Cystic Fibrosis in 2017

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MRC & Asthma UK Centre in Allergic Mechanisms of Asthma

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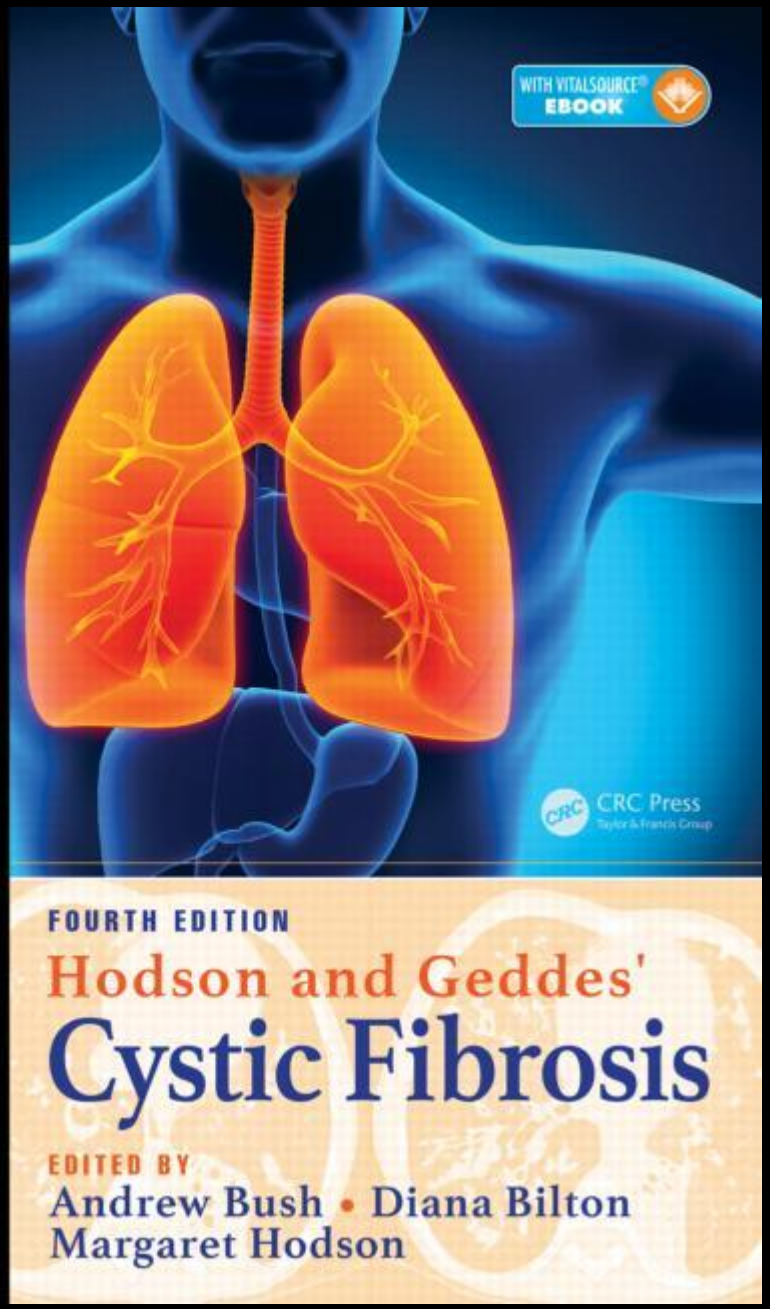
A lifetime of specialist care

U-BIOPRED



Disclosures

- One COI relevant to this presentation

Aims of the Presentation

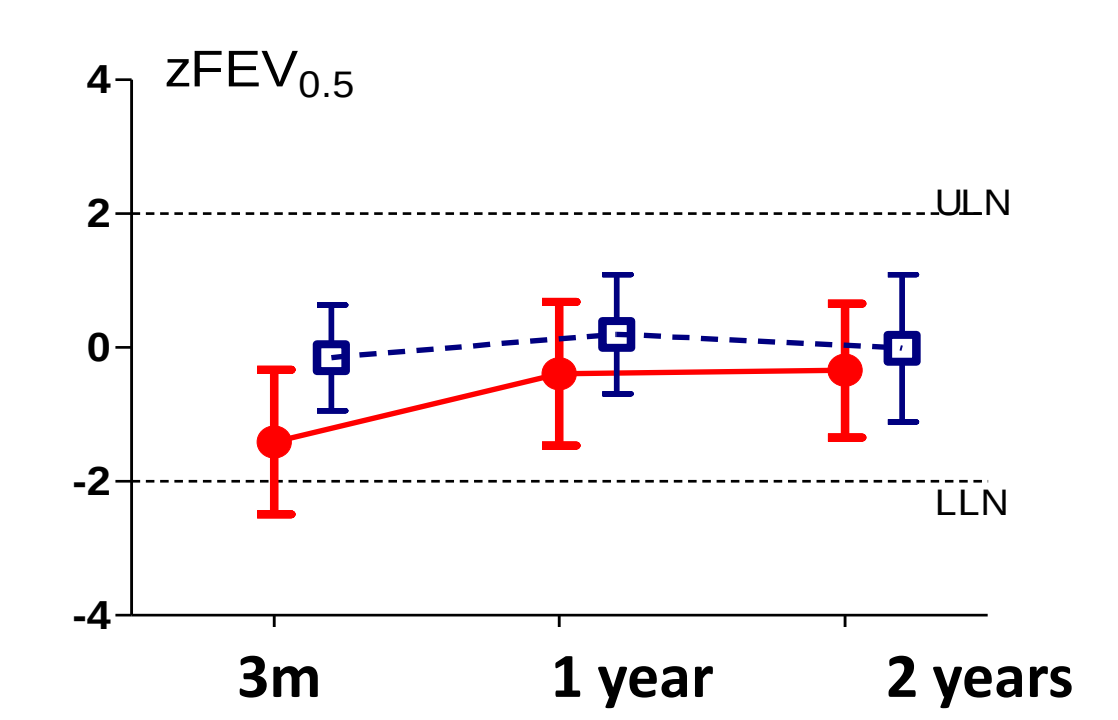
- I will set the scene with where we were as a contrast to where we are now and where we are going in terms of patient health and treatments

- I will discuss where we are and where we are going with novel treatments, specifically gene therapy, PTC correction, and the novel small molecules which are potentiators, correctors and amplifiers

New drugs

- **Where we were and where we are: 21st century CF patients**

NBS Diagnosis: Serial measurements $FEV_{0.5}$ to 2 years of age



Data presented as mean (SD)

☐ Healthy controls

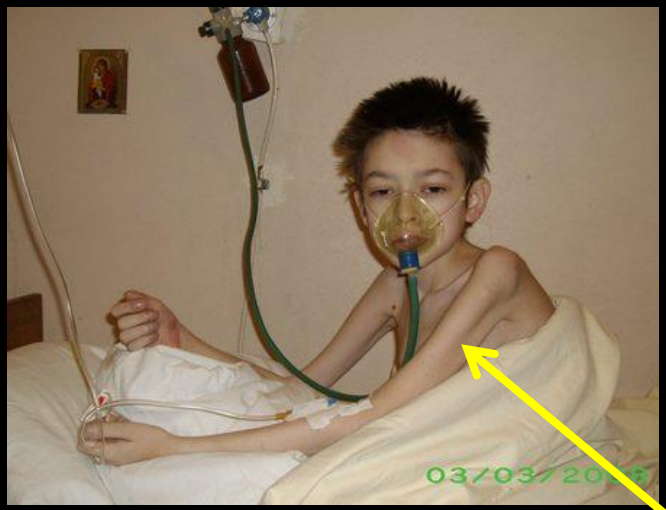
● CF

- Signif ↓in $FEV_{0.5}$ in CF at 3m improved by 1y, then stabilised
- Mean (95% diff) CF-controls at 2y -0.3 (-0.8; 0.2)z, p= 0.229]
- Δ $FEV_{0.5}$ in CF from 1-2y = 0.06 z-scores, similar to controls (p=0.29)

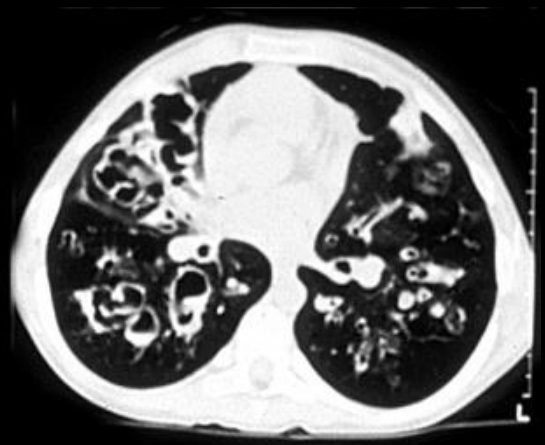
New drugs

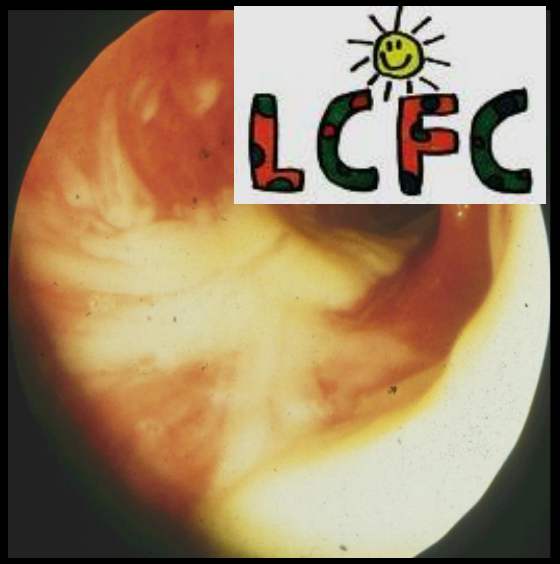
- Where we were and where we are: 21st century CF patients

- **Where we were: CF treatments**



CFTR Gene mutation





Nutrition
- **PERT**
- **Supplements**
- **Insulin**

Impaired Cl^- se[illegible] Na^+/H_2O absorbtion

Thick, dehydrated mucus

Bacterial infection & inflammation

Small airway plugging

Bronchiectasis

Respiratory failure

Airway clearance (various methods)

Mucus rheology
- **rhDNase**
- **7% HS**
- **mannitol**

Antibiotics
- **oral**
- **nebulized**
- **intravenous**

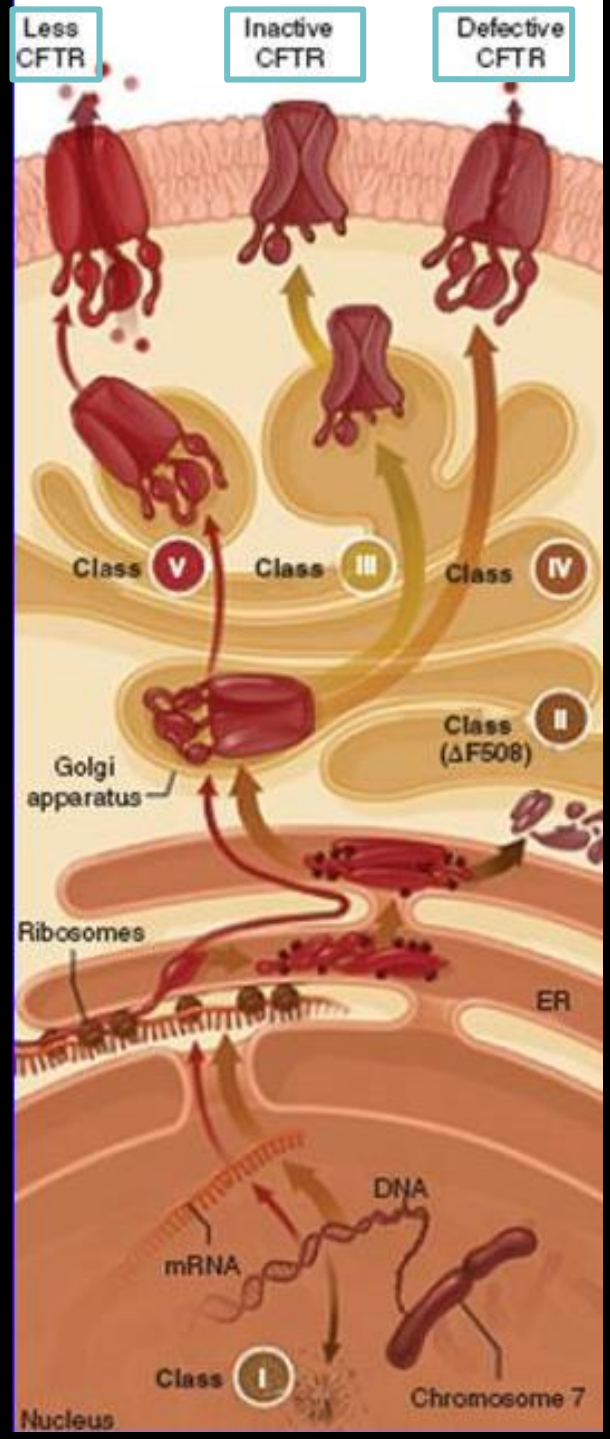
Anti-inflammatory?

The Way We Were

- Sick at diagnosis, playing catch-up: now, they are WELL, with normal lung function and nutrition
- Still treating the consequences of disease
  - Infection, inflammation
  - Malnutrition
- Trying to detect downstream complications ever sooner
- Benefits of treatment becoming less obvious as many very well

New drugs

- Where we were and where we are: 21st century CF patients
- Where we were: CF treatments
- **Where we are going: from firefighting to treating the basic defect**



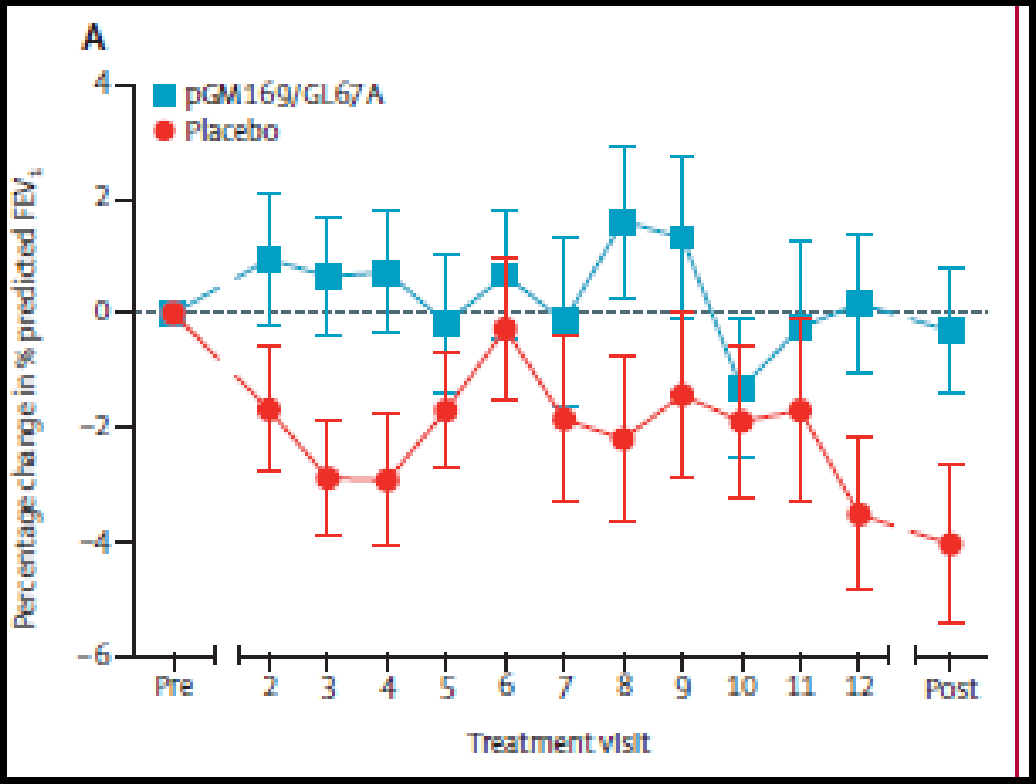
- **Class 1: (W142X)**
  - CFTR not made (nonsense)
- **Class 2: (ΔF508)**
  - CFTR made
  - Cannot fold properly
  - Cellular dustbin

- **Other classes all reach cell surface**

- **Class 3: (G551D)**
  - Won't open
- **Class 4: (R117H)**
  - Opens but nothing can pass through
- **Class 5:**
  - Not enough
- **?Class 6:**
  - Turnover too rapid

Gene therapy: all classes!

- First trial of not ‘does it work’ but ‘does it make a difference’ – i.e. real therapy
- Double blind, RCT, 140 CF patients age ≥12 years
- Monthly gene therapy (n=78) or placebo (n=62) for one year, 1^{ry} outcome FEV_1
- Improved FVC, gas trapping; safe

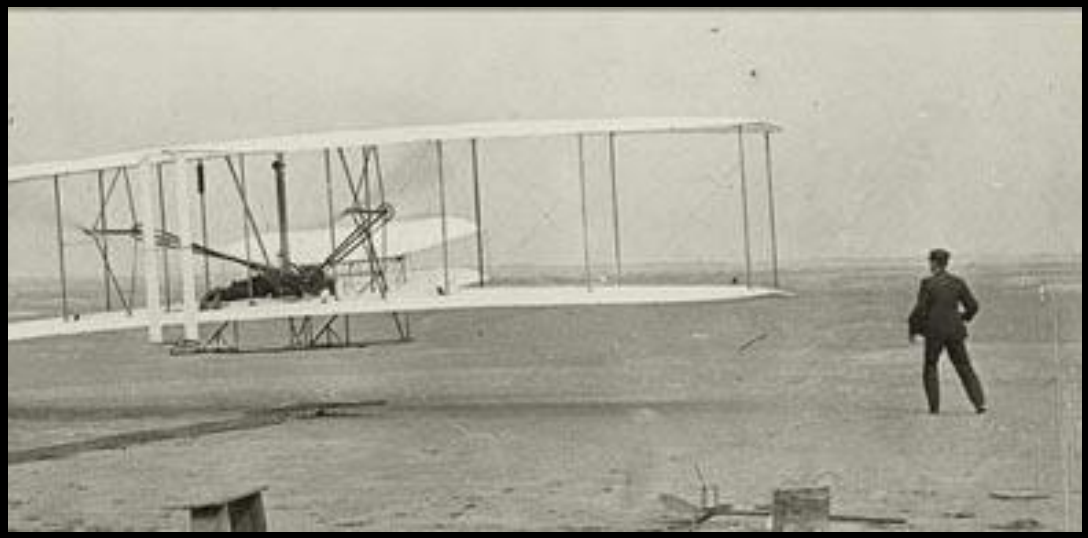


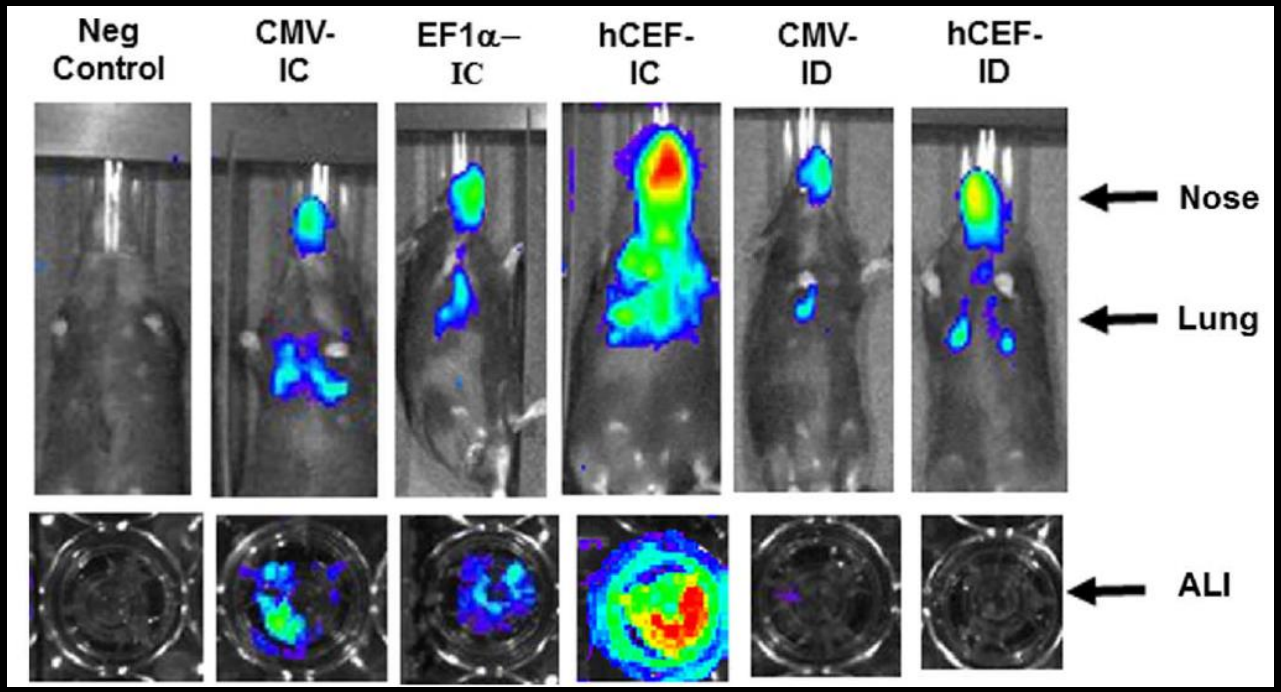
LRM 2015; 3: 684-91

What does it mean?

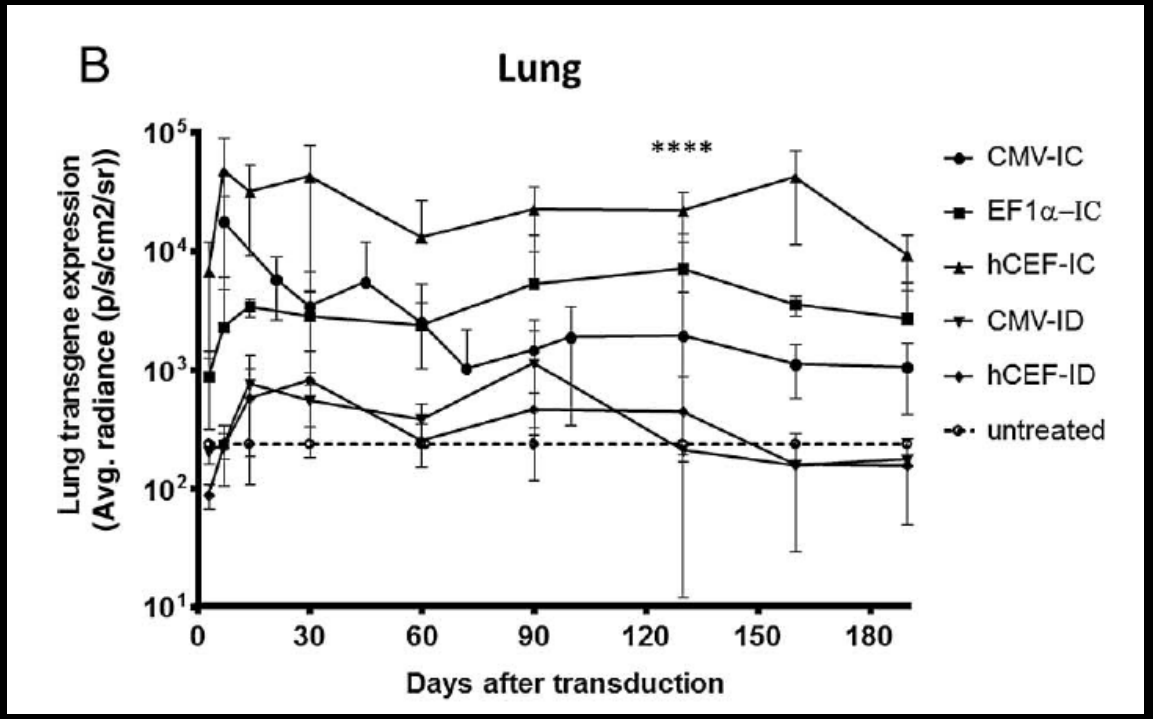
What we want

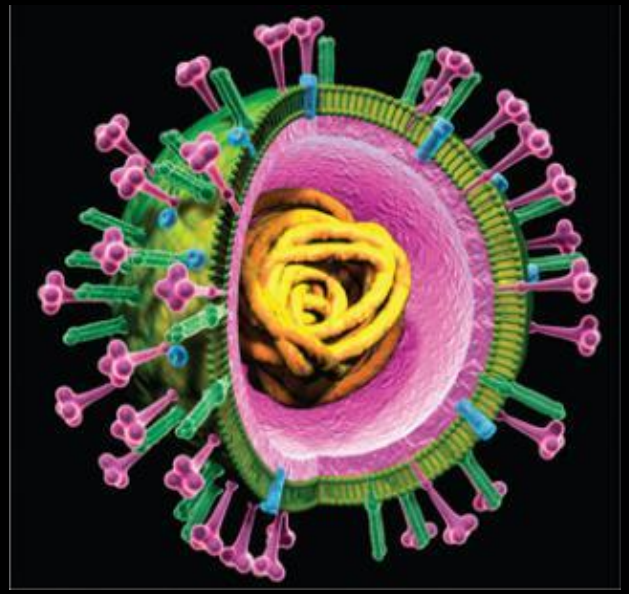
Where we are



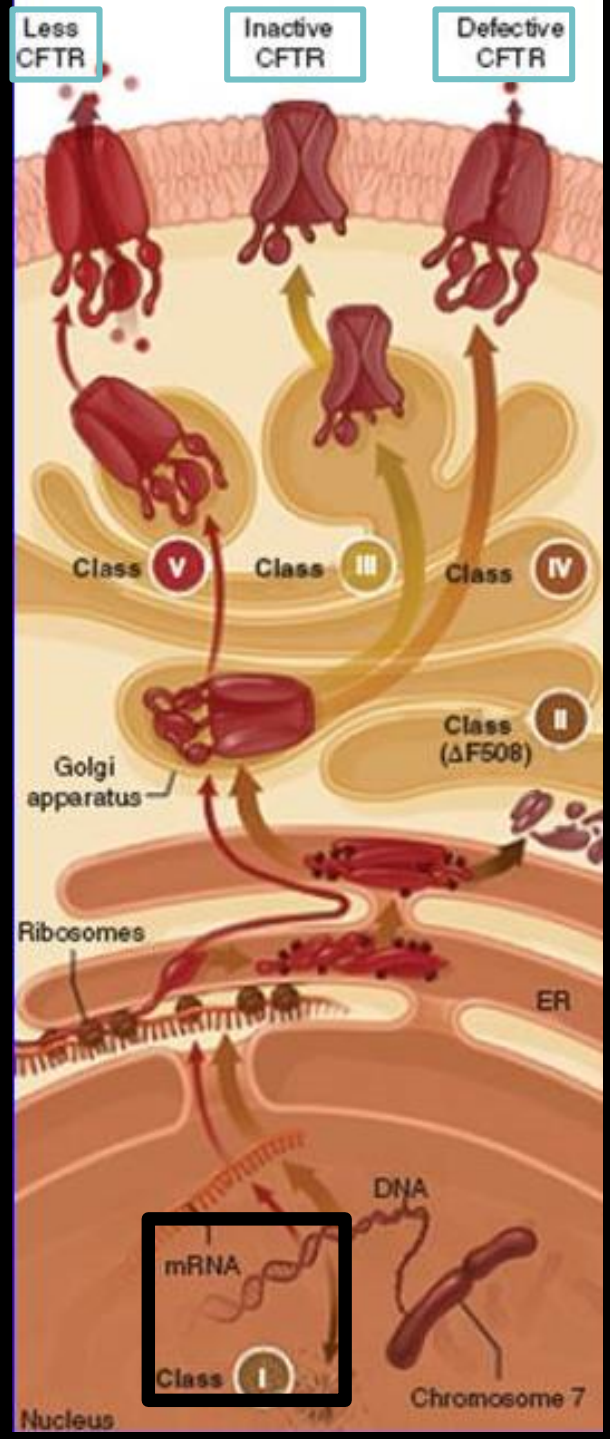


The Future: Lentivirus?



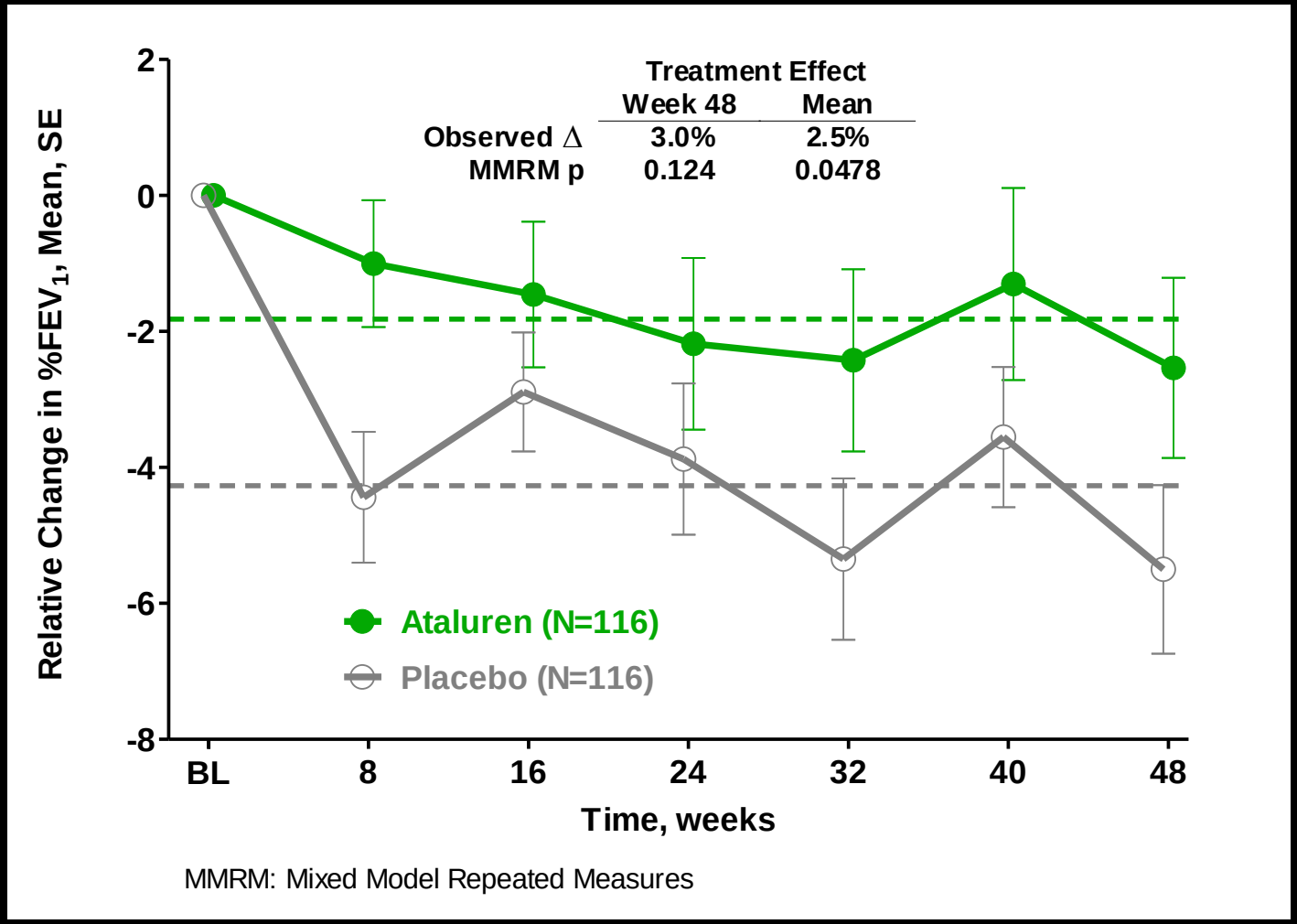


Thorax 2017; 72: 137-147



- **Class 1**:
  - CFTR not made (nonsense)

Ataluren: change in FEV_1



MMRM: Mixed Model Repeated Measures

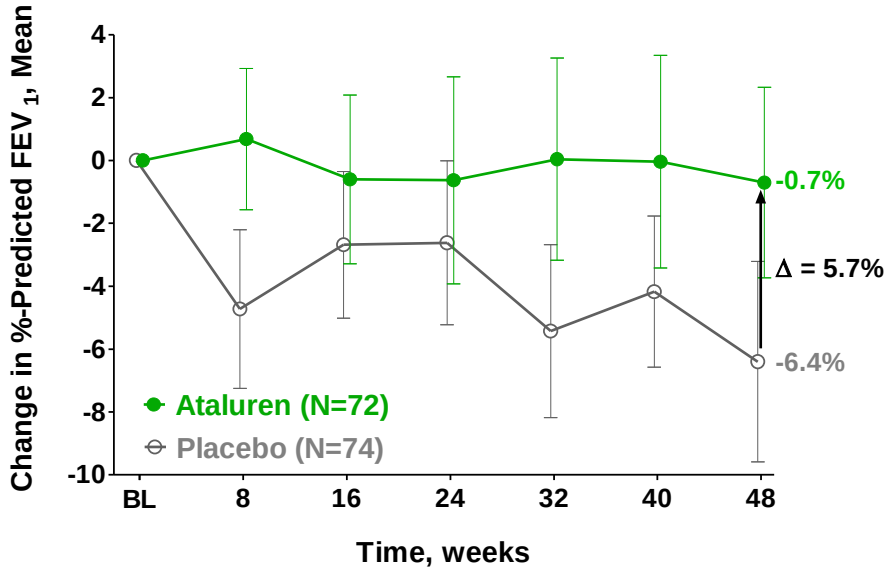
Post hoc analysis in patients not taking inhaled aminoglycosides

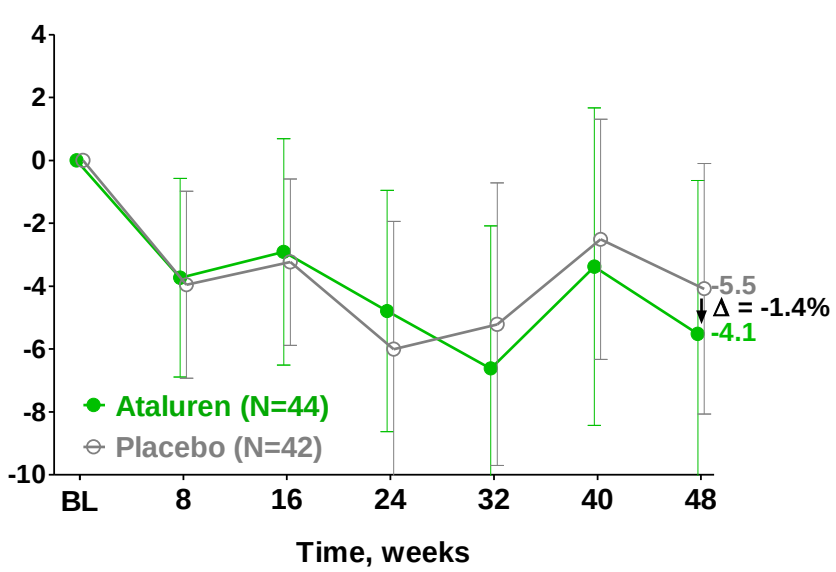
No Inhaled Aminoglycosides

Week 48 Δ = 5.7%
p = 0.008*

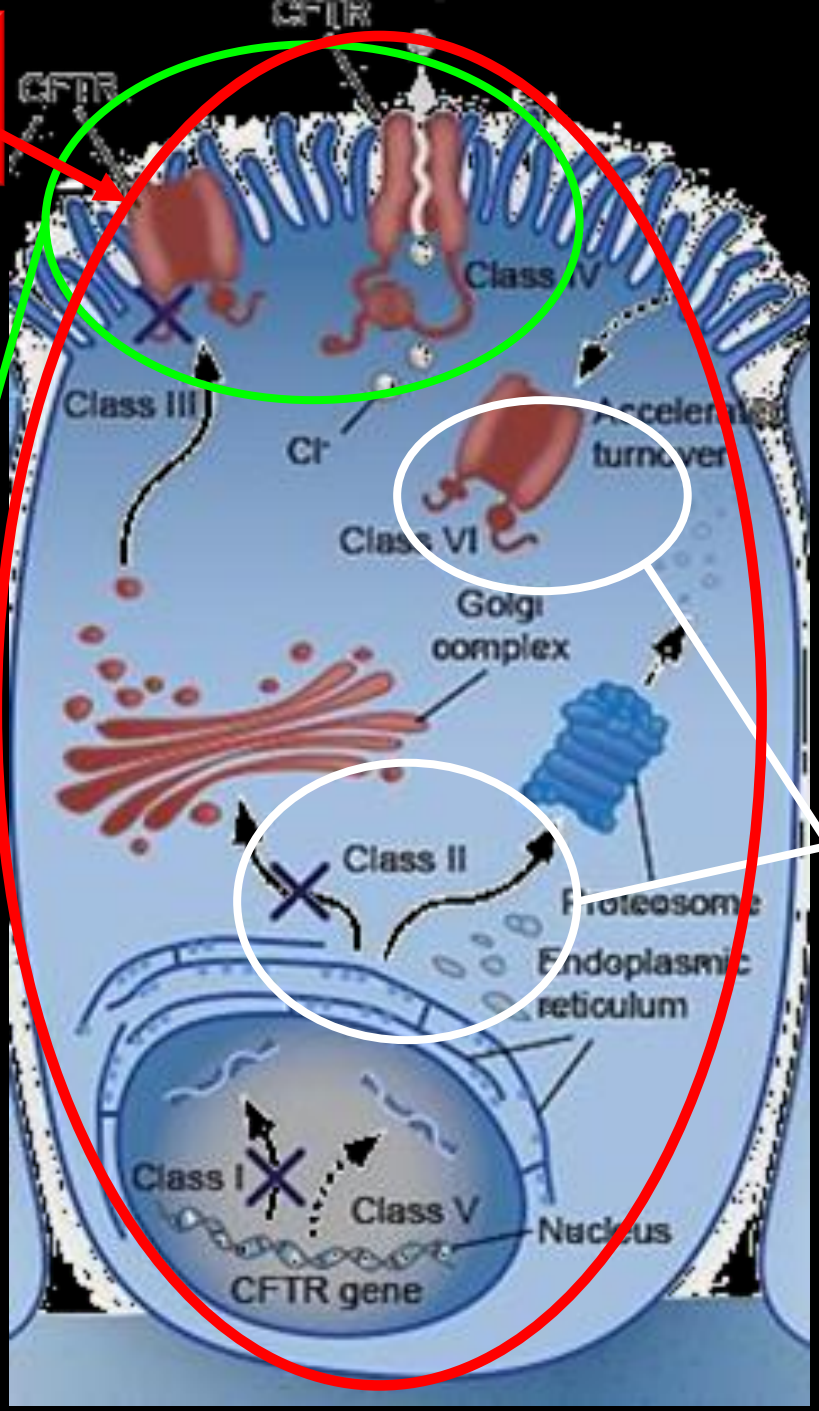
Any Inhaled Aminoglycosides

Week 48 Δ = -1.4%
p = 0.43





CFTR Amplifiers:
All classes, increases CFTR levels



Reduced *FUNCTION* at the cell surface

POTENTIATORS

VX-770

Reduced *QUANTITY* at the cell surface

CORRECTORS

VX-809
VX-661

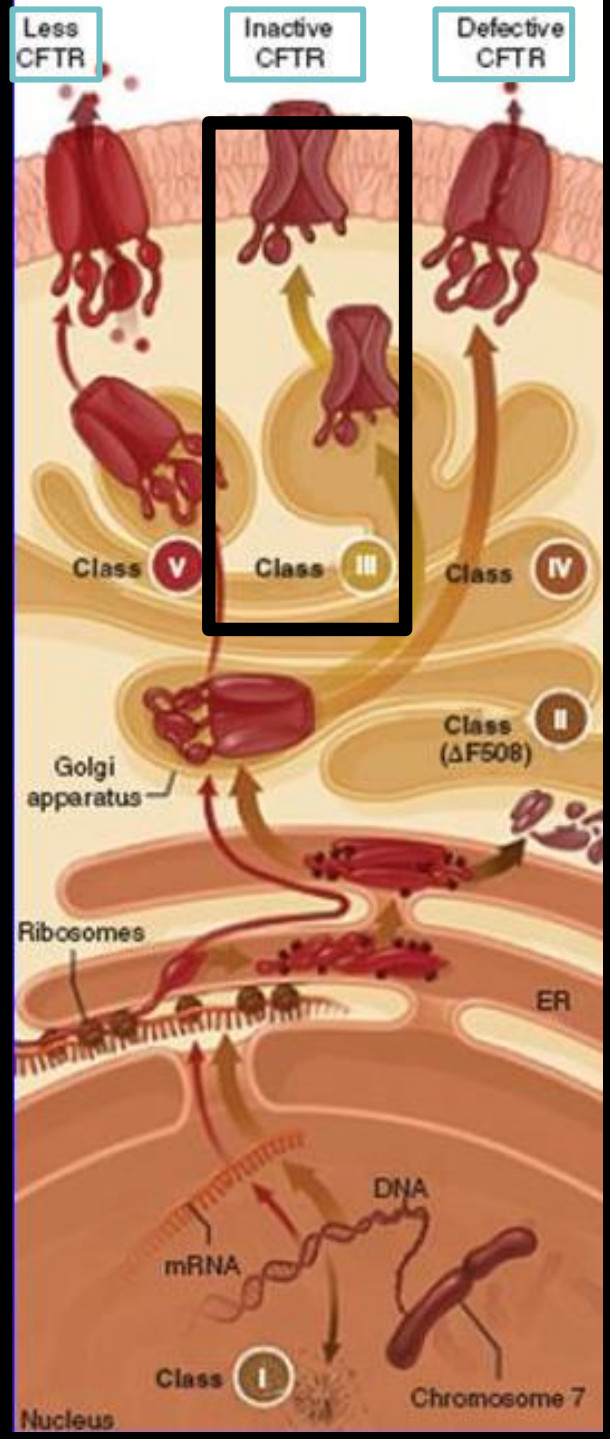
Drug Discovery – Then and Now

THEN

One compound, three year PhD

NOW

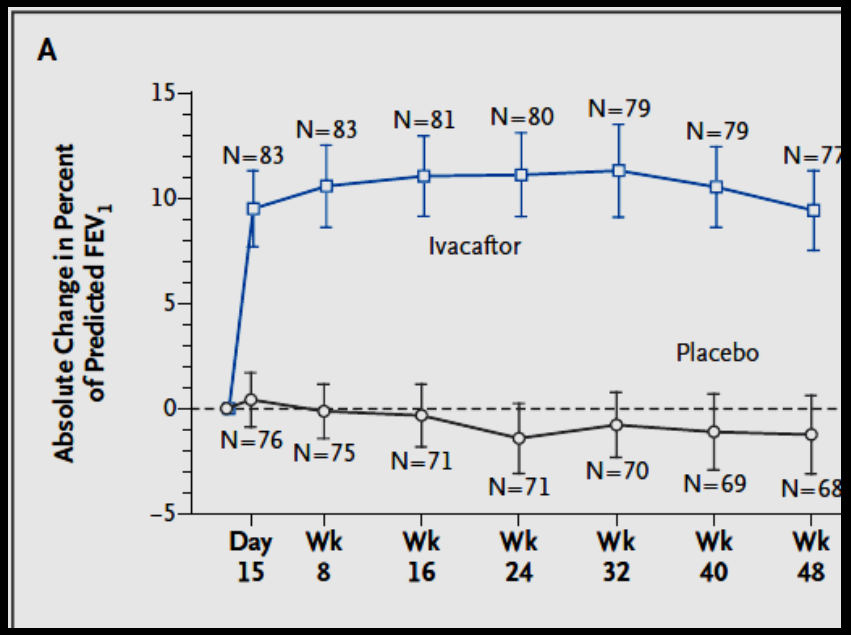
Thousands of compounds in one morning

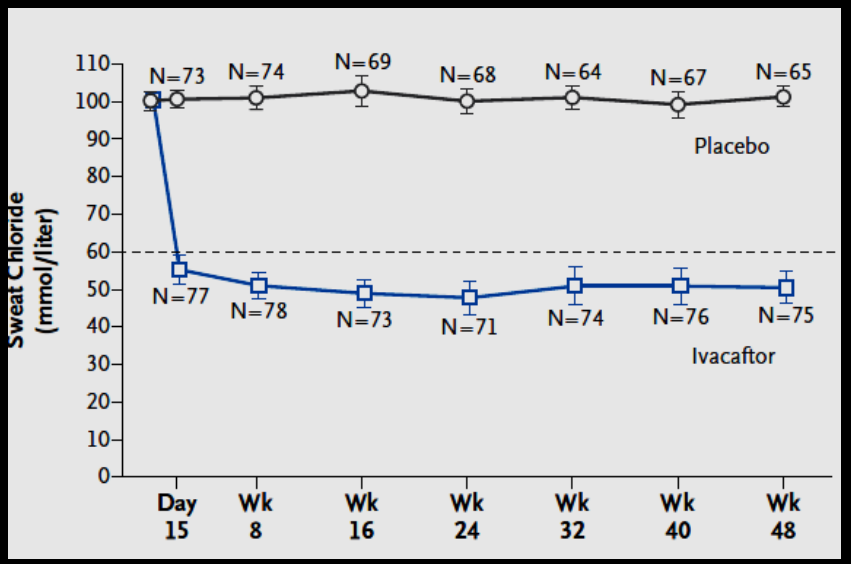


- **Class 3**:
  - **Won't open**

A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

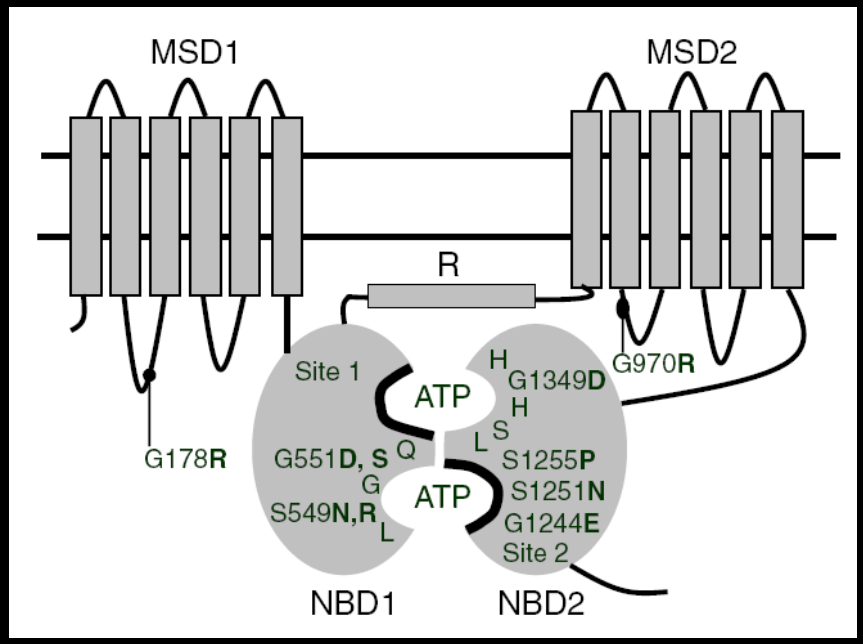
- **Randomised, double-blind, placebo controlled trial**
- **CF patients ≥ 12 years, ≥ one *G551D-CFTR* mutation**
- **150 mg bd VX-770 (n=84) vs. placebo (n=83)**
- **Duration 48 weeks, 1^{ry} endpoint FEV_1**
- **Also increases in weight, quality of life**
- **BUT! Cost!!**

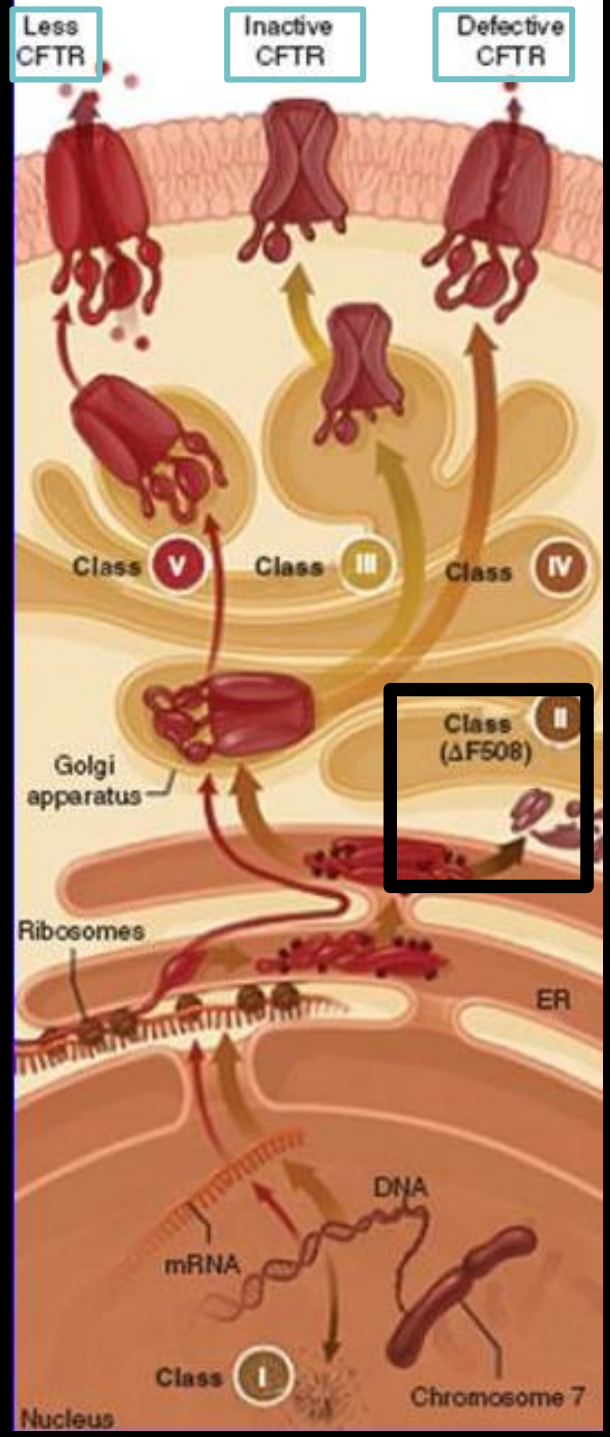




Other Ivacaftor Work

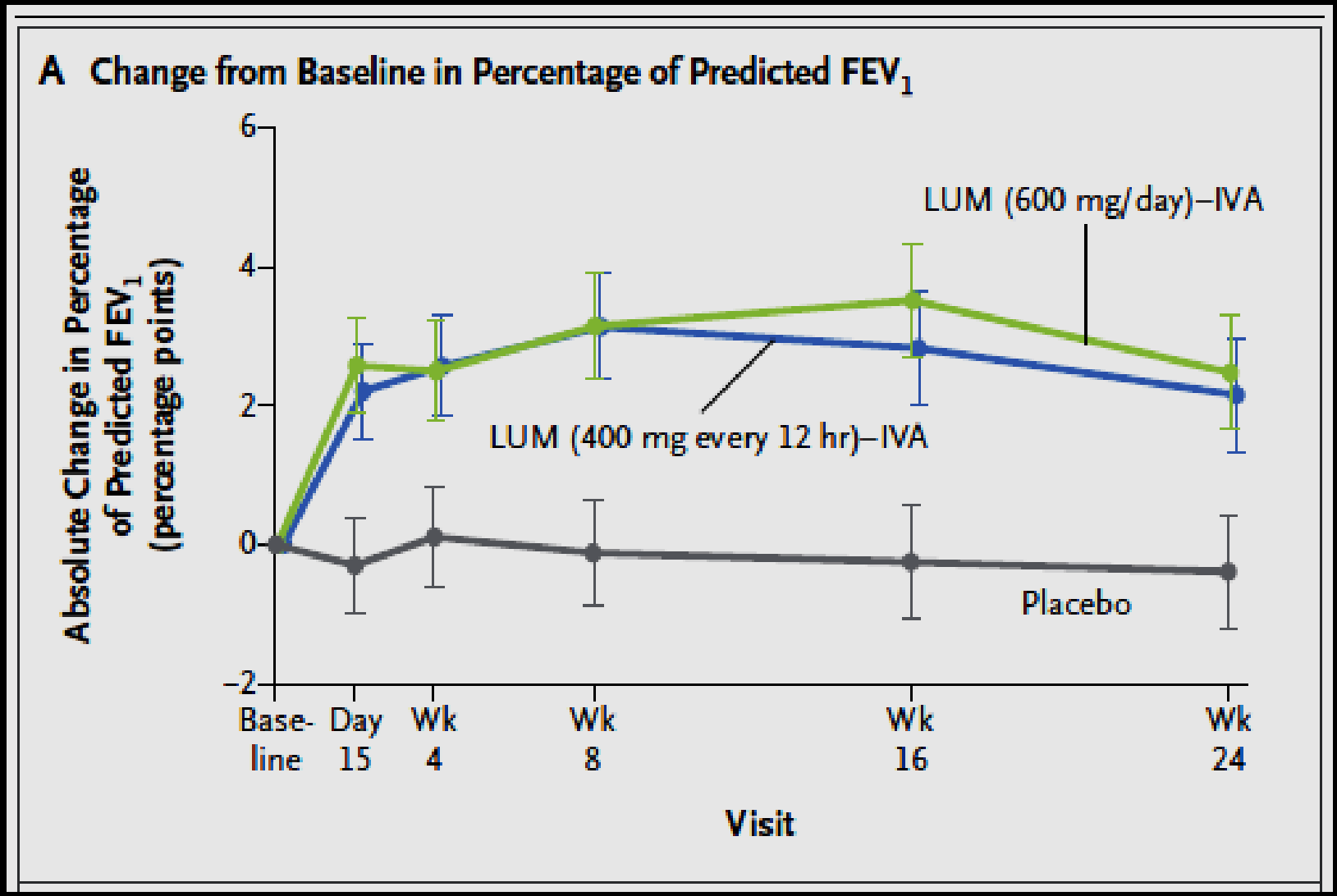
- Works in young children age 6-11 years
  - *Am J Respir Crit Care Med 2013; 187: 1219-25*
- Works in mild disease, FEV_1>90%
  - *Lancet Respir Med 2013; 1: 630-8*
- Safe in young children age 2-6
- Works in other rare gating mutations



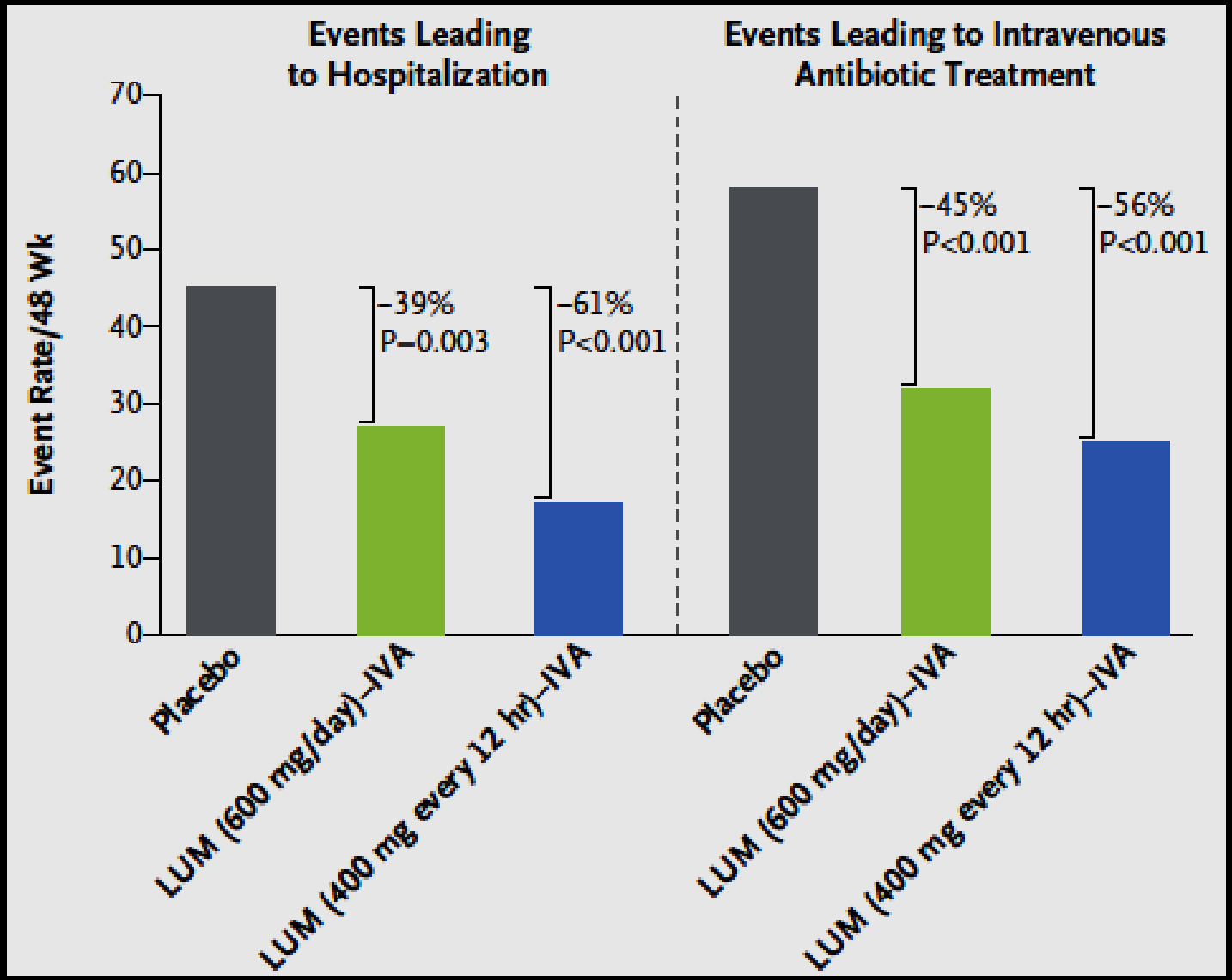


- **Class 2**:
  - CFTR made
  - Cannot fold properly
  - Cellular dustbin

Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*



Secondary End-Point: PEx

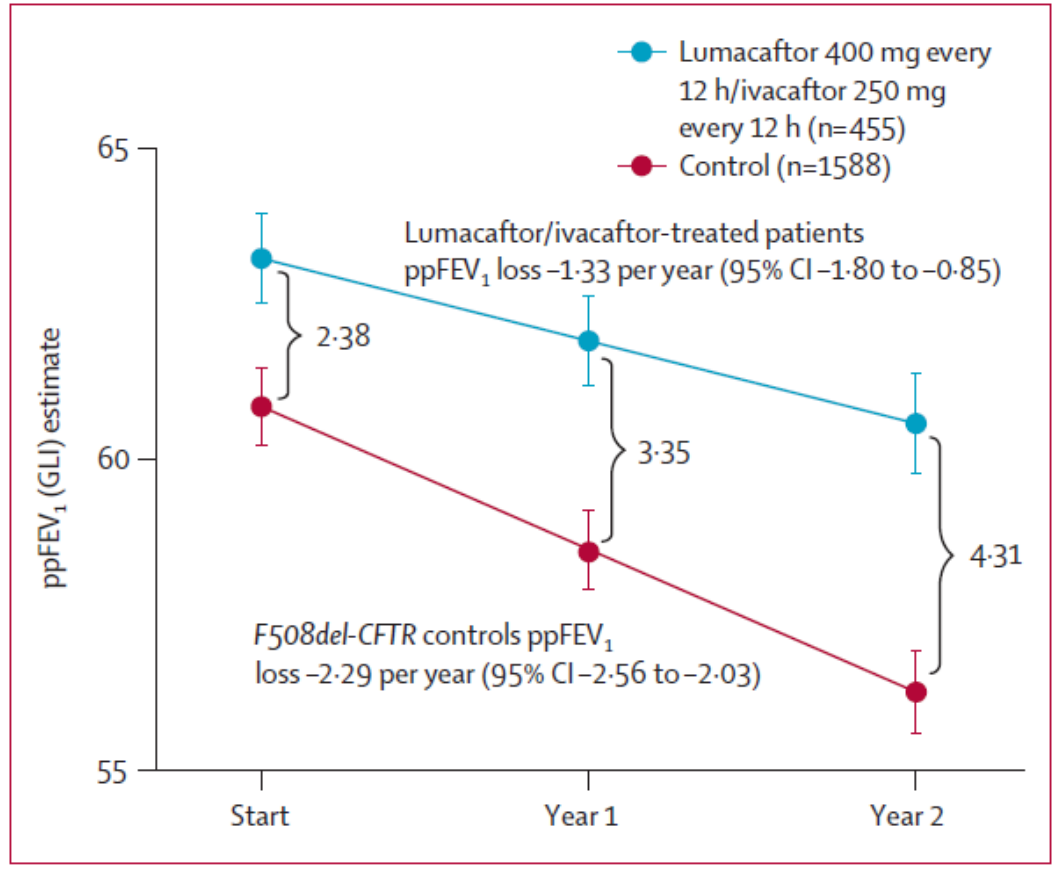


Conclusions

- A typically superbly constructed and executed trial
- A very exciting CONCEPT: another molecular therapy, this time for a common CF mutation
- The RESULTS are no more exciting than many standard meds, and not all trial patients received all these meds
- Value for money would price it comparable to standard meds, e.g. £10K/year – at ivacaftor prices, does not represent value for money
- Also remember RISK as well as benefit

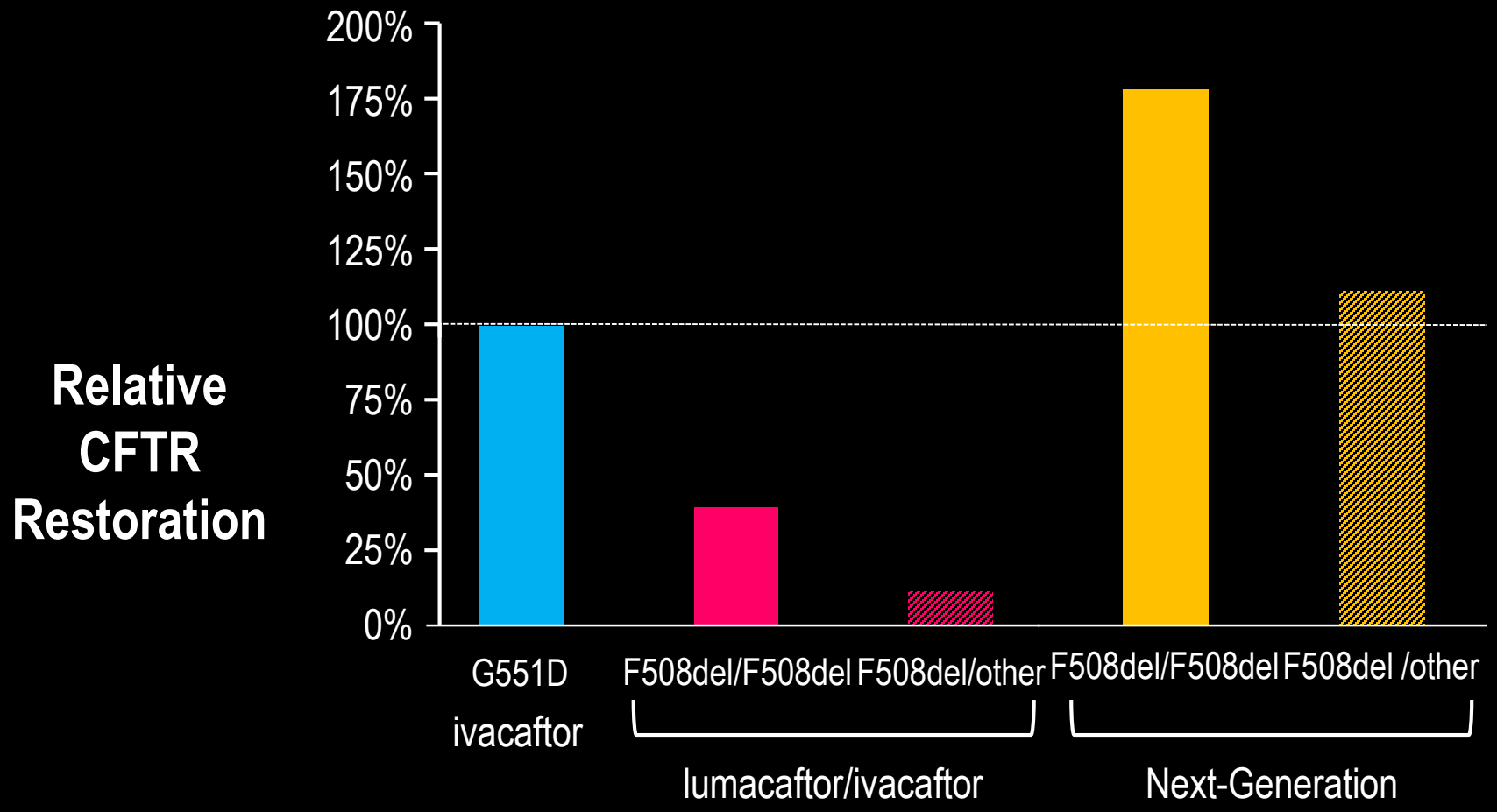
Traffic-Transport Follow Up

- 516 patients continued 96 weeks open label FU
- BMI continued to improve, PFTs stable at small improvement, Pex rate remained reduced
- Generally safe (HT, Pex, cough, sputum, haemoptysis)
- Compared rate of decline with 'matched registry patients'

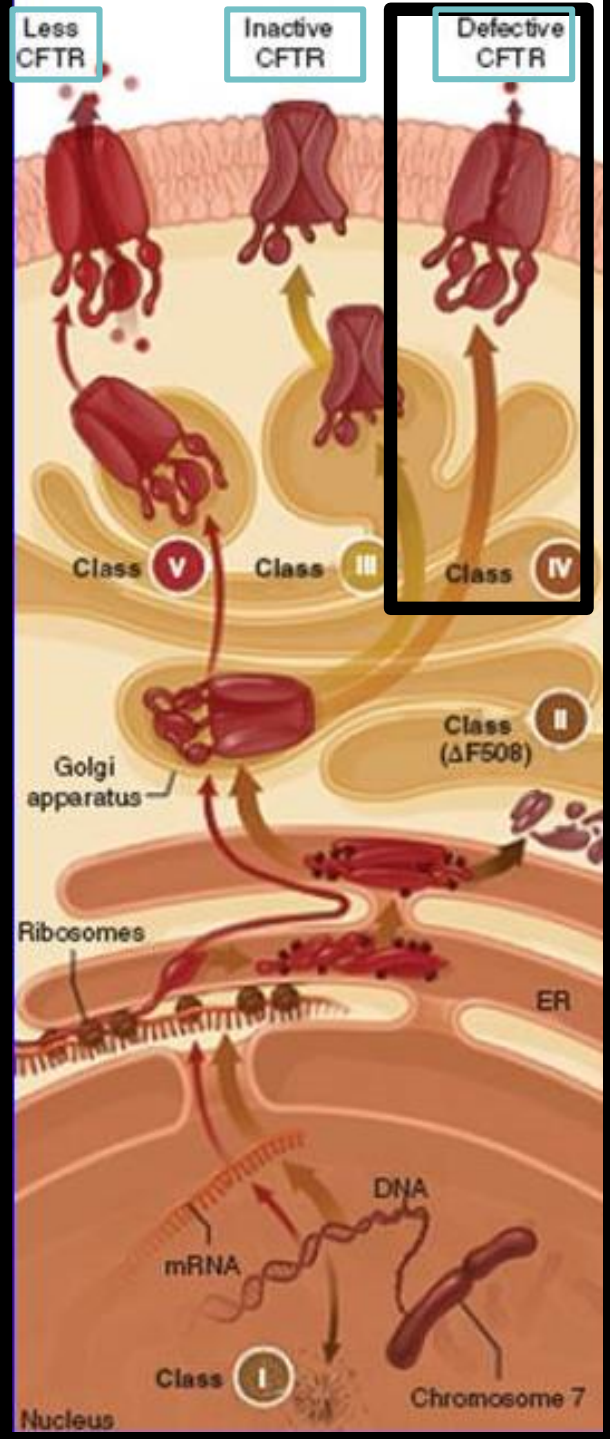


Lancet Respiratory Medicine 2017; 5: 107-18

Emerging (next-generation) F508del corrector molecules



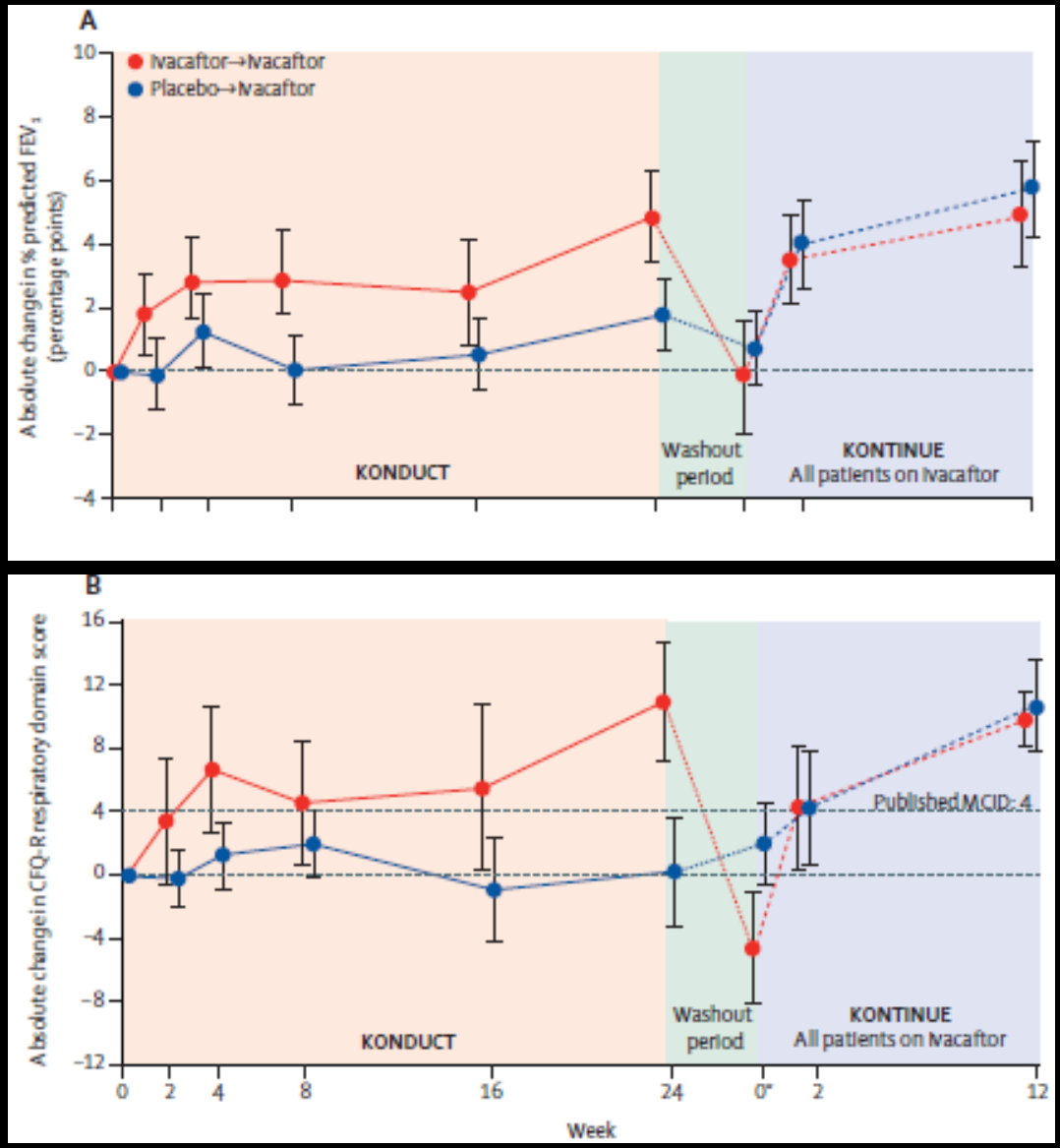
Presented by Eric Sorscher, Plenary 1 NACFC 2016



- **Class 4**:
  - Opens but nothing can pass through

Ivacaftor in R117H

- 24 weeks, double blind RCT in 69 CF patients age ≥6 years with ≥1 R117H, 1^{ry} outcome FEV_1
- Sub-analyses by age (6-11, 12-17, >18 years) and FEV1 (<70%, 70-90%, >90%)
- Medication was safe and well tolerated
- Overall group – no difference in FEV_1, CFQ-R improved



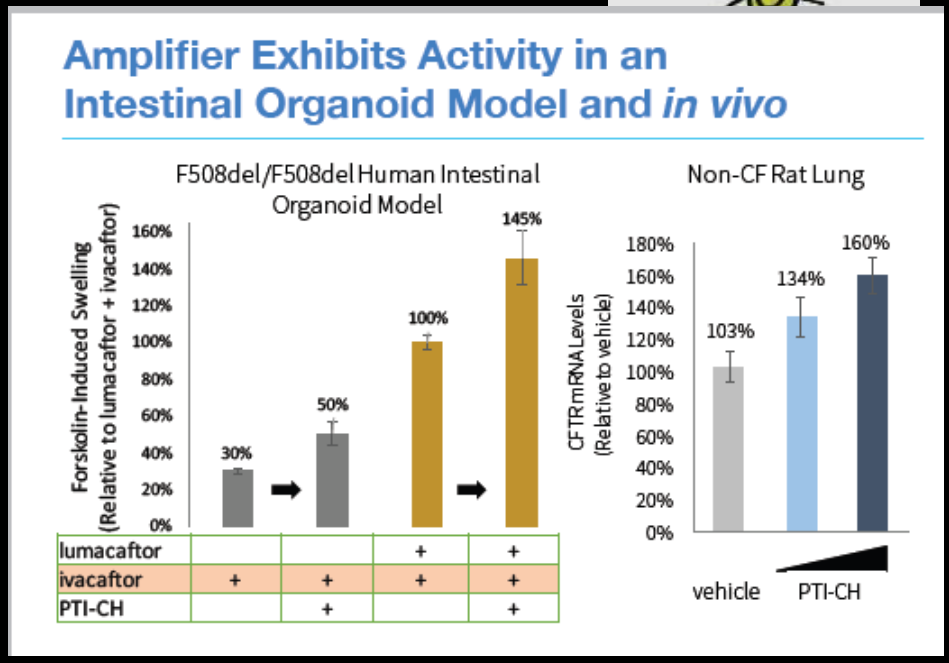
Further results

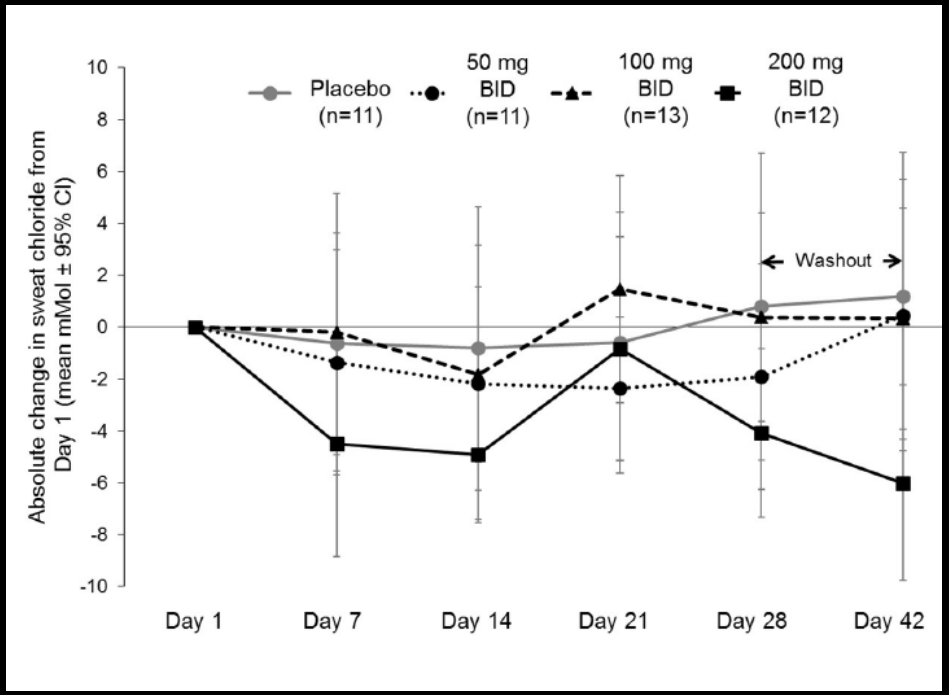
- There were changes in sweat chloride (-24 mmol/l, 95% CI -28 to -19.9)
- Patients over age 18 years did show a significant improvement in FEV1 as well as CFQ-R
- CONCLUSION: Maybe reserve for advanced disease?

LRM 2015; 3: 524-33

CFTR Amplifiers

- Stabilise CFTR mRNA and increases CFTR immature protein, providing additional CFTR substrate for CFTR modulators and potentiators
- Work across all genotypes
- *In vitro* activity (*Pediatr Pulmonol 2016; 51 S45: 207-8*)
- *In vivo* small reductions of sweat [Cl^-] (*Donaldson SH, JCF epub*)





New drugs

- Where we were and where we are: 21st century CF patients
- Where we were: CF treatments
- Where we are going: from firefighting to treating the basic defect
- **Summary and conclusions**

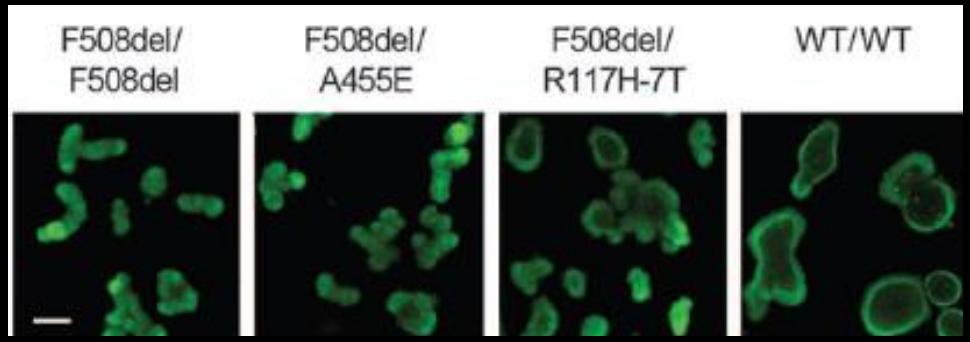
Modulator pipeline is diverse & robust

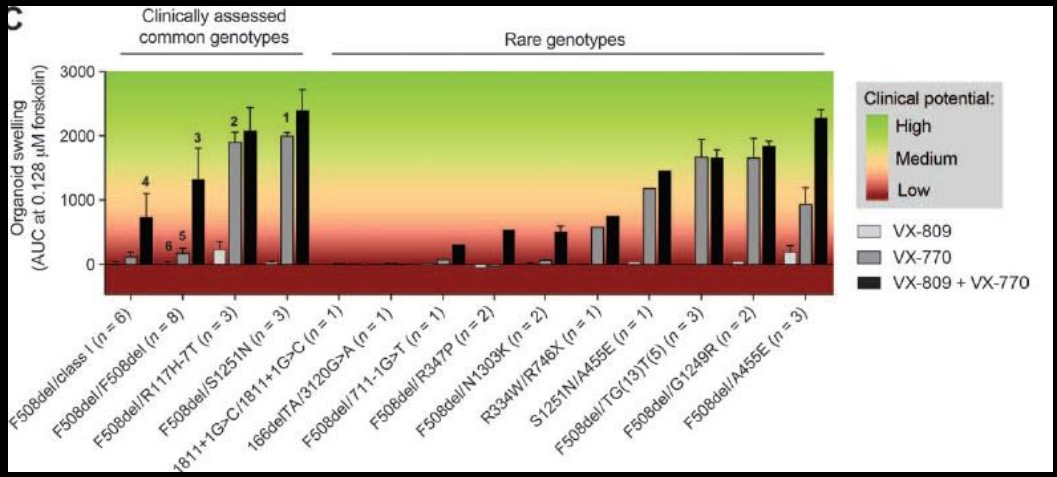
name	class	Phase 1	Phase 2	Phase 3
PTI-428	amplifier			
GLPG2451	potentiator			
GLPG2222	corrector			
GLPG2665	corrector			
QBW267	corrector			
CTP-656	potentiator			
BAY 63-2521	corrector			
FDL169	corrector			
N91115	GSNOR inhibitor			
VX-152	corrector			
GLPG1837	corrector			
VX-440	corrector			
VX-661	corrector			
ataluren	read-through			

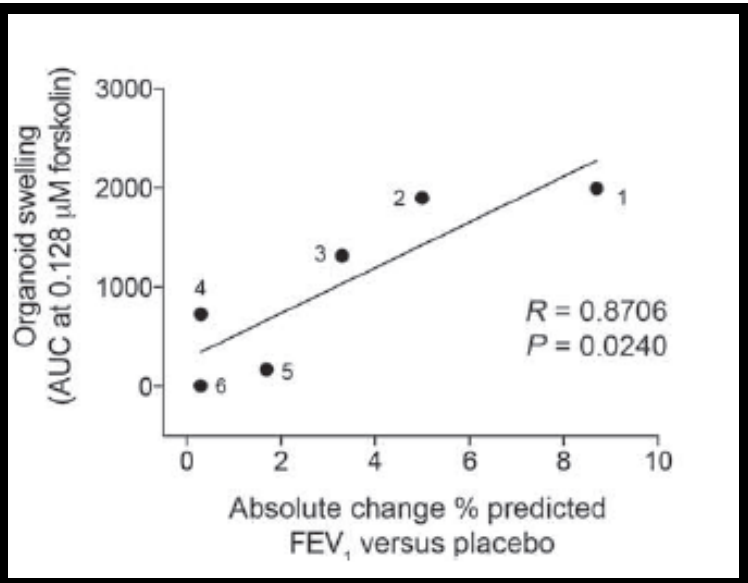
So we need personalised medicine!

- Rectal biopsies can be formed into organoids, and CFTR stimulated with Forskolin
- Organoid swelling differs between genotypes and individuals with the same genotype
- Organoid swelling predicts FEV_1 response

Dekkers, Sci Translat Med epub







Summary & Conclusions

- In 2017 we are moving from ‘CF patient’ to ‘well person who happens to have CF’
- Improved health means benefits of treatment will be harder to demonstrate, and safety issues become even more important
- We are moving from downstream firefighting to exciting designer ways of treating the basic defect
- There are a huge number of exciting compounds in the pipeline, but paying for them will not be easy!

Thanks for listening