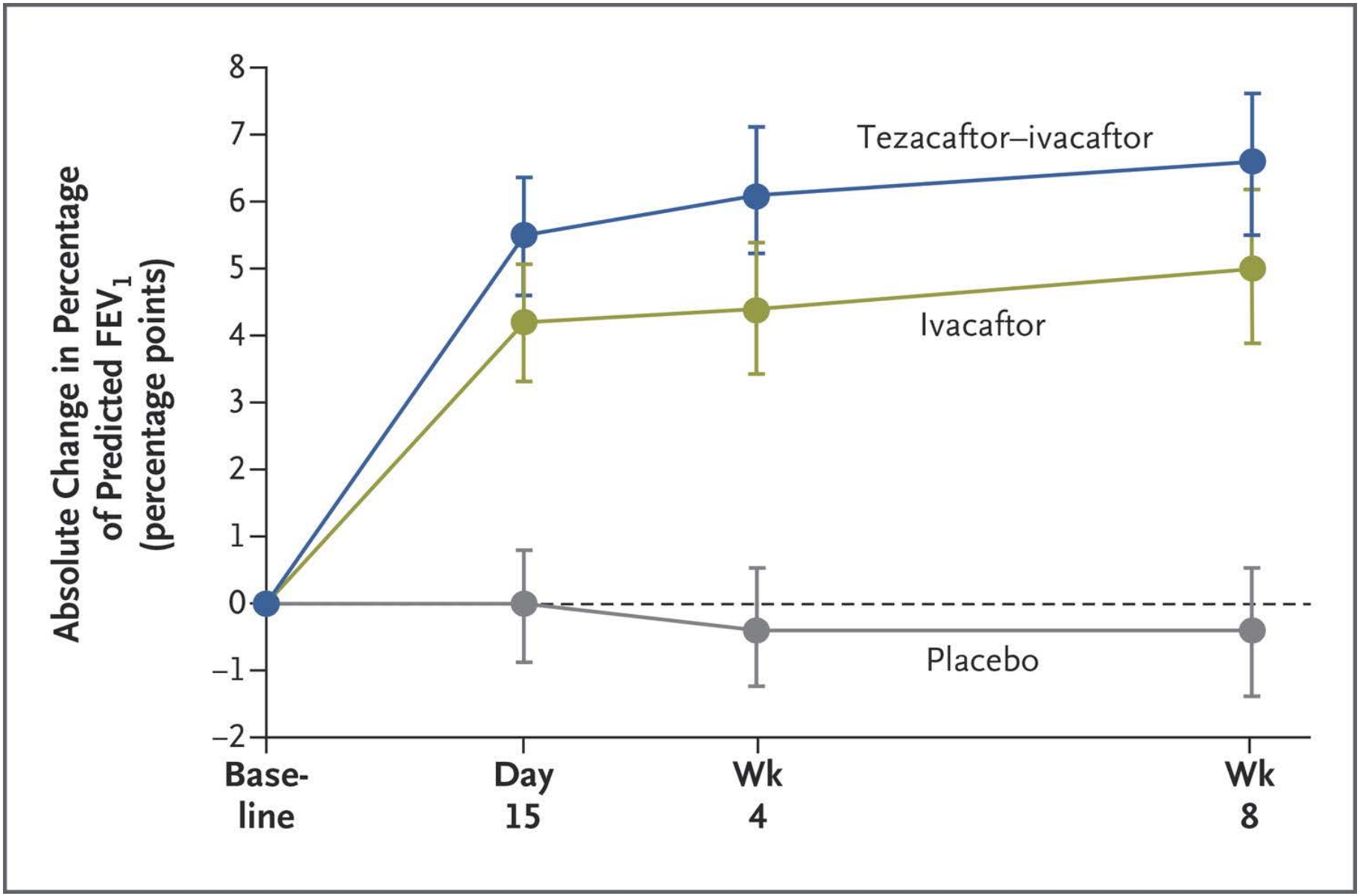


N Engl J of Medicine, Nov 3, 2017



N Engl J of Medicine, Nov 3, 2017

Tezacaftor / Ivacaftor vs Ivacaftor vs Placebo in delF508 /RF CF patients

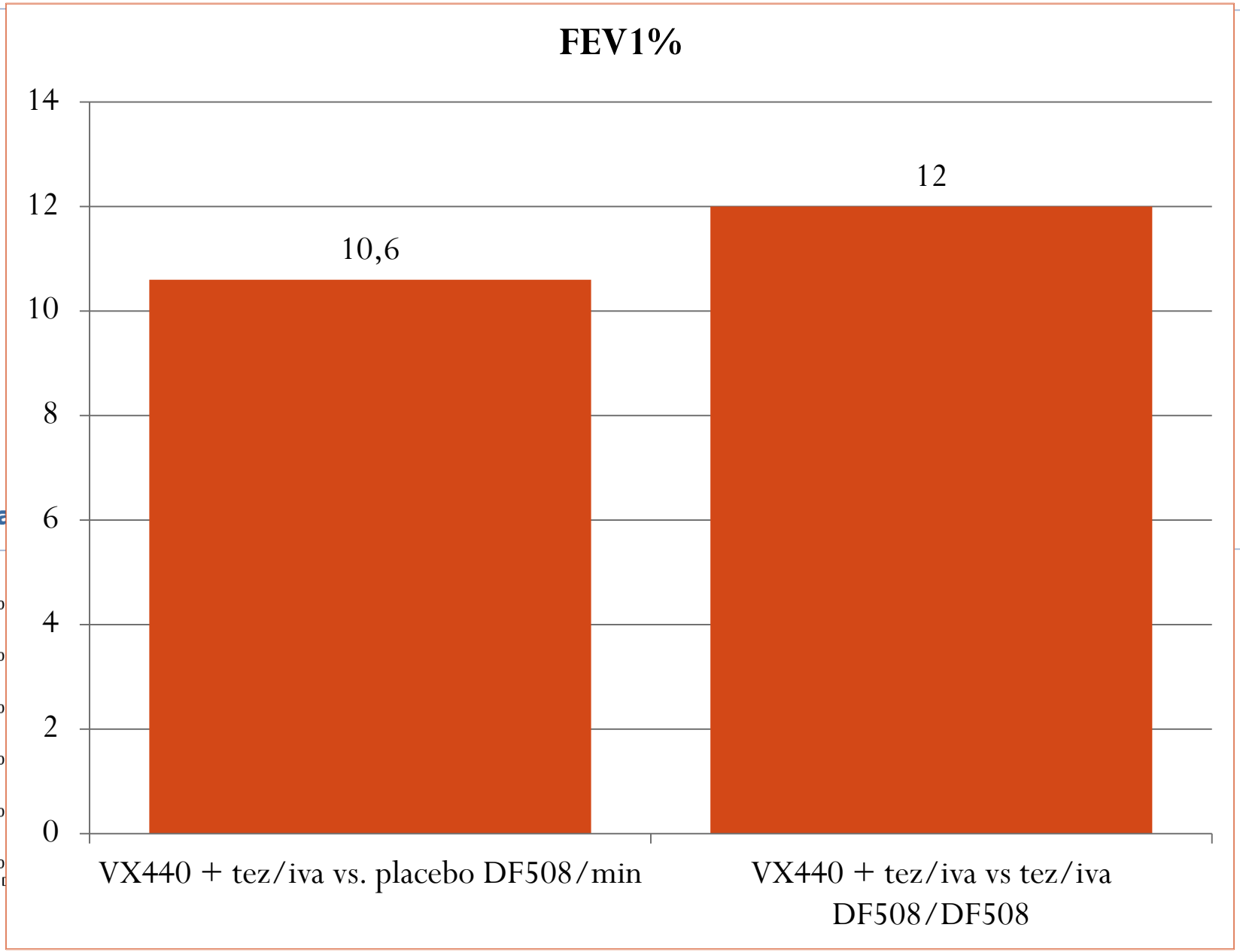


N Engl J of Medicine, Nov 3, 2017

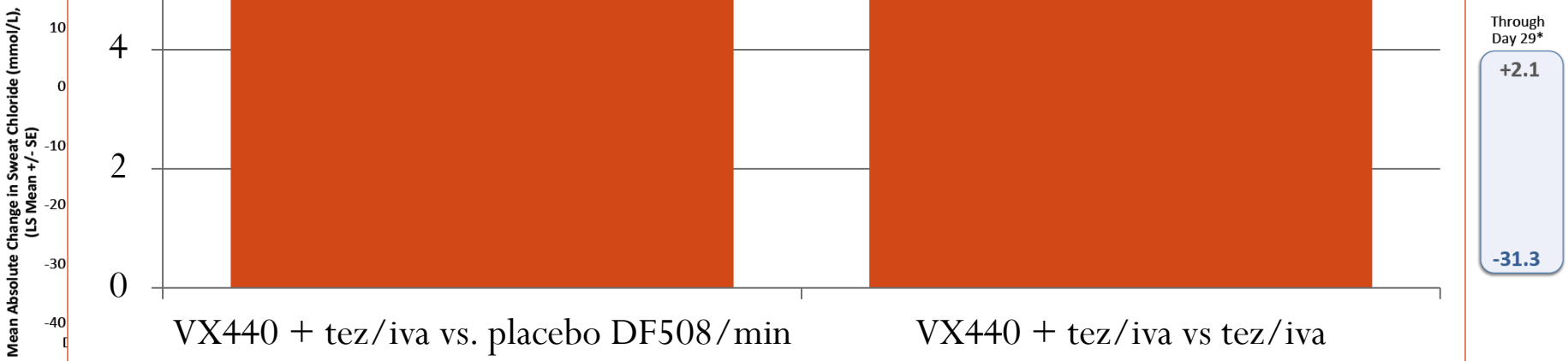
Second generation correctors/combinations

- ~10% increase in absolute predicted FEV_1
  - Same as ivacaftor in G551D
- Significant sweat chloride reductions
- Phase 2 studies to determine optimum combinations

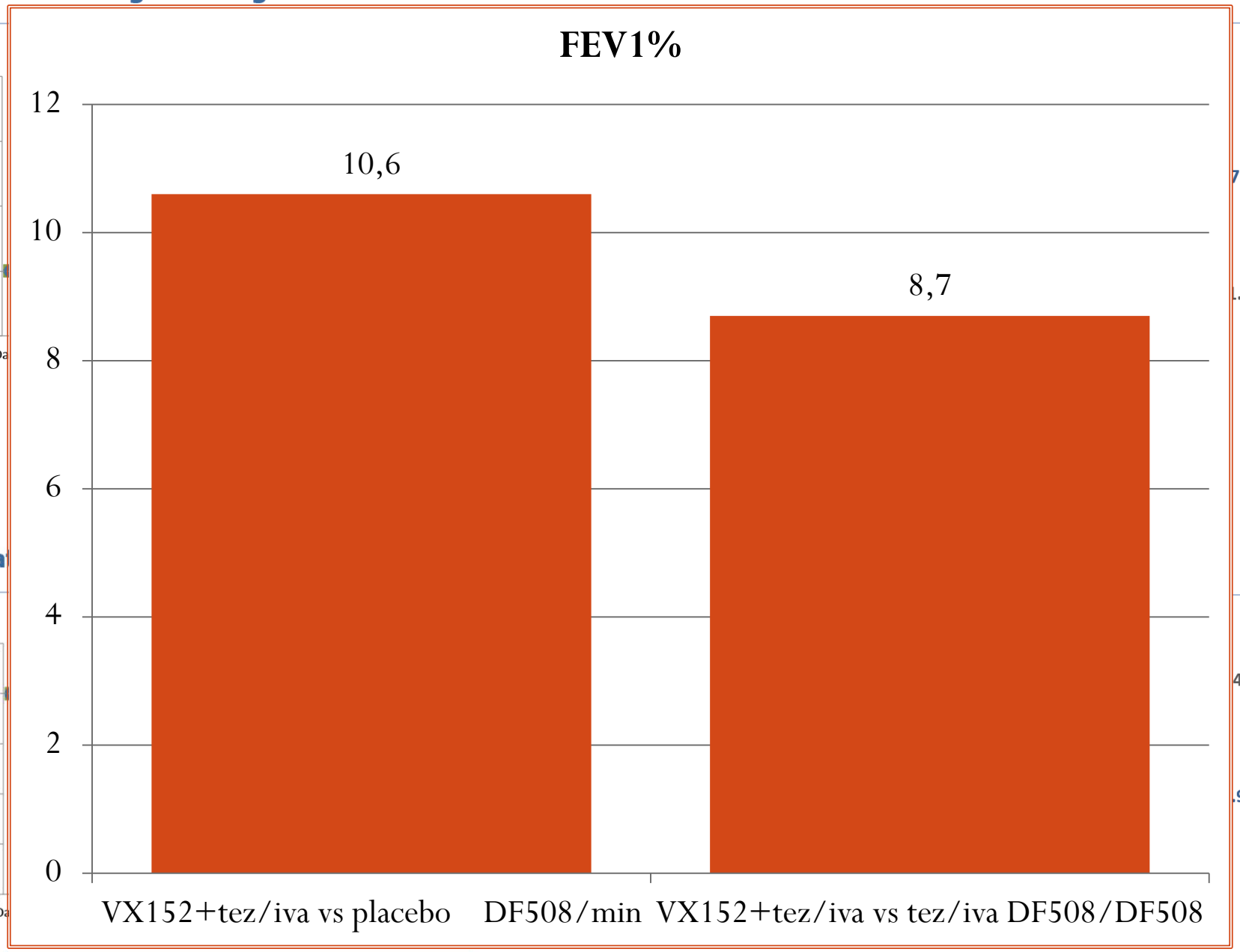
Absolute Change in Lung Function Over Time



Swea



Absolute Change in Lung Function Over Time



Mean Absolute Change in ppFEV$_1$ (Mean +/- SE) (Percentage Points)

15 10 5 0 -5

Placebo | VX-152 100 mg + TEZ/IVA | VX-152 200 mg + TEZ/IVA

TEZ/IVA | VX-152 200 mg + TEZ/IVA

7.3

1.4

4

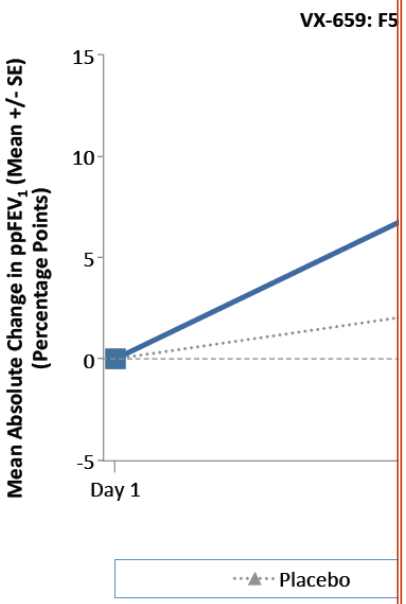
.9

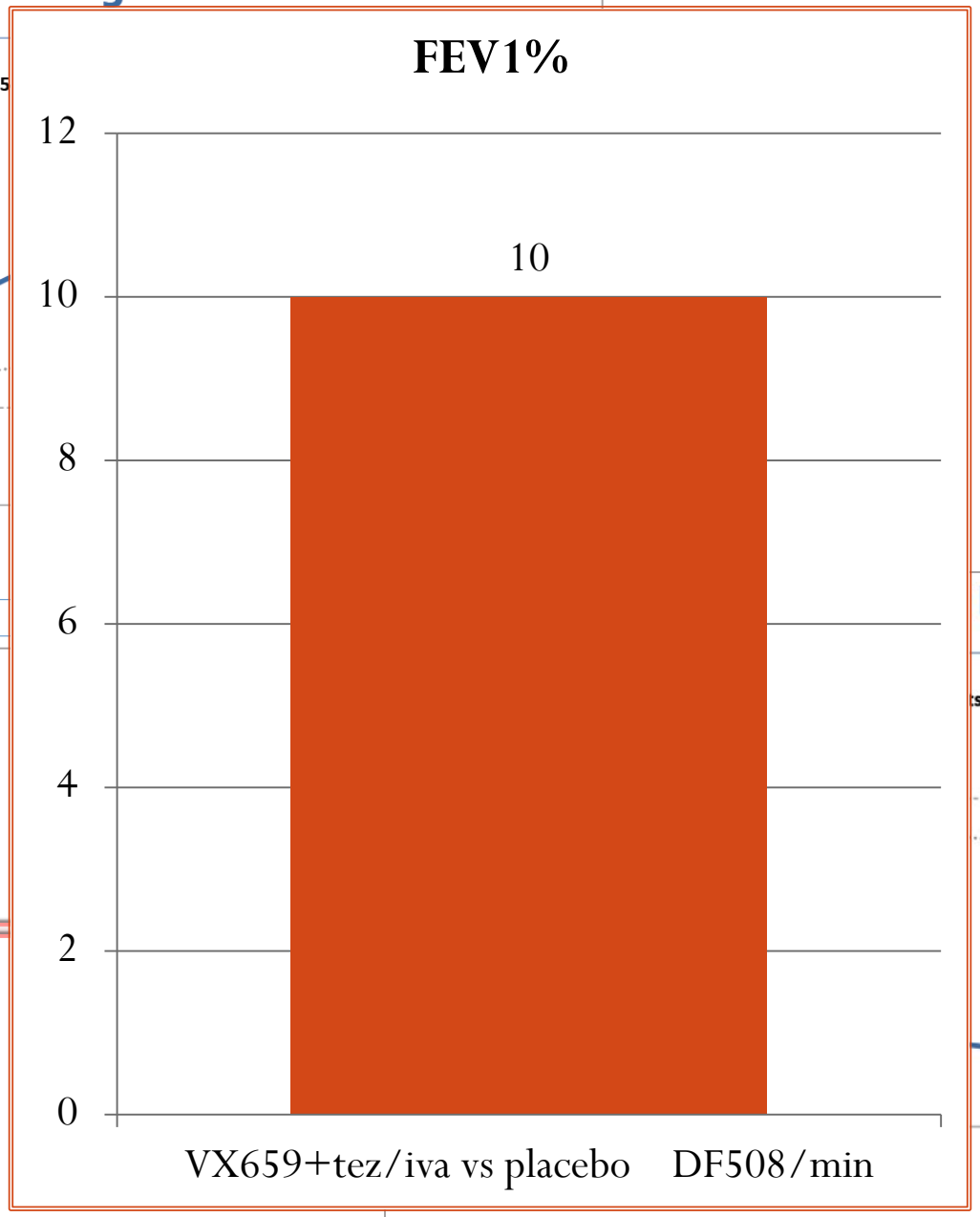
Swea

Mean Absolute Change in Sweat Chloride (mmol/L), (Mean +/- SE)

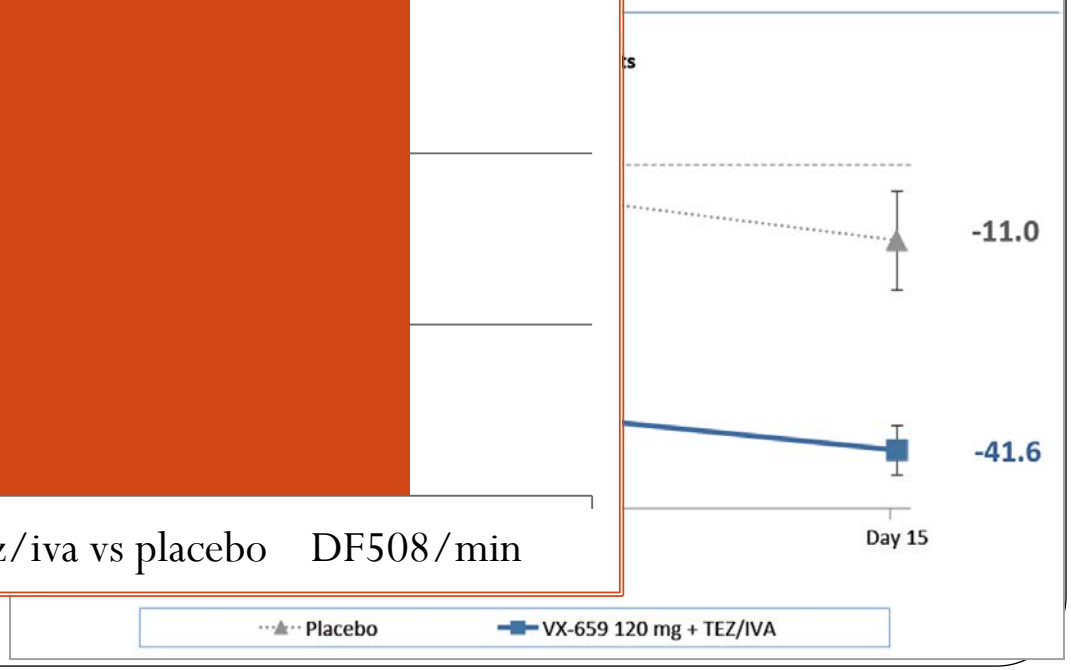
10 0 -10 -20 -30 -40

Absolute Change in Lung Function Over Time





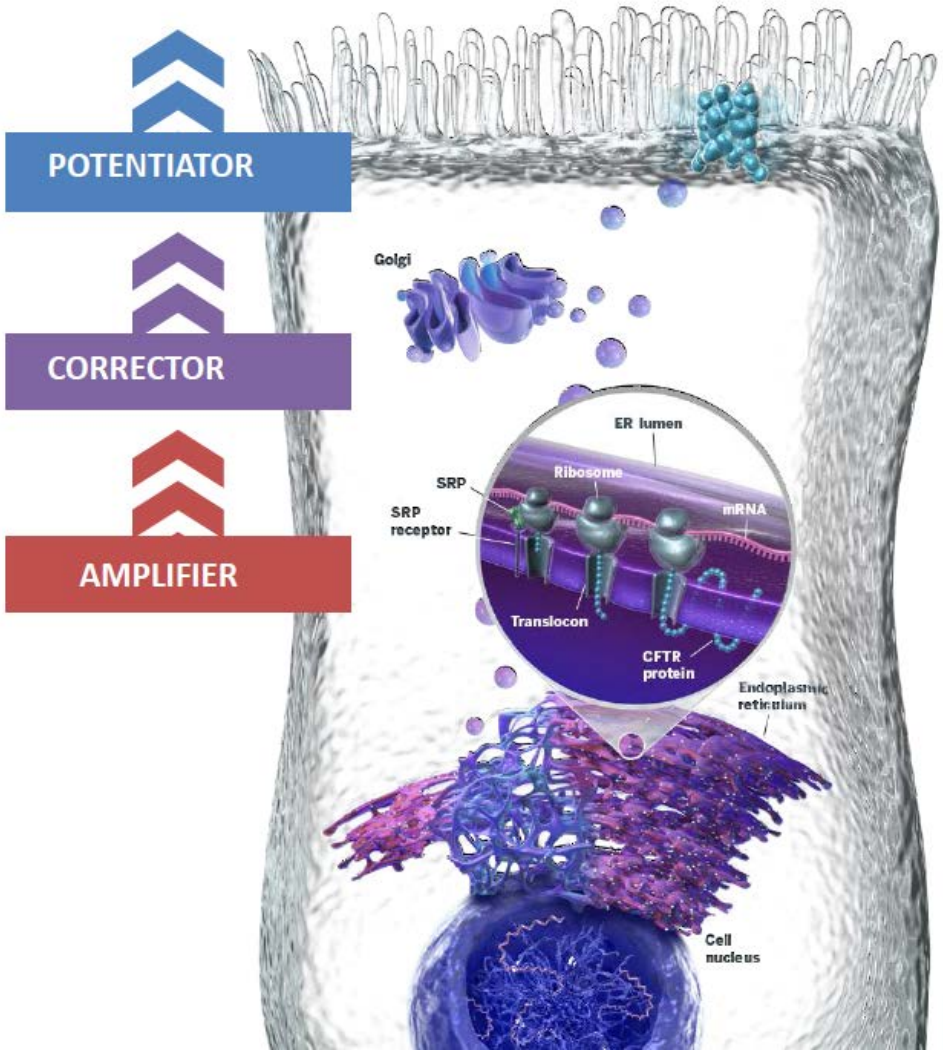
Reduced



VX-

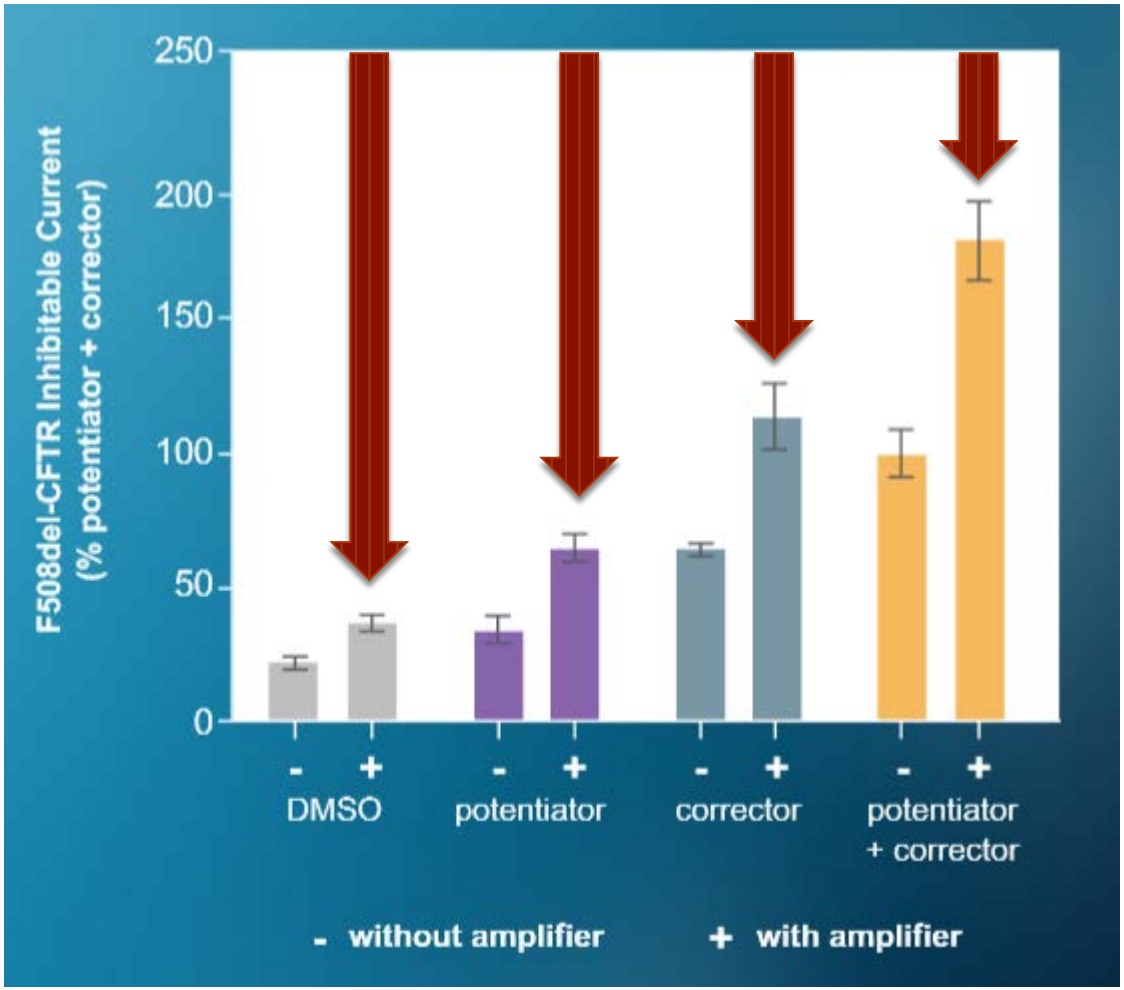
CFTR amplifier

- Proteostasis, PTI-428
- Novel class of action
- Increases amount of CFTR protein substrate

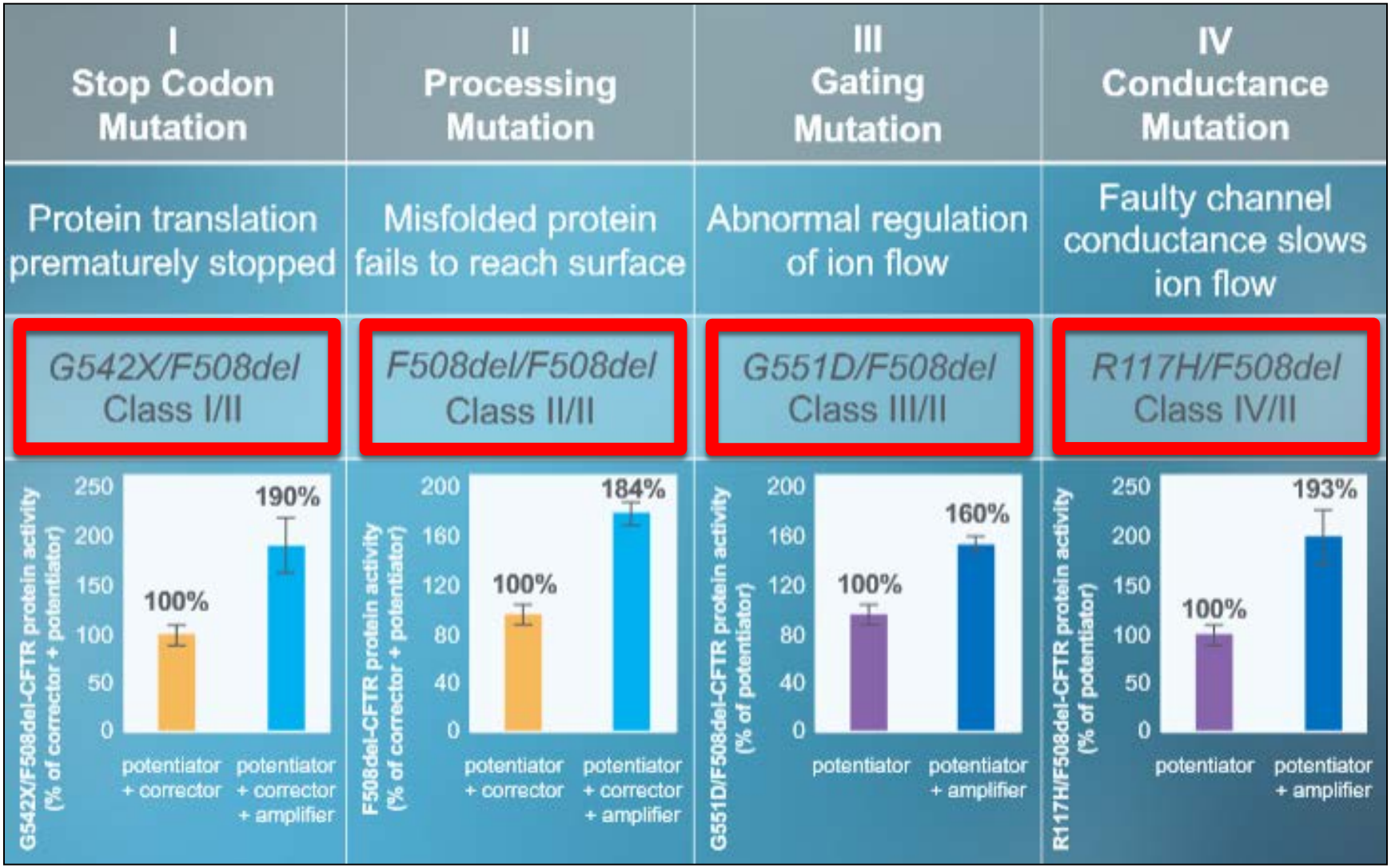


CFTR amplifier

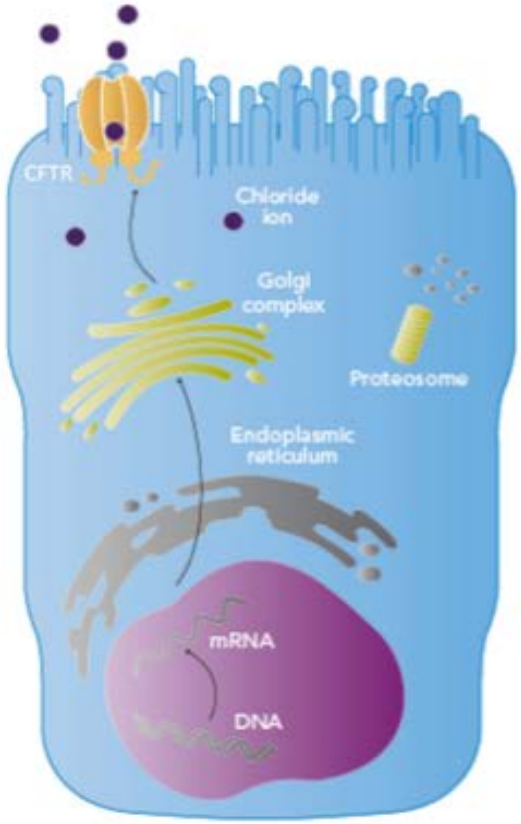
- Works in addition to other modulators
- Part of Proteostasis pipeline



Amplifier works across all classes of defect



Biological Understanding of CF Provides Path to Develop Medicines for All Patients



Adapted from Lukacs GL, et al. *N Engl J Med.* 2003;349:1401-04.

Biological Problem	Therapeutic Approach
Defective CFTR Function	**Potentiator** kalydeco (ivacaftor)
Defective CFTR Protein Trafficking and Folding	**Correctors** ORKAMBI (lumacaftor/ivacaftor) tezacaftor (VX-661) VX-440 VX-152 VX-659
Defective Protein Synthesis	**Genetic Approaches** Gene Editing (CRISPR) mRNA (Moderna) Gene Therapy

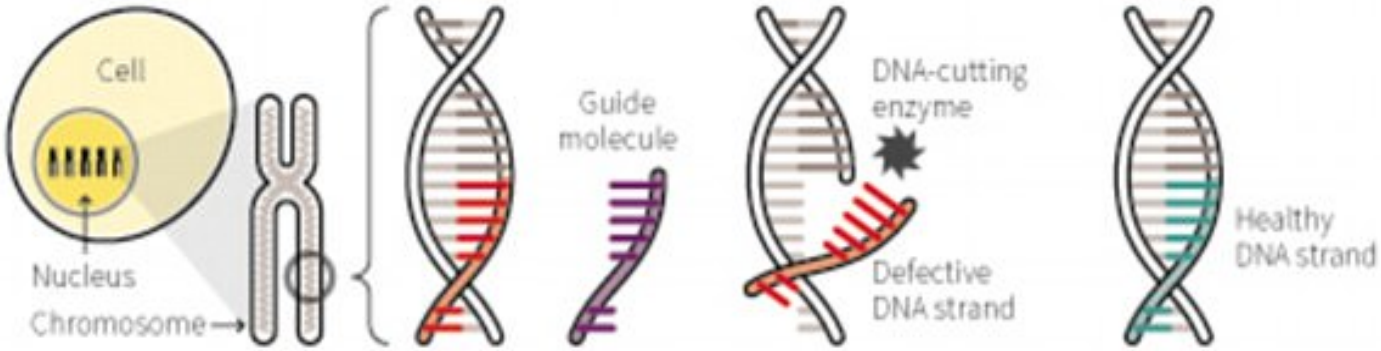
Market Realist

Source: Vertex Pharmaceuticals Investor Presentation

DNA editing

A DNA editing technique, called CRISPR/Cas9, works like a biological version of a word-processing programme's "find and replace" function.

HOW THE TECHNIQUE WORKS



A cell is transfected with an enzyme complex containing:

- Guide molecule
- Healthy DNA copy
- DNA-cutting enzyme

A specially designed synthetic guide molecule finds the target DNA strand.

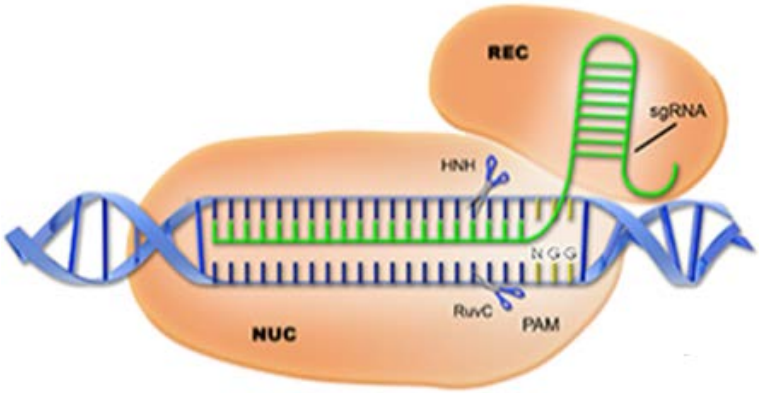
An enzyme cuts off the target DNA strand.

The defective DNA strand is replaced with a healthy copy.

Sources: Reuters; Nature; Massachusetts Institute of Technology

REUTERS

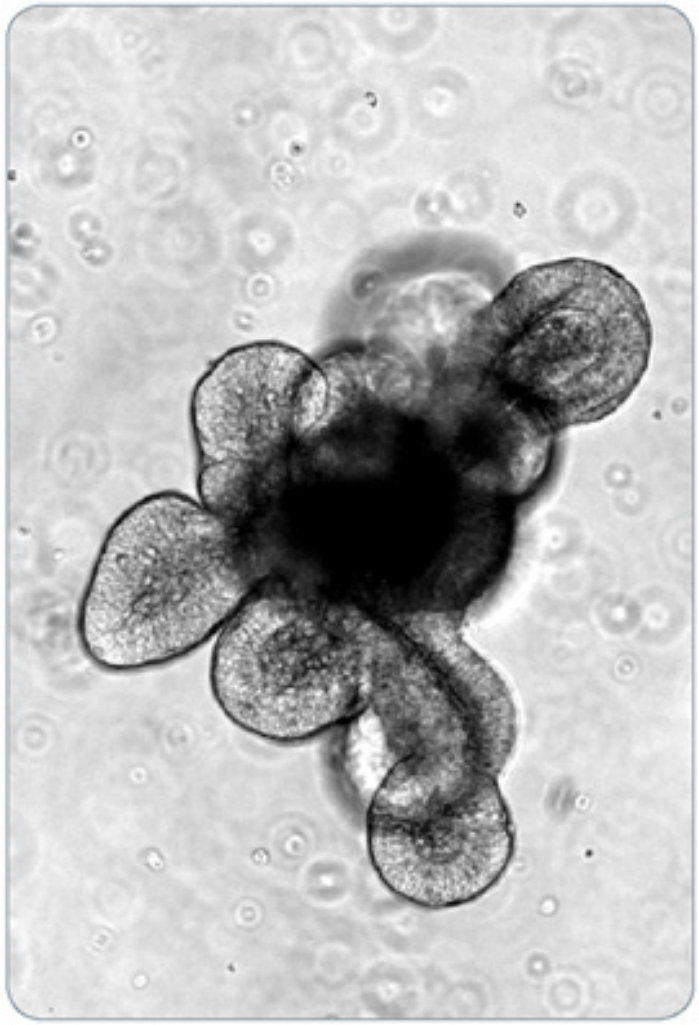
Gene editing

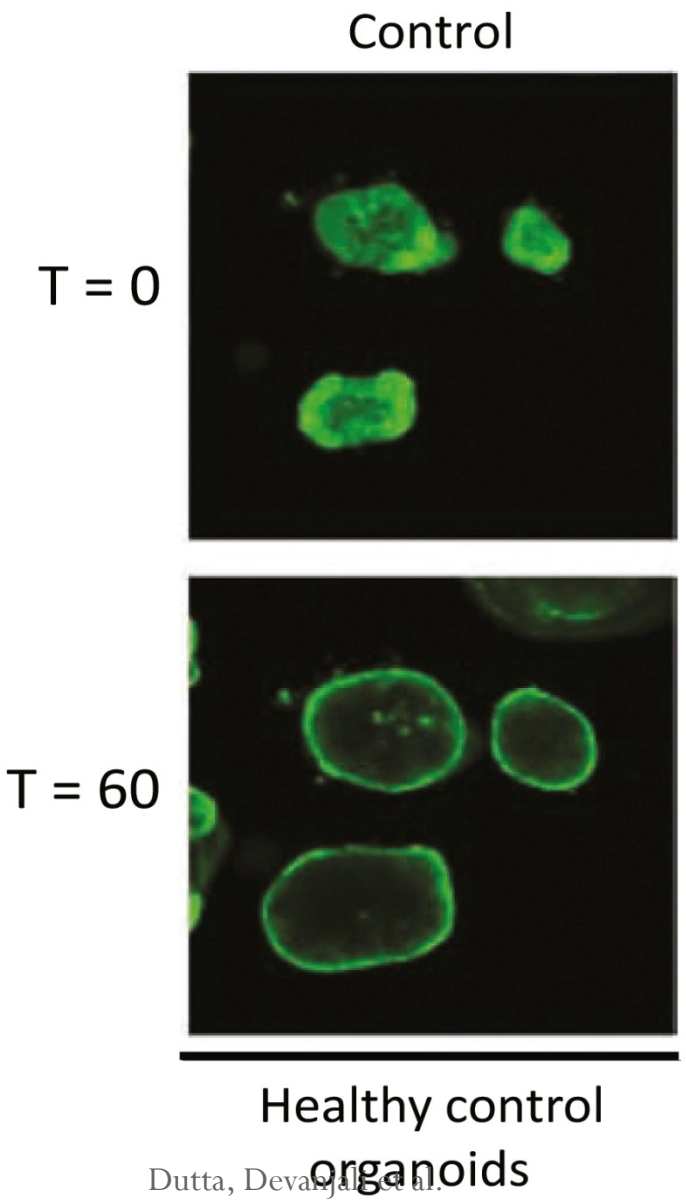


- Allows precise modification of genes
- Early in vivo data promising
- Barriers
  - Delivery in vivo
  - “Off target effects”
  - Ethical considerations

Organoids

- 3D cell culture retaining some functions of the organ of origin
- Intestinal organoids derived from rectal biopsies
- Swell in the presence of forskolin if CFTR functioning

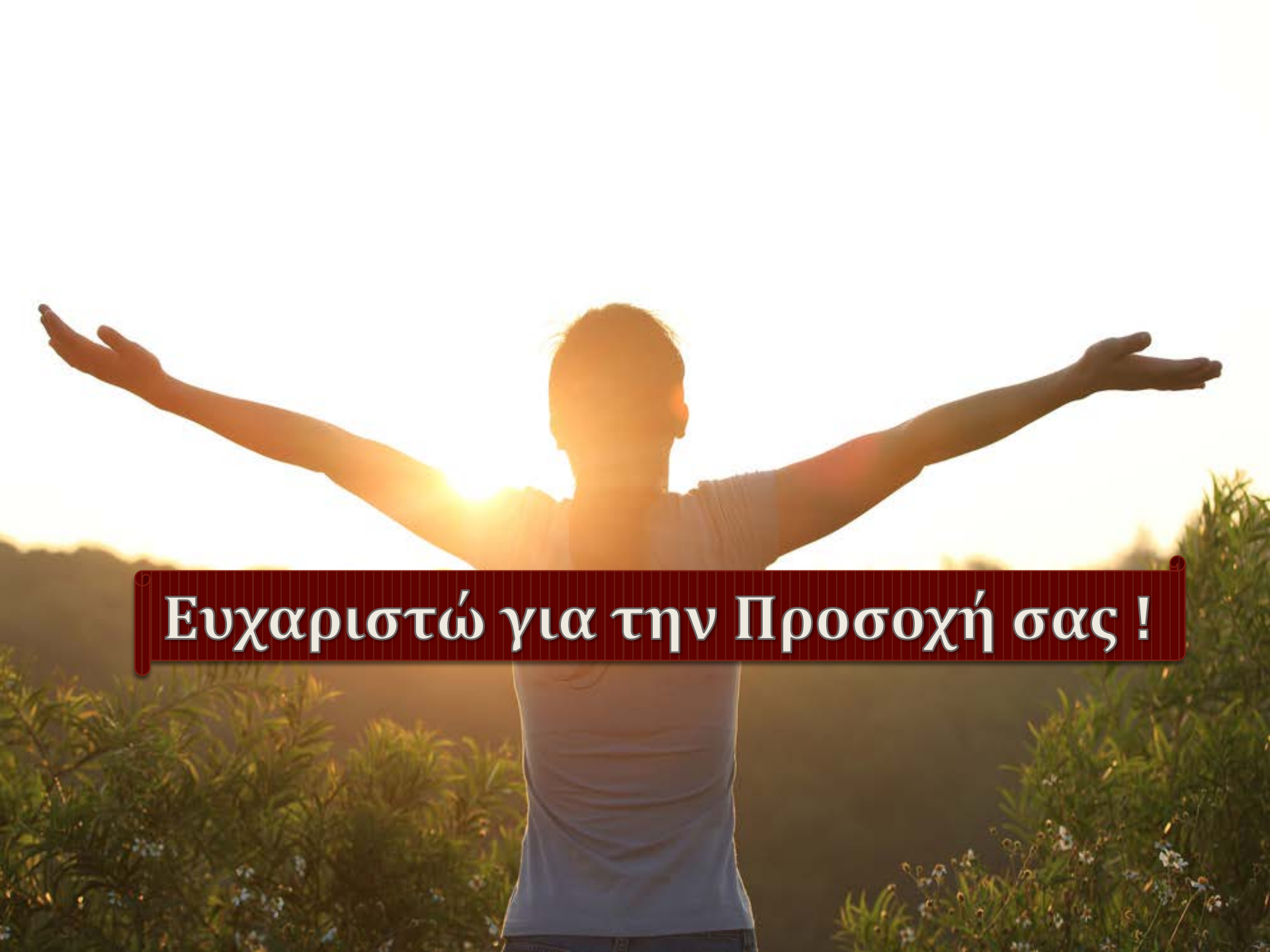




Dutta, Devanjali et al.
Trends in Molecular Medicine , Volume 23 , Issue 5 , 393 - 410

Συμπερασματικά…

- Πολλά νέα φάρμακα που αφορούν την συμπτωματική θεραπεία της νόσου βρίσκονται σε προχωρημένη φάση κλινικών μελετών
- Έχει ανοίξει ο δρόμος της ΄΄εξατομικευμένης΄΄ θεραπείας της κυστικής ίνωσης (στόχος οι μεταλλάξεις του συγκεκριμένου ασθενούς)
- Ενθαρρυντικά δεδομένα στην γονιδιακή θεραπεία
- Νέες μέθοδοι για την αξιολόγηση της αποτελεσματικότητας των θεραπευτικών παρεμβάσεων



Ευχαριστώ για την Προσοχή σας !