Cystic Fibrosis
the future

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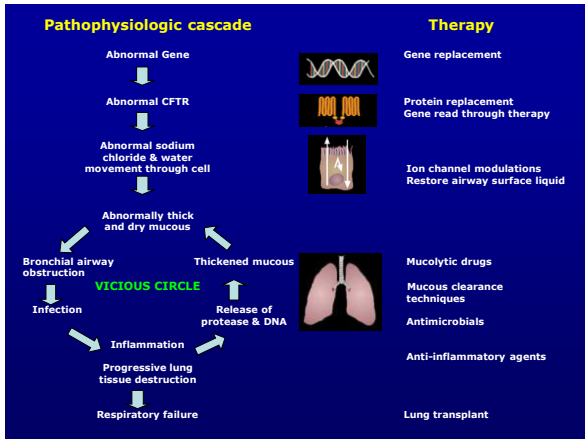
UZ Gasthuisberg, mucoteam Leuven



Pulmozyme®

= DNAse

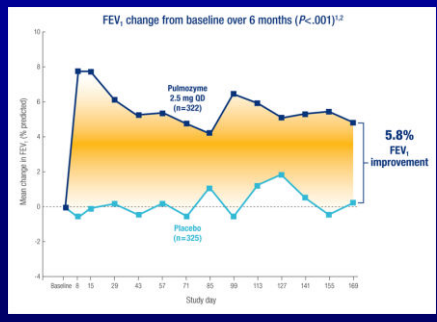
lysis of DNA bacteria and inflammtory cells

Stabilisation of lung function

Aerosol 1 x / day
- ≥5 years old
- LF < 10% decline/year

Side effect: hoarseness

Pulmozyme®



Tobi®

Inhalation of tobramycine

chronic colonisation of Pseudomonas aeruginosa

stabilisation of lung function

less respiratory exacerbations

side effect: resistance
hoarseness and tinnitus

Tobi®

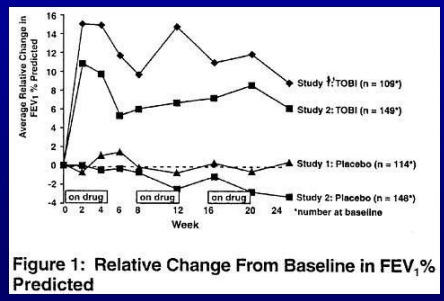
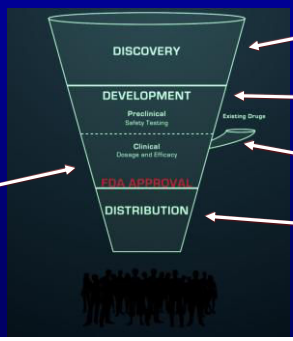


Figure 1: Relative Change From Baseline in FEV_1% Predicted

Therapeutics Development Program



Discovery Awards

Therapeutics Development Awards

Low-hanging Fruit

CF Services Pharmacy

Therapeutics Development Network

2002

2004

Hypertonic saline

- NaCl 7%

  osmotic effect

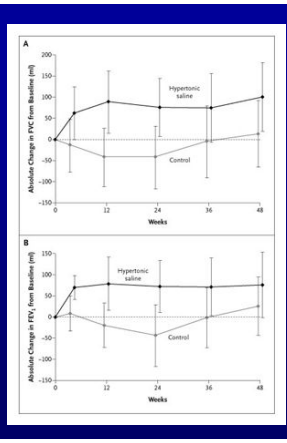
  less respiratory exacerbations

  slight improvement of lung function

side effect: bronchospasm, dyspnea, pharyngitis

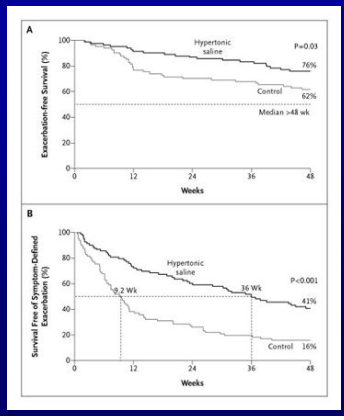
NEJM 2006 354,3

Lung function



NEJM 2006 354,3

Exacerbations



NEJM 2006 354,3

Azithromycine

Anti-inflammatory properties:

inhibits biofilm formation, quorum-sensing of P aeruginosa

stimulates phagocytosis

reduces mucus production and cytokine production

Stabilisation of longfunction

Less respiratory exacerbations

Less use of antibiotics

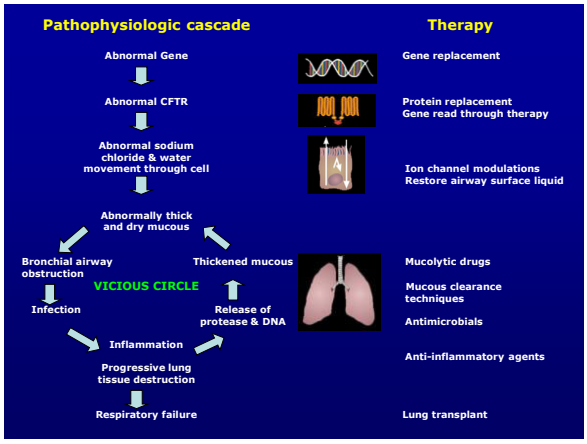
Inhaled Antibiotics in Development

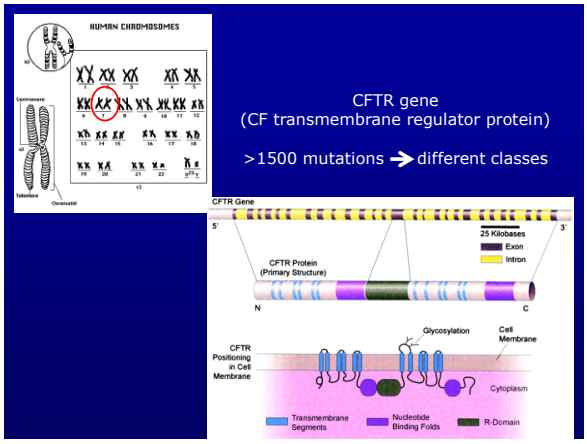
- **Inhaled monobactam**
  Aztreonam Lysine for inhalation (Gilead)
- **Inhaled flouroquinolones**
  Ciprofloxacin Dry Powder for Inhalation (Bayer)
  Levofloxacin Solution for Inhalation (MPEX)
  Inhaled Liposomal Ciprofloxacin (Aradigm)
- **Inhaled aminoglycosides**
  Tobramycin Dry Powder for Inhalation (Novartis)
  Arikace (liposomal amikacin) (Transave)
- **Inhaled aminoglycoside/phosphonic acid**
  Tobramycin/Fosfomycin for Inhalation (Gilead)

'Disease modifying drugs'

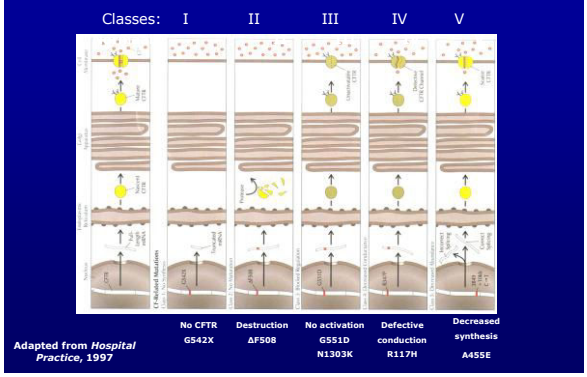
Designed to cure the core problem of CF

- Gene therapy
- Protein repair
- Influence on ion fluxes
  - more chloride outside
  - less sodium inside
- More water on the epithelial layer





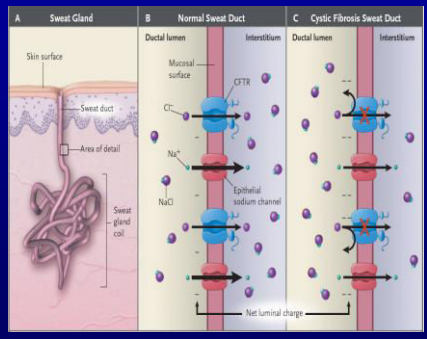
CFTR mutation



Activity of Cl channel

- Sweat test
  Pilocarpine iontoforesis
  abnormal: Cl > 60 mEq/l
  normal: Cl < 30 mEq/l
- Nasal potential difference test(NPD)
  Cl secretion (nose)

Transepithelial chloride transport: Sweat Test



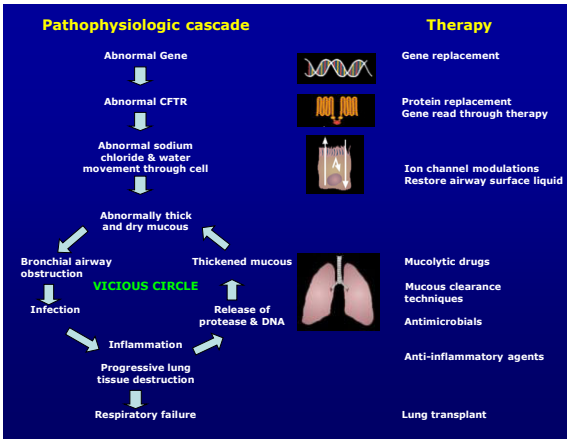
Transepithelial chloride transport: Nasal Potential Difference (NPD):

Gene Therapy

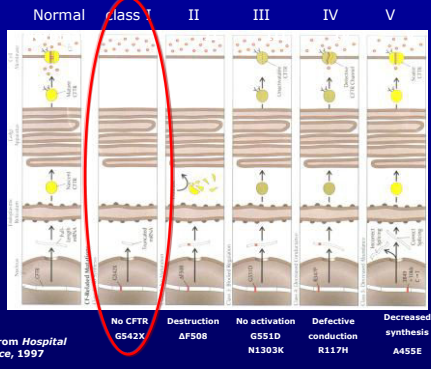
First choice as real curative therapy

BUT

- vector problem
- duration
- insufficient clinical effect



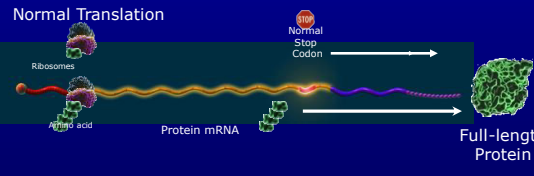
CFTR mutation
effect on CFTR protein function



Adapted from *Hospital Practice*, 1997

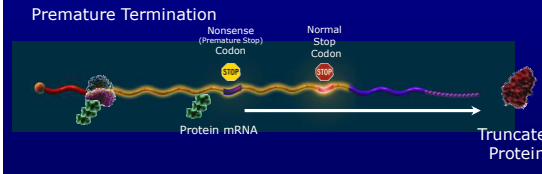
Normal 'translation' of genetic information

⟶ a full-length protein is synthesised

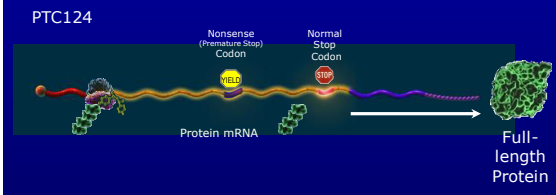


Nonsense mutation = premature stop of 'translation'

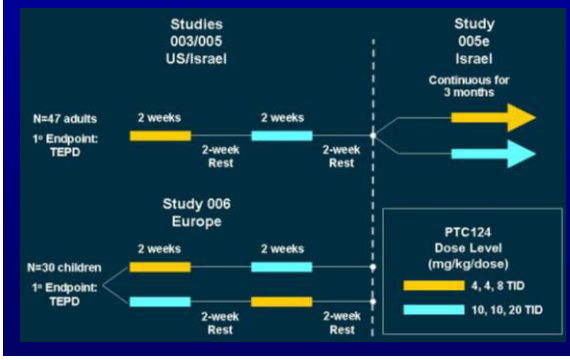
⟶ truncated protein



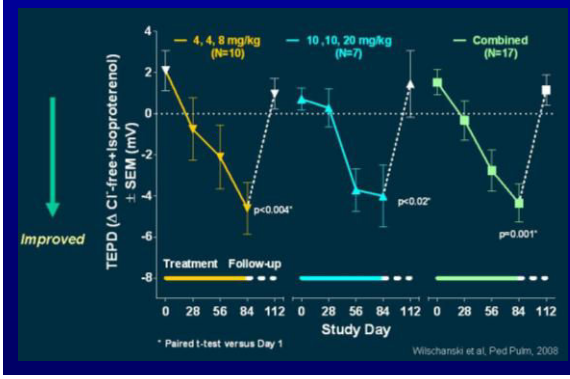
PTC124 ignores the nonsense mutation



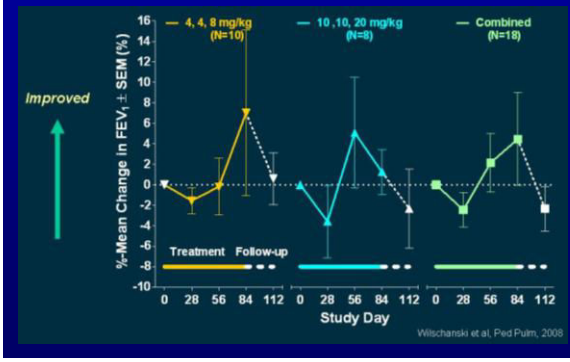
Phase 2a studies met PTC 124



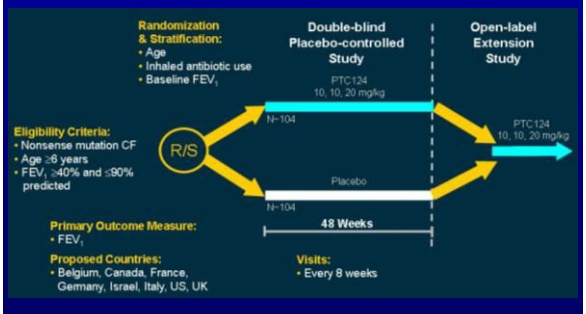
PTC124 ameliorates NPD



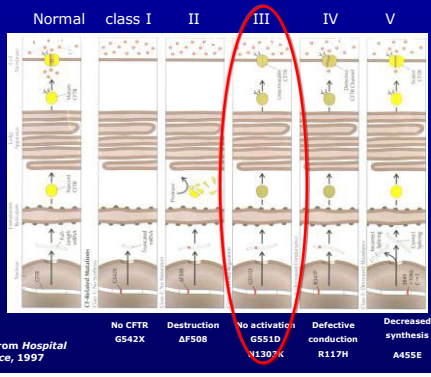
PTC124: slight positive effect on FEV_1



PTC124 phase 2b/3 is planned



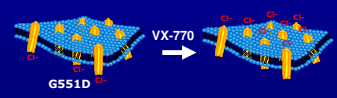
CFTR mutation
effect on CFTR protein function



Adapted from *Hospital Practice*, 1997

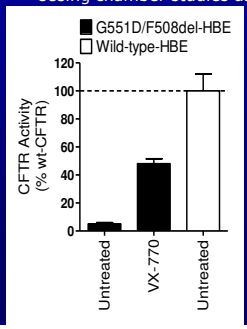
Potentiator

Potentiator:
Increase activity of CFTR channel



Potentiator VX-770 increase CFTR activity cell cultures

Ussing chamber studies using G551D/F508del-HBE cultures



Single donor lung
All data expressed as % wt-CFTR
N = 7
EC50 for G551D/delF508 = 238 +/- 200

Phase 2a Study of VX-770

Primary Endpoints:
- Safety and tolerability

Secondary Endpoints:
- Biomarkers of CFTR activity and lung function
- PK parameters

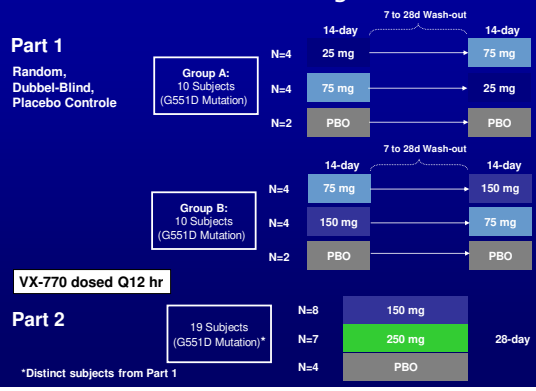
Subjects with G551D were chosen for the initial study due to the normal trafficking of G551D-CFTR to the cell surface

Nasal Potential Difference
Direct measure of CFTR function and other ion channels in the upper airway

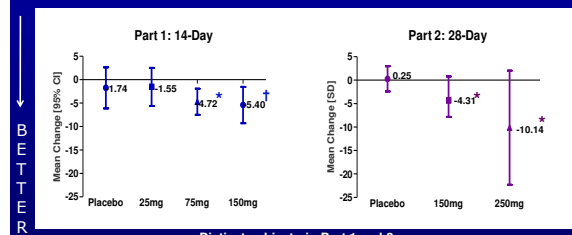
Forced Expiratory Volume (FEV_1)
Measure of lung function

Sweat Chloride Concentration
Measure of CFTR function that is commonly used to diagnose CF

Studie Design



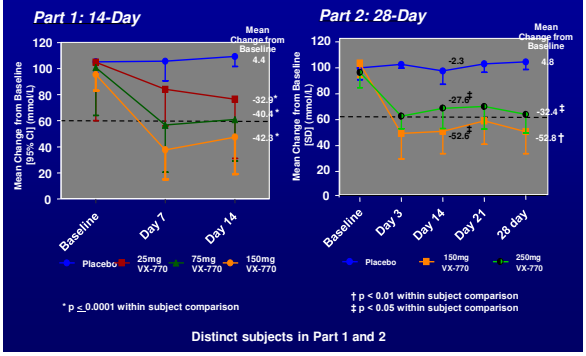
Change in NPD with VX-770 (mv)



* p < 0.005
† p < 0.010
within subject comparison

* p < 0.05
within subject comparison

Change in sweat chloride with VX-770

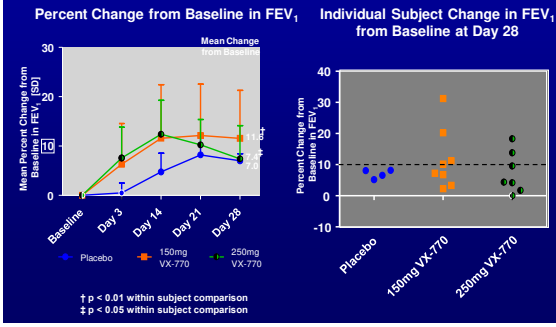


* p ≤ 0.0001 within subject comparison

† p < 0.01 within subject comparison
‡ p < 0.05 within subject comparison

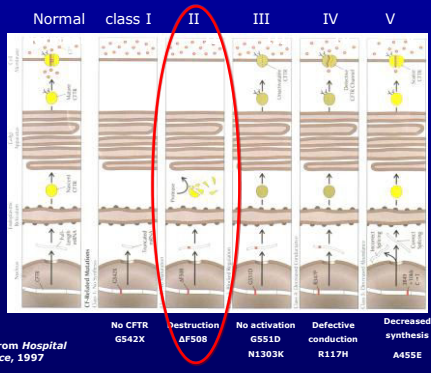
Distinct subjects in Part 1 and 2

Improvement of FEV_1 with VX-770



† p < 0.01 within subject comparison
‡ p < 0.05 within subject comparison

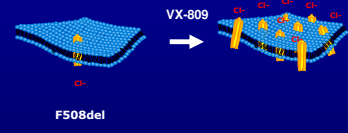
CFTR mutation
effect on CFTR protein function



Adapted from *Hospital Practice*, 1997

Correctors

Corrector:
get more CFTR channels
in cell surface



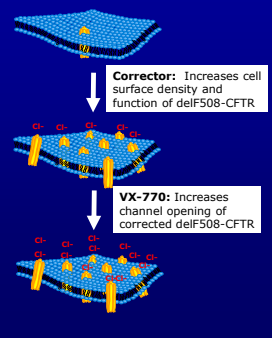
Vertex Program

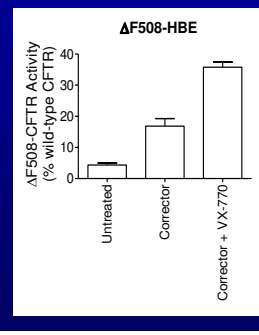
- Oral medication
- Dubbel doel:

Potentiator:
Increase activity of CFTR channel

Corrector:
get more CFTR channels
in cell surface

Corrector and potentiator Effect on delF508 CFTR Activity





VX-770 and VX-809 Development Status

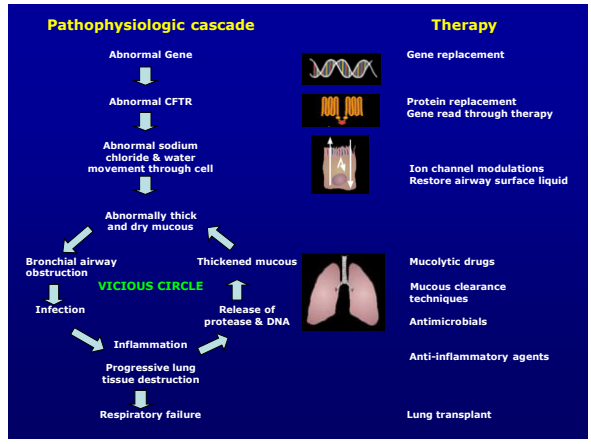
VX-770:

- Continue analysis of the Phase 2a study
- Phase 3 studies were initiated in may 2009

  randomized, double-blind, placebo-controlled

VX-809:

- Phase 1 healthy volunteer studies
- Phase 2 safety study in delF508 patients in 2009



Denufosol

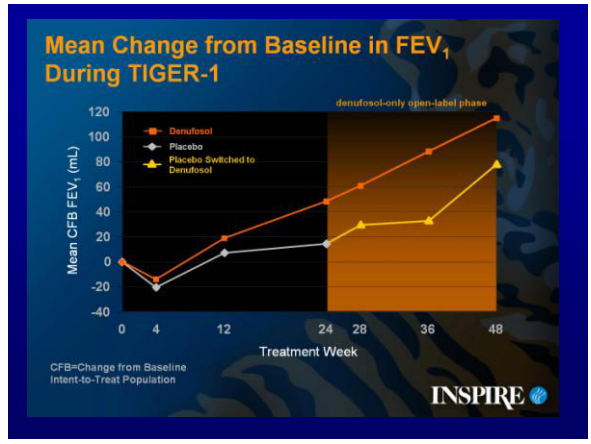
- P2Y2 activator

  activation of alternative chloride channels

  improvement of Airway surface liquid

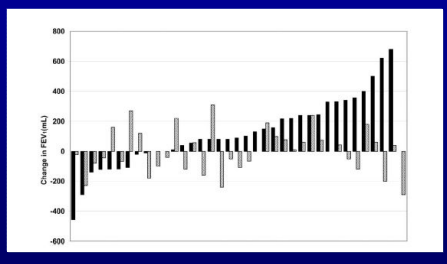
  improvement of mucociliary transport

side effect: temporarily lower FEV_1



'Bronchitol' = mannitol
a sugar attracting water

better lung function



M P

Chest 2008

A current challenge for investigators and patients

- One goal is a better way to measure improvement
  - Nasal Potential Difference testing
  - 'Lung clearance index'
    a more accurate lung function test
- We want better drugs
- We want quality and efficient research
  - A European network for CF research
- A lot of work for investigators and patients

Our goal is to 'cure' CF

Realistic expectations

We never know in advance which drug will be a success for future treatment of CF