Cystic Fibrosis
Recent Advances

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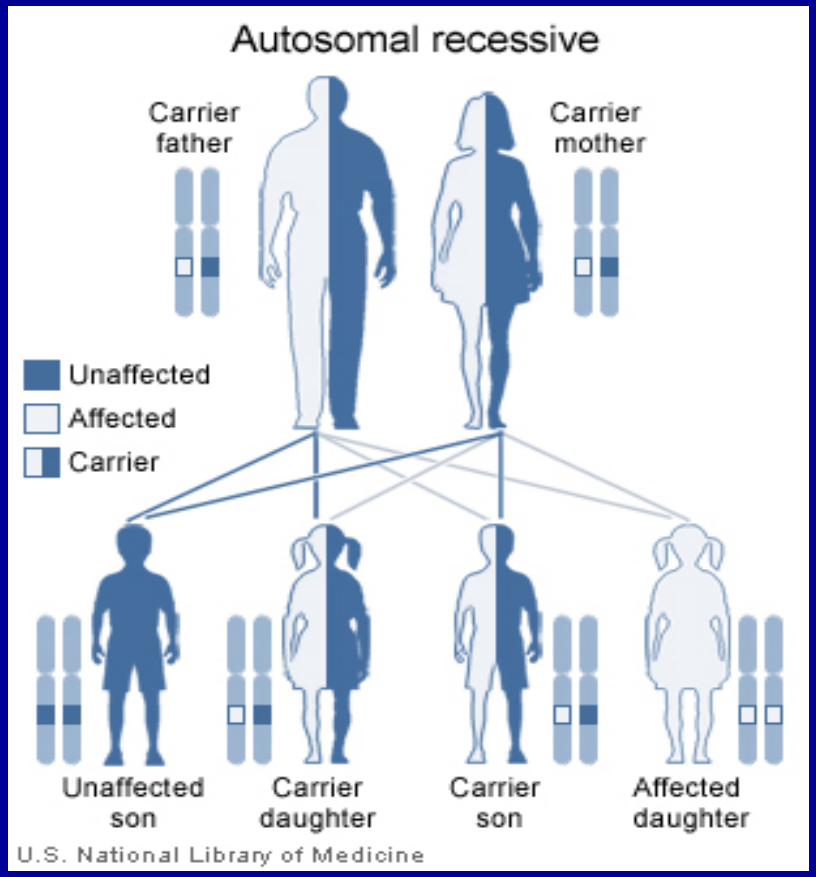
Respiratory Paediatrician
Great Ormond Street Hospital
London

Licking the forehead crossways:
If one perceives a salty taste
the child is called bewitched and is feared
soon to die

Ancient infant cleansing ceremonies
in: *The treatment of uncanny effects*

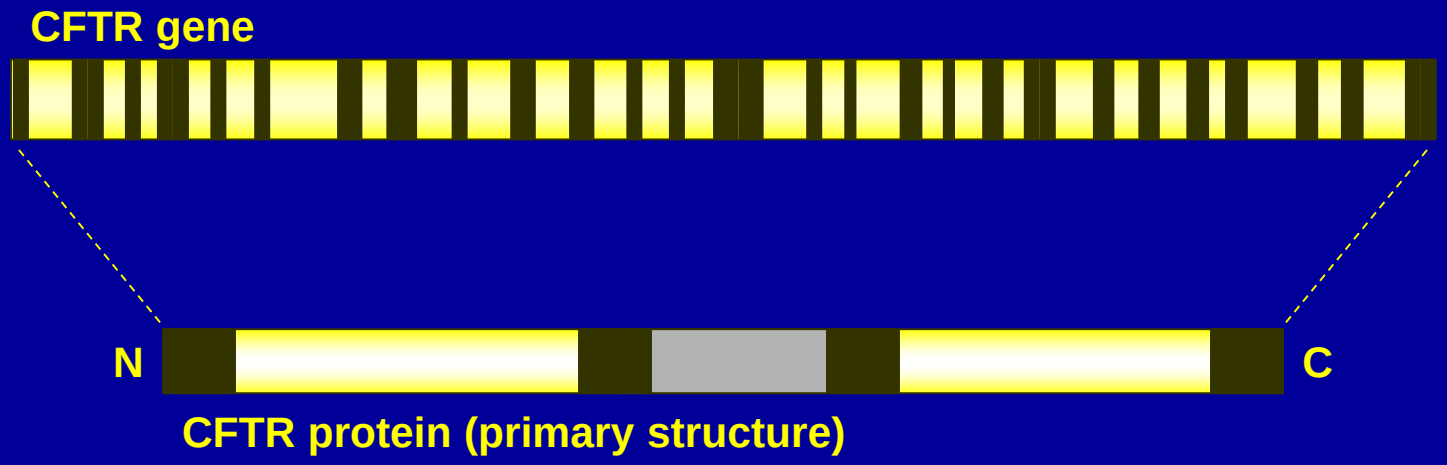
How do we get CF?



- Genetic disorder passed on through both parents.
- Parents are carriers but no symptoms.
- Often no family history of CF.
- In the UK 1:23 people are carriers and 1:4 chance of each baby being affected.
- Over 2000 different genotypes discovered.

Cystic Fibosis Transmembrane Conductance Regulator Protein: CFTR

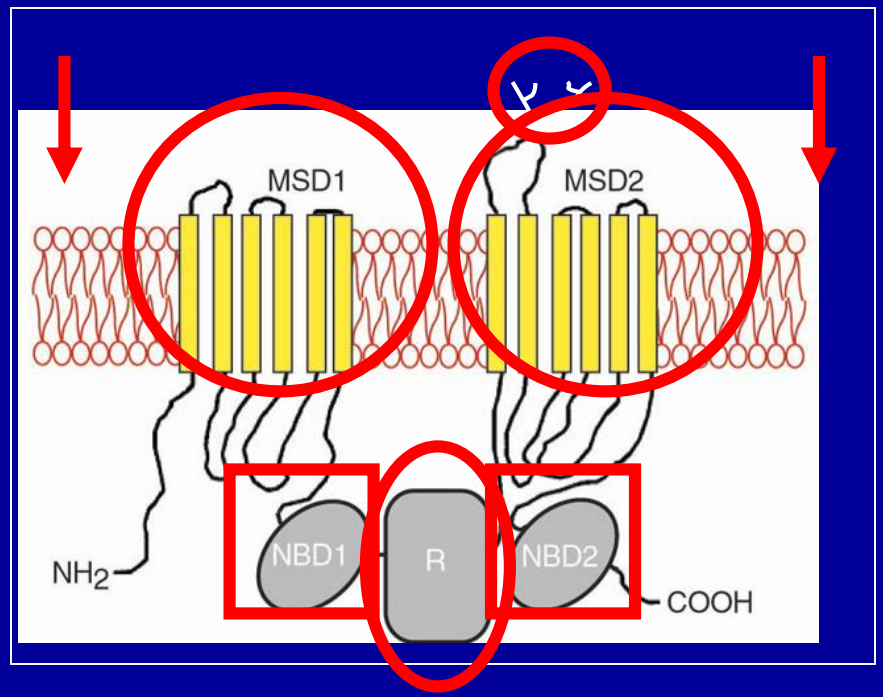
Chromosome 7



Riordan JR, et al. *Science*. 1989.
Rommens JM, et al. *Science*. 1989.
Kerem B, et al. *Science*. 1989.

CFTR Protein

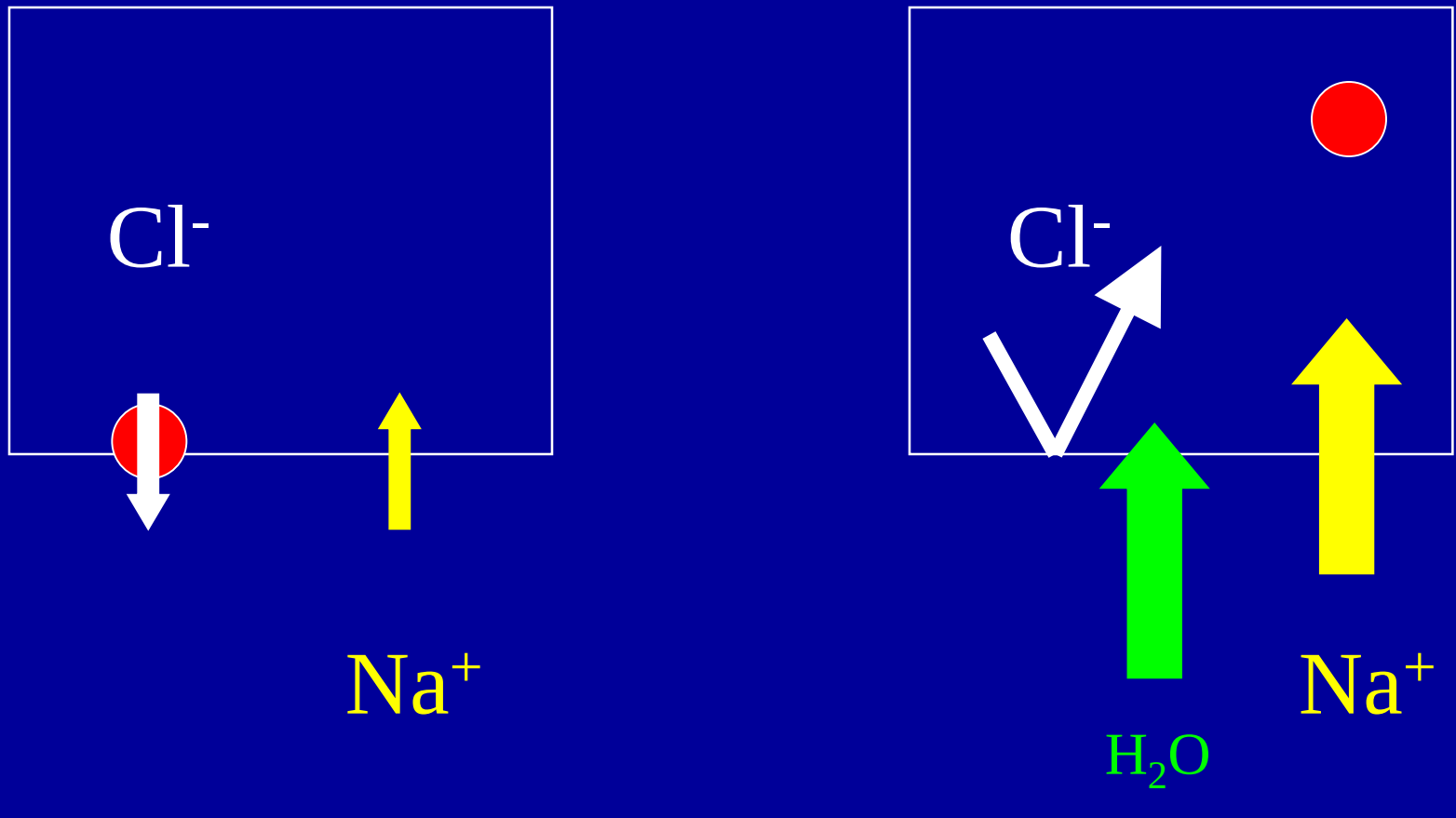
- 1480 amino acids
- MW ~170 kD
- Member of ATP-binding cassette (ABC) superfamily
- 2 six-span membrane-spanning domains (MSD)
- 2 nucleotide-binding domains (NDB)
- Unique, highly charged regulatory (R) domain
- Posttranslational modifications
- Localizes to the apical cell membrane



Riordan JR, et al. *Science.* 1989.
Ratjen F, et al. *Lancet.* 2003.
Collins FS. *Science.* 1992.
Vankeerberghen A, et al. *J Cyst Fibros.* 2002.

Normal

CF



Cystic fibrosis is a disease that:

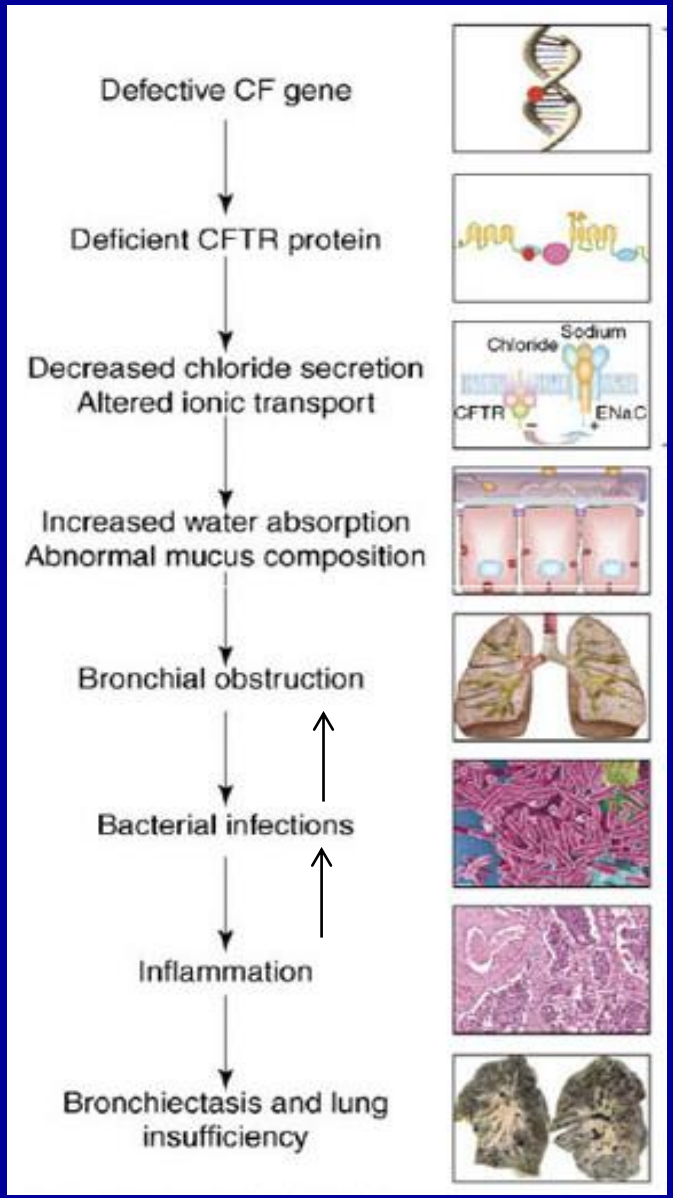
- Arises from two disease-forming mutations in the gene for CFTR on chromosome 7
- that results in changes to the fluid and electrolytes on cell surfaces
- that leads to abnormal mucus and inflammatory response
- that predisposes to obstruction and infection
- that produces end organ disease to tubular structures - *upper and lower airways, vas deferens, gut, liver, pancreas, sweat glands*
- Progressive disease which is life limiting: mean survival into adult years.

What organs are affected by CF

- Lungs
- Sinuses
- Pancreas
- Pancreatitis
- Arthropathy
- Vas deferens
- Liver disease
- Nasal polyps
- Rectal prolapse
- CF related diabetes
- Salt losing syndrome
- Inflammatory conditions of the gastro intestinal tract

Cystic Fibrosis - lung disease:

Disease Timeline



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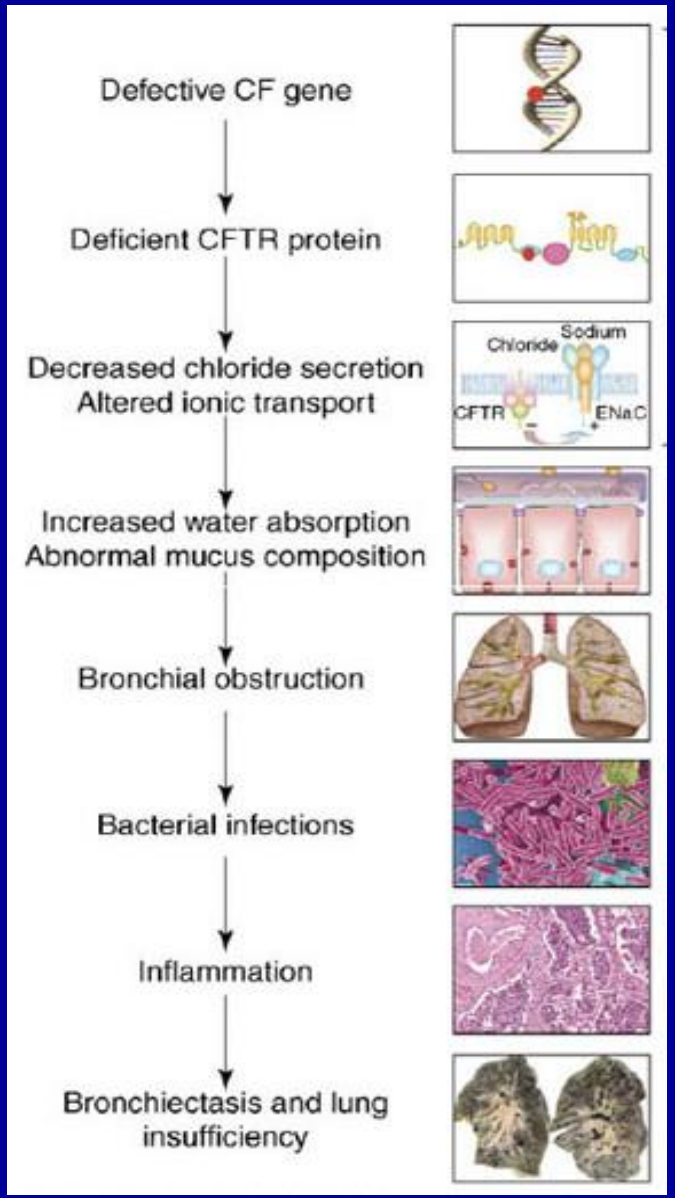


Mucolytics

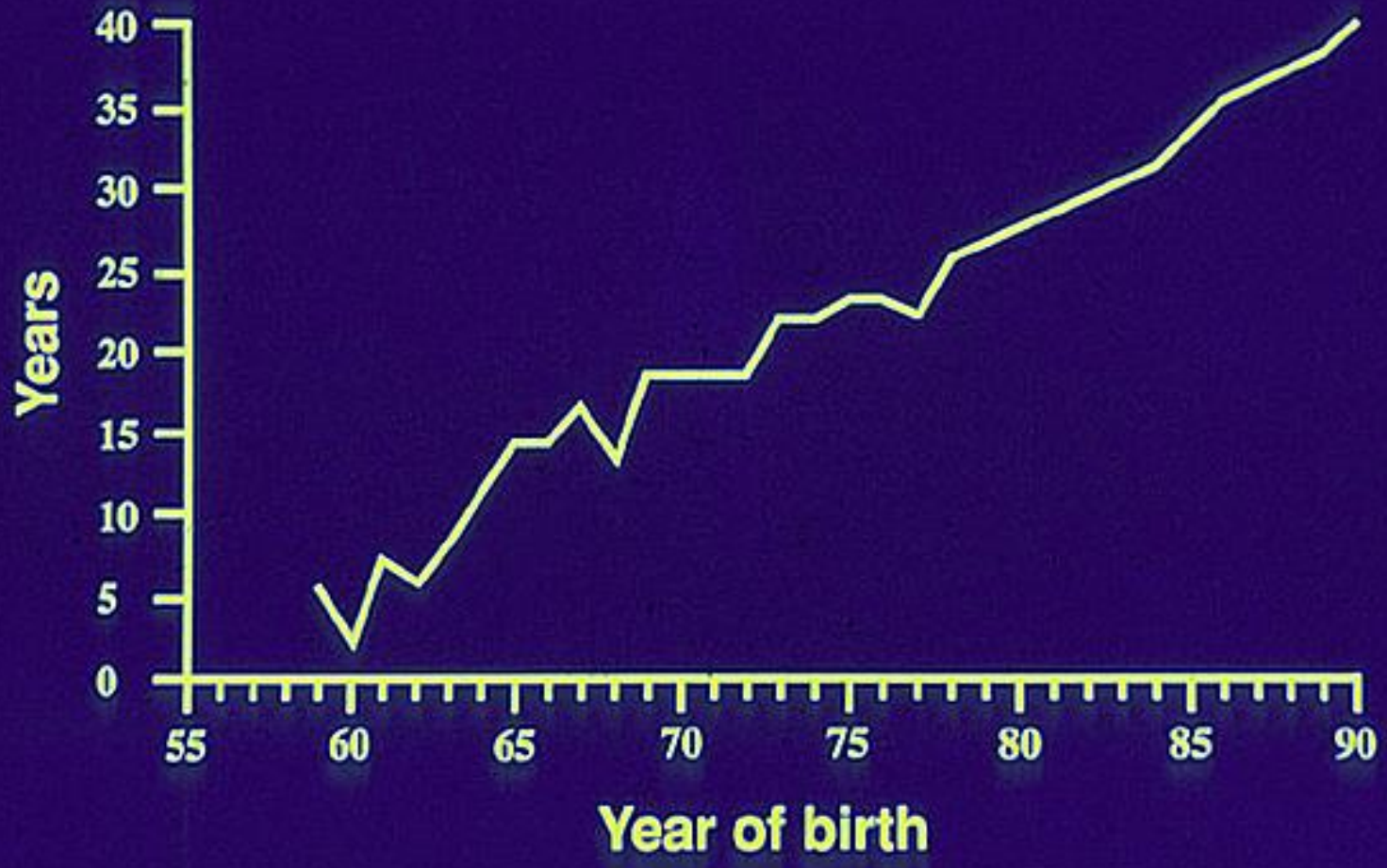
Airway Clearance

Antimicrobials

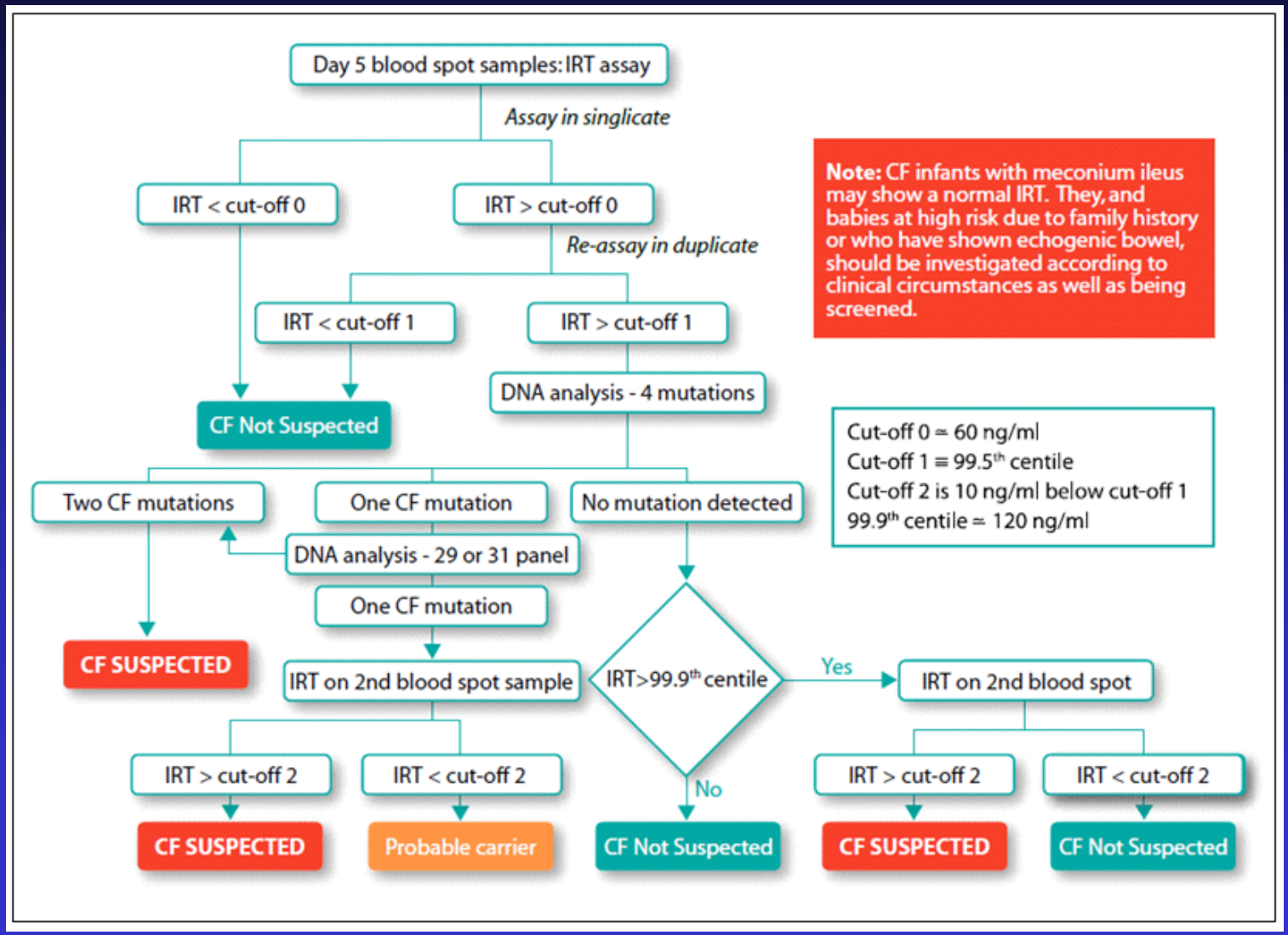
Anti-inflammatories

Lung Transplantation

Median survival by year of birth from 1959 to 1990



NEWBORN SCREENING FOR CF



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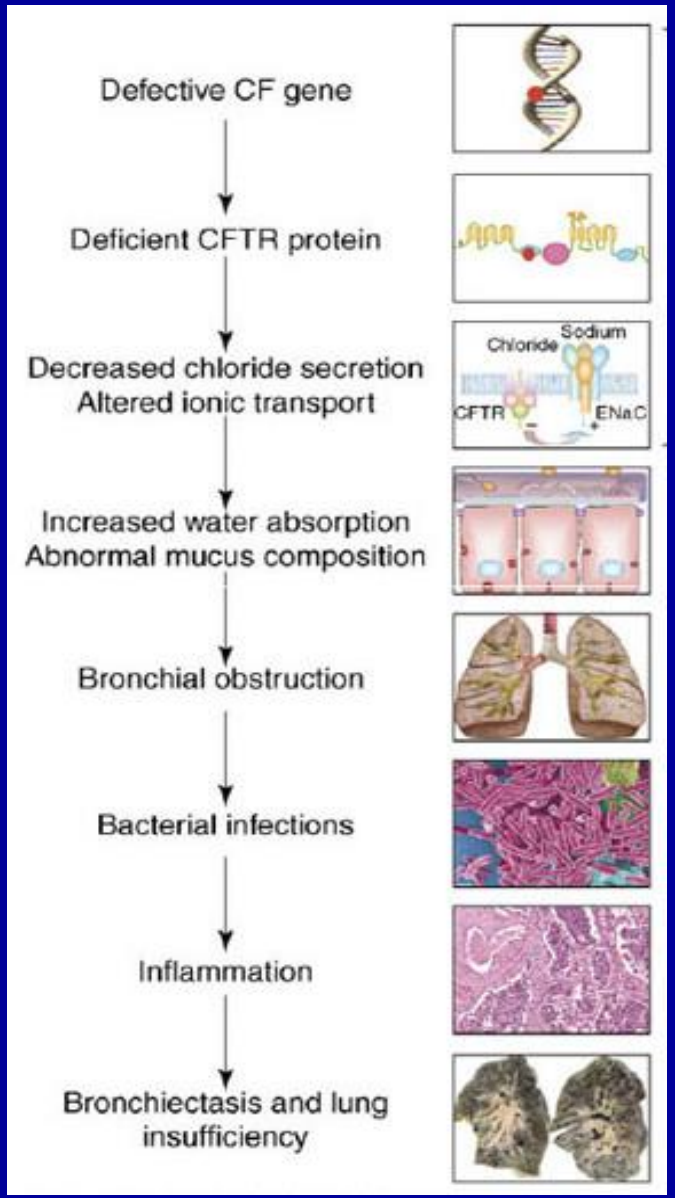
Disease Timeline



Correction of Electrolytes

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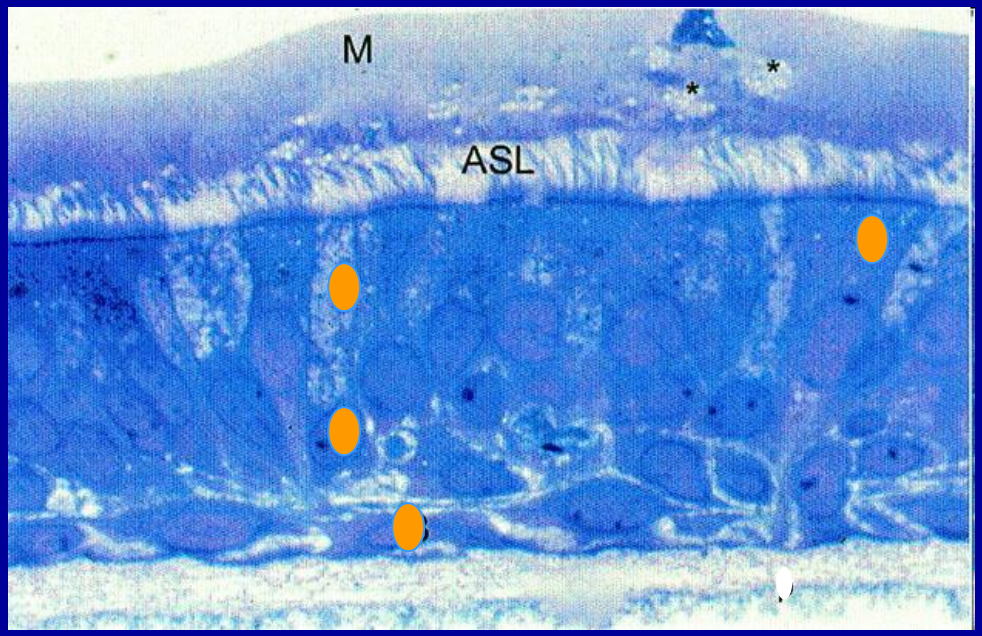
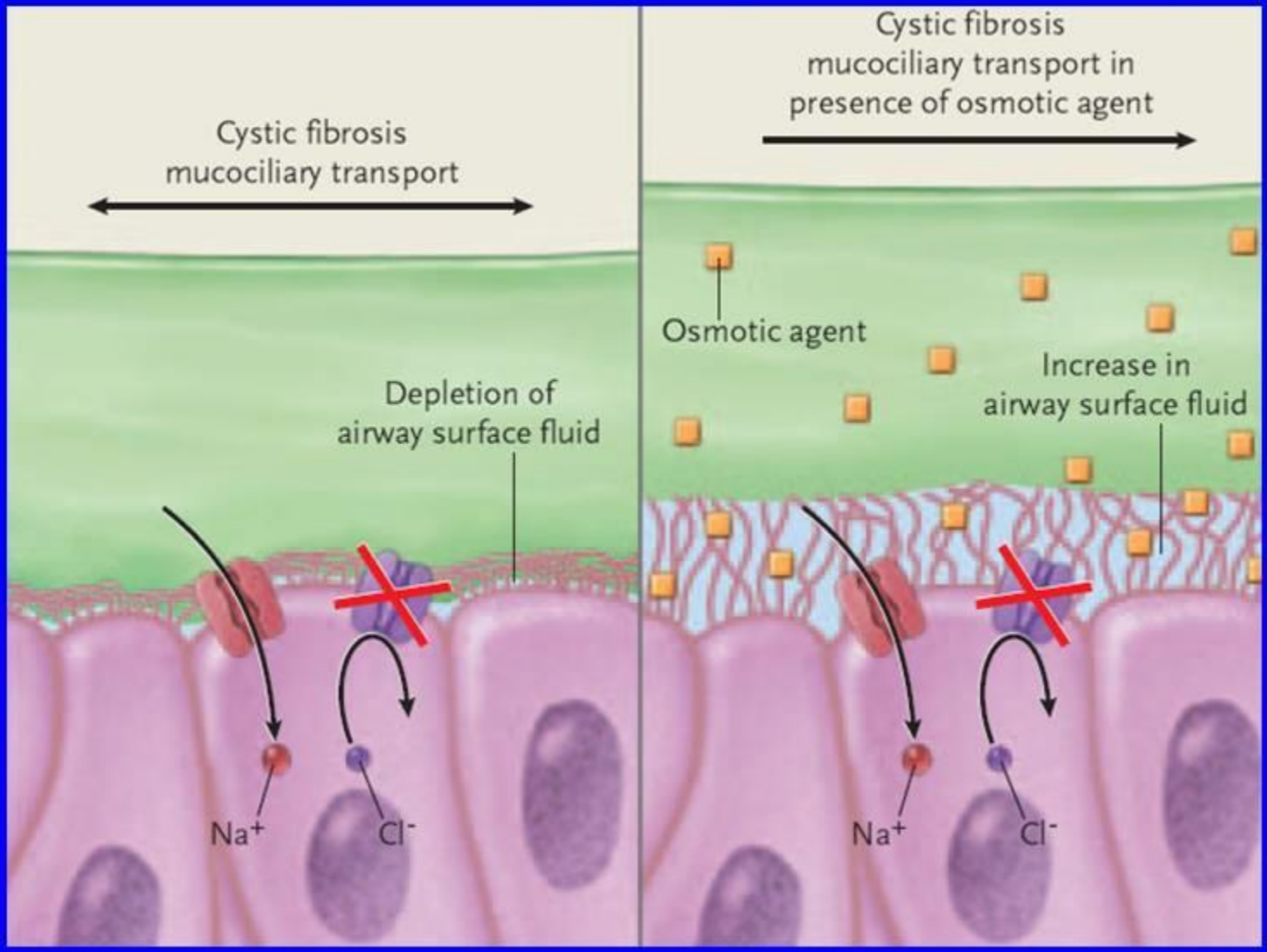
Lung Transplantation

Airway Surface Liquid



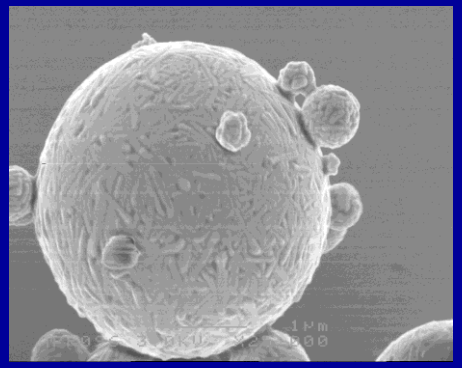
Osmotic Treatment in CF

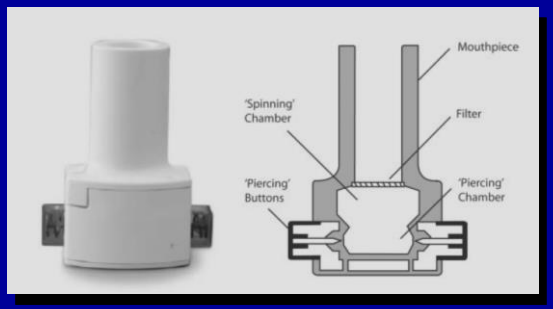


Ratjen F *NEJM* 2006

Mannitol - A naturally occurring sugar alcohol.

- A potent osmotic agent
- Mannitol dry powder
  - 400mg = 10 x 40mg caps (bd)
  - 2 - 5 minutes dosing time
  - Respirable particles - 3µm
  - No carrier
  - Small portable inhaler
  - No cleaning or preparation time





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2011
EMA/CHMP/474477/2011
EMEA/H/C/001252

Questions and answers

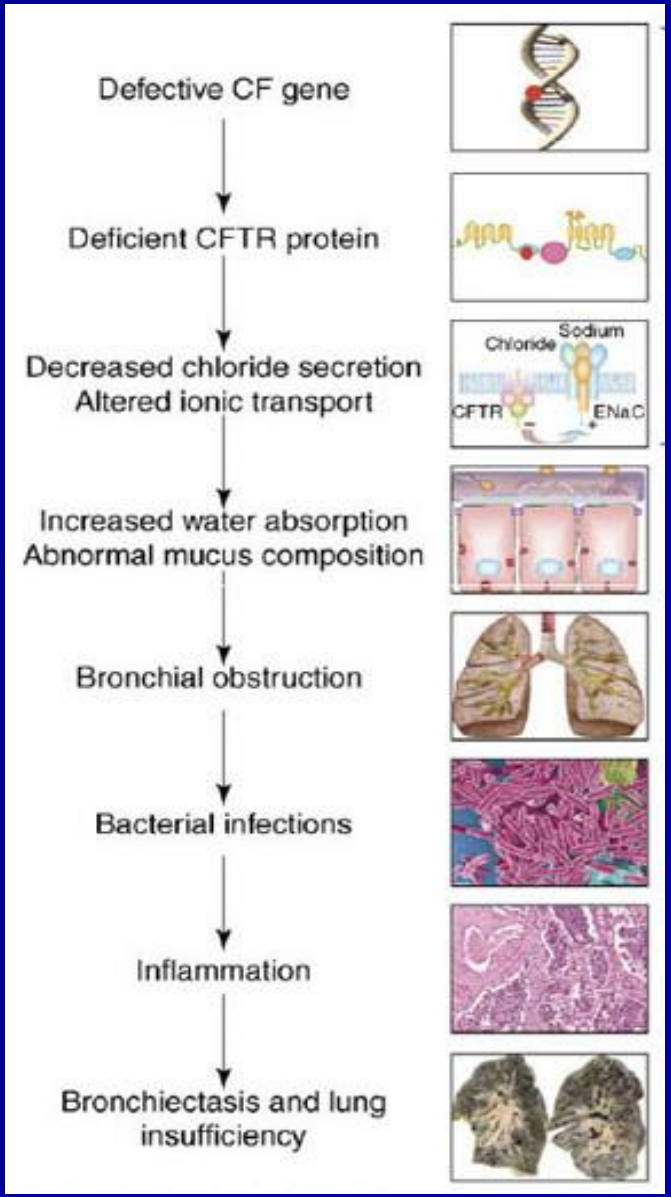
Refusal of the marketing authorisation for Bronchitol

mannitol

On 23 June 2011 the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Bronchitol, intended for the treatment of cystic fibrosis.

Cystic Fibrosis - lung disease:

Disease Timeline



Replace Gene

Correction of Electrolytes

Mucolytics

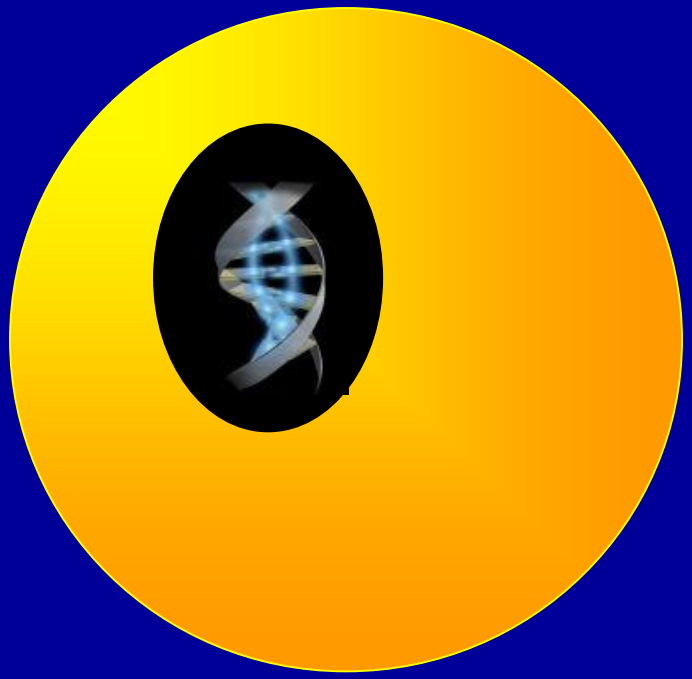
Airway Clearance

Antimicrobials

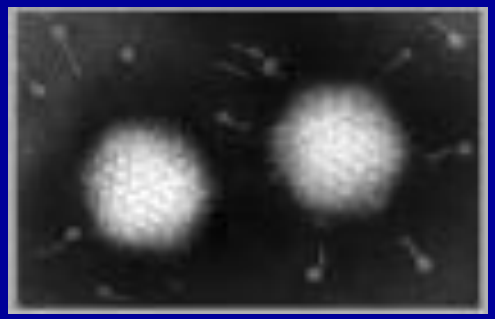
Anti-inflammatories

Lung Transplantation

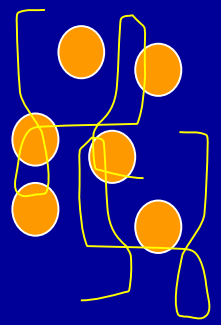
Gene Therapy



Viruses



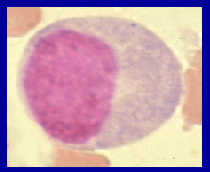
Synthetic



Barriers to airway gene therapy

1. CF mucus
2. Mucociliary escalator

3. Immune recognition



4. Cell surface glycocalyx

6. Nuclear membrane

5. Lysosomal destruction

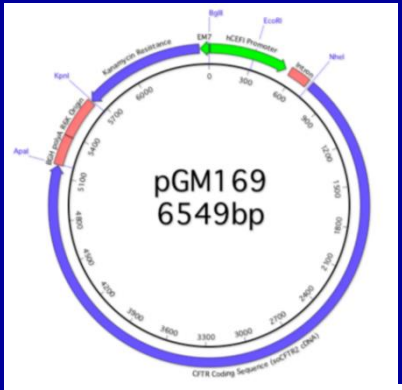
Vectors

Viral

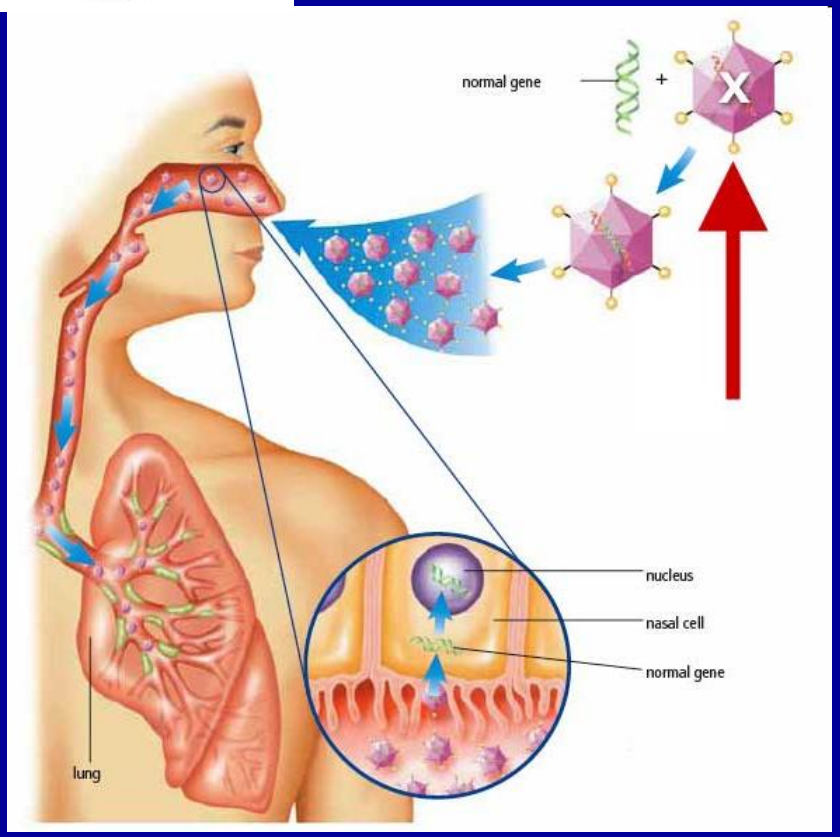
- Ad, AAV
- Accessibility of receptors & pseudotyping
- Integration?
- Superficial epithelium:
  - Repeated application
- Progenitor cells
  - Potential long effect
- Inflammation
- Repeatability issues

Non-viral

- Cationic liposomes, polymers, naked DNA
- ? efficiency
- Non-integrating
- Likely less inflammation (CPG)
- Repeatable



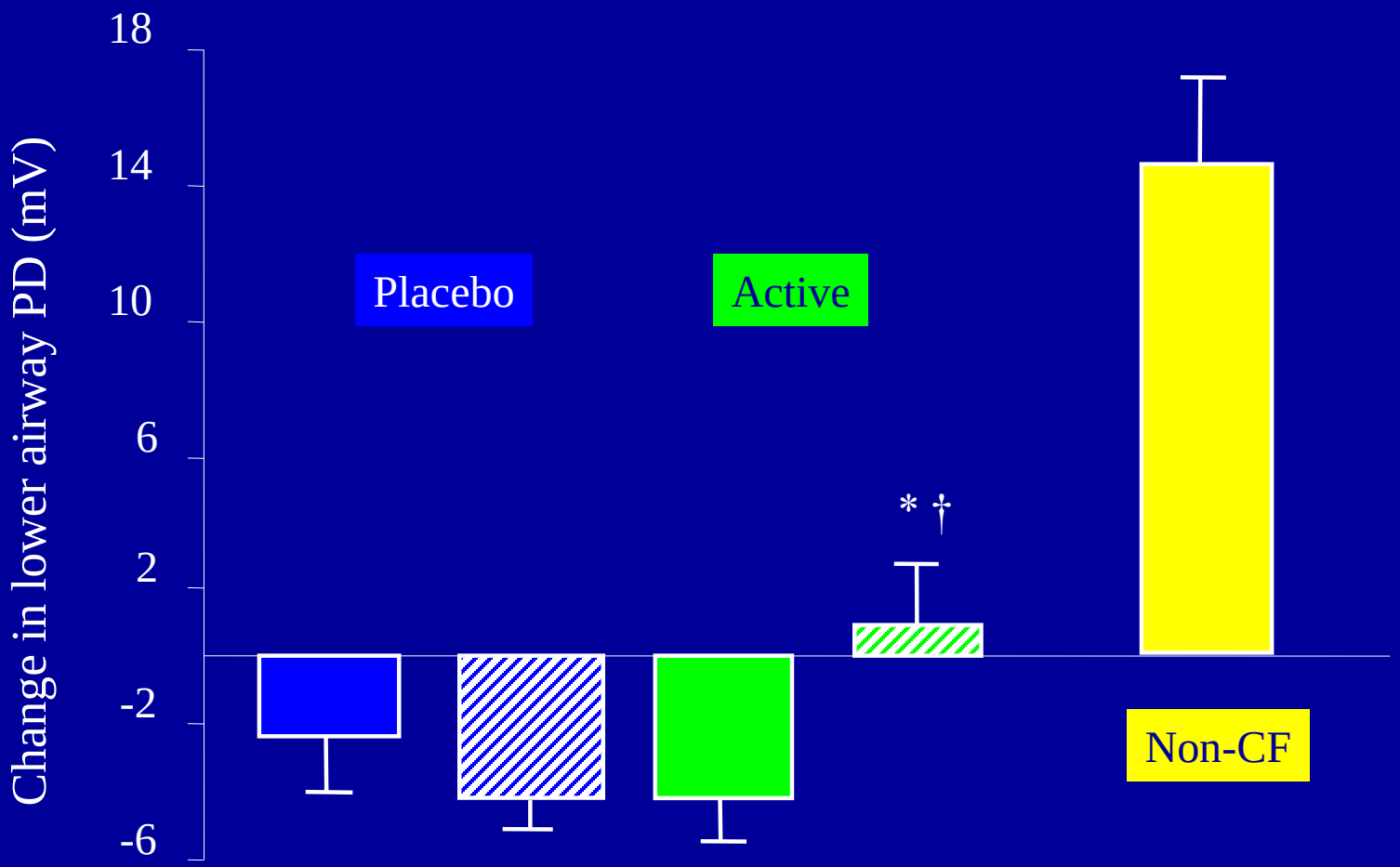
CF gene therapy



- Work for all genotypes
- Insertion correct gene into airway cells
- Fraught with problems
- Pilot (safety) study completed
- Phase 2 Multidose trial (monthly for one year)
- Recruited all 124 patients July 2013
- Results 2015

RESULTS published 2015

- 62 received the placebo
- 78 received gene therapy
- At 12 months follow up the FEV1 improved in the treatment group by 3.7%
- Further improvements in efficacy and consistency of response are needed.



Alton E *et al*. *Lancet* 2015

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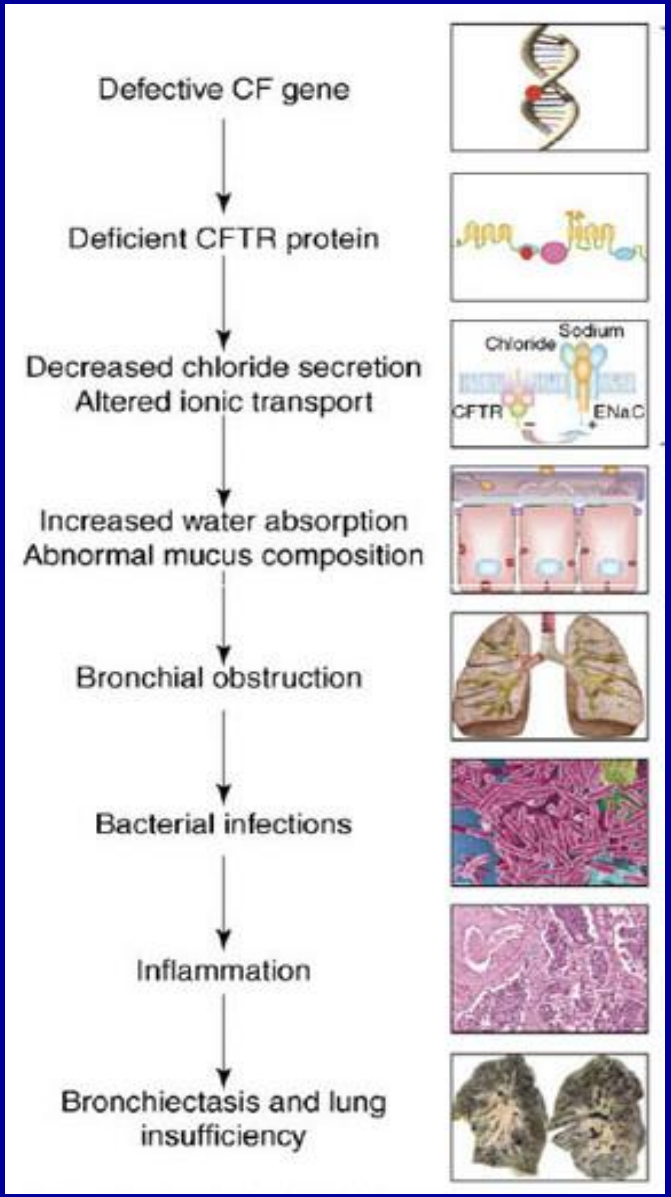

Replace Gene

Improve CFTR efficiency

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Antimicrobials

Anti-inflammatories

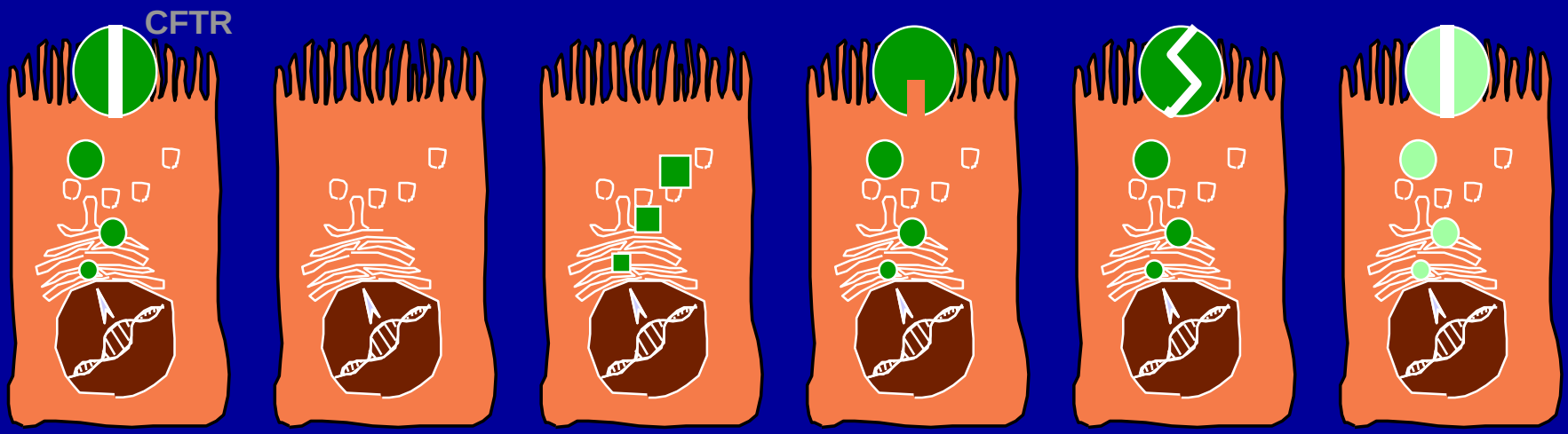
Lung Transplantation

High throughput screening

- Assay random/ selected chemicals
- Screen 5-10,000 daily
- Assays for limited function only
- Chemically modify each ‘hit’
- Early hits being explored

- Promising approach

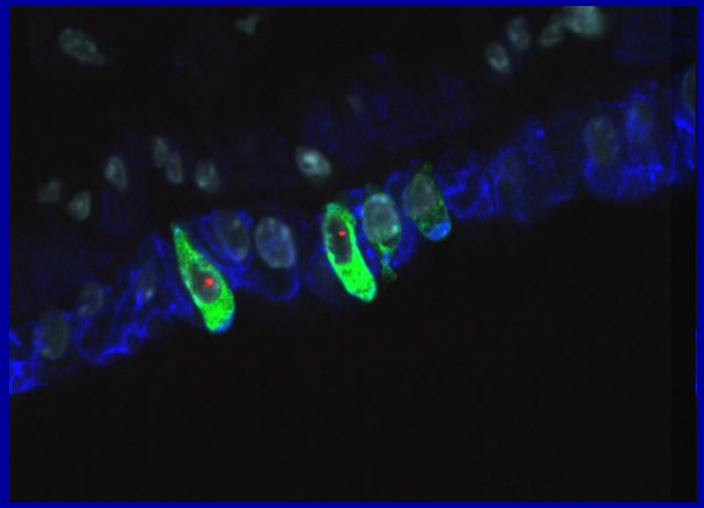
Molecular Consequences of CFTR Mutations



Normal	I	II	III	IV	V
	No synthesis	Block in processing	Block in regulation	Altered conductance	Reduced synthesis
	Nonsense G542X	AA deletion ΔF508	Missense G551D	Missense R117H	Missense A455E
	Frameshift 394delTT				Alternative splicing 3849+10kbC→T
	Splice junction 1717-1G→A				

VX770

- Acts as gating potentiator (opens the faulty gene in the cell wall)
- Class III mutations (G551D)
- Phase II. 20 patients. VX770 150mg bd 14 days



- **FEV_1 ↑ 10.1% (220ml)**
- **Sweat Cl^- ↓ 95.5 to 53.2 mmol/L**
- **Nasal PD change - 5.4mV**

VERTEX

Phase 3 Study of VX-770 Showed Profound and Sustained Improvements in Lung Function (FEV1) and Other Measures of Disease Among People With a Specific Type of Cystic Fibrosis

- Relative mean improvement in lung function of approximately 17% from baseline compared to placebo achieved by people treated with VX-770; mean absolute improvement from baseline of approximately 10.5% compared to placebo; both measures through 24 and 48 weeks -

- Significant improvements in all key secondary endpoints for VX-770; patients were 55% less likely to experience a pulmonary exacerbation, had significant reductions in sweat chloride and, on average, gained nearly 7 pounds -

- Discontinuations due to adverse events were less frequent among people treated with VX-770 -

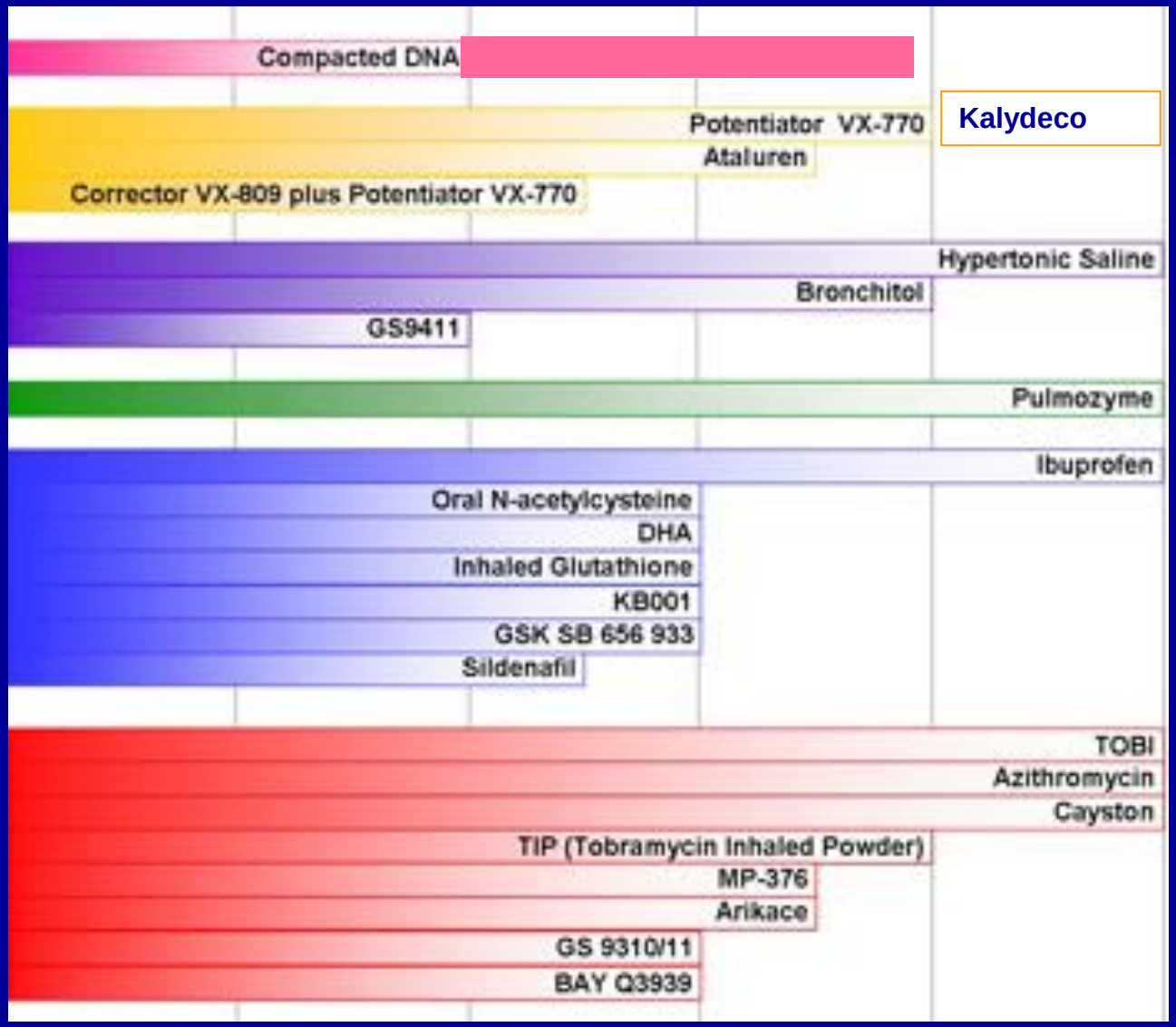
- Data support Vertex plan to submit U.S. and European regulatory applications for approval in the second half of 2011 -

2012: US food and drug agency (FDA) approved the use of Kalydeco

CF 6 years and older who had the gene mutation G551D (<4% of CF patients) – now available for all ages.

Cost: $294,000 per person per year

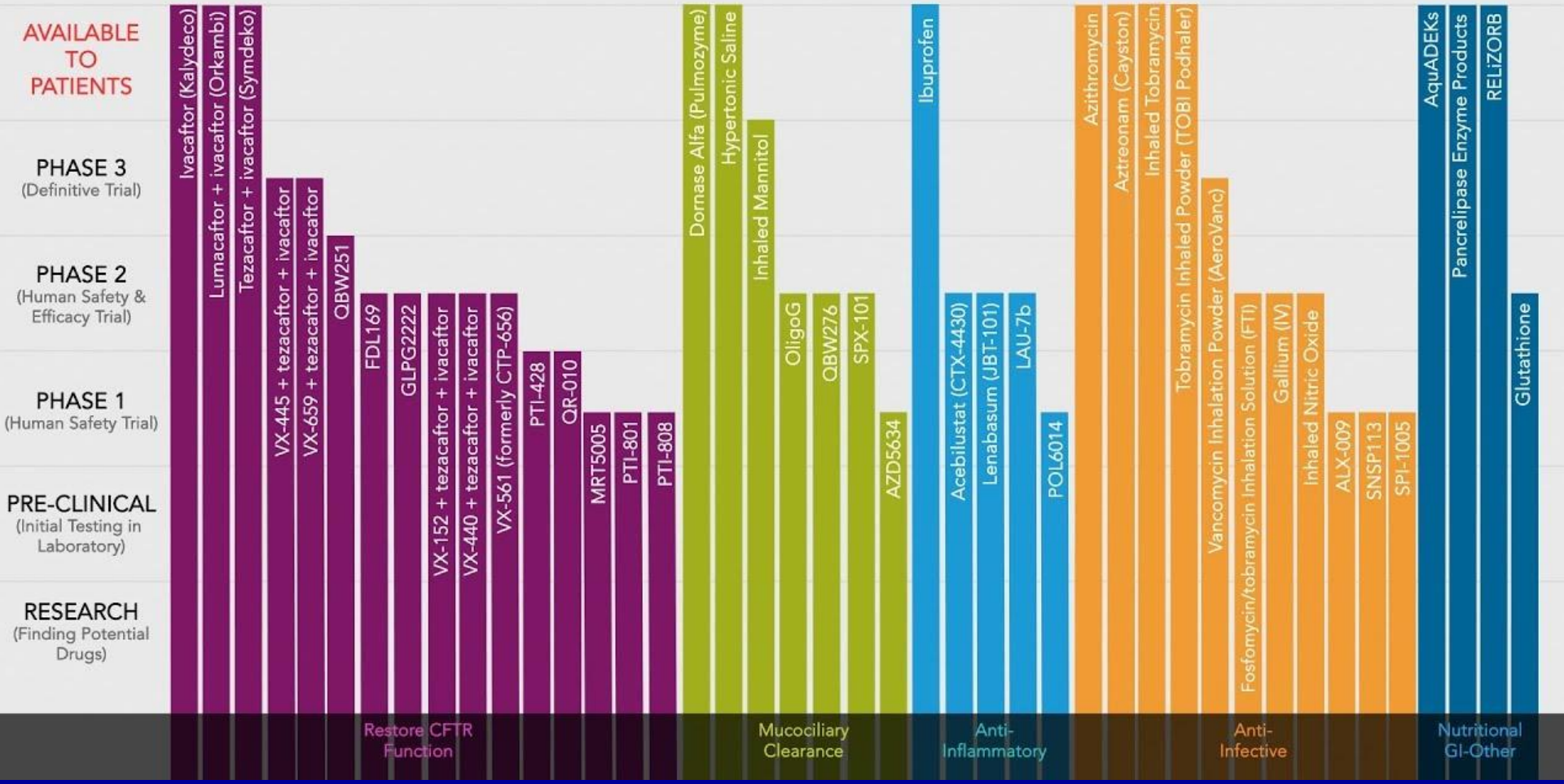
IN 2012



http://www.cff.org/research/DrugDevelopmentPipeline/

Cystic Fibrosis Foundation Therapeutics Pipeline

2018



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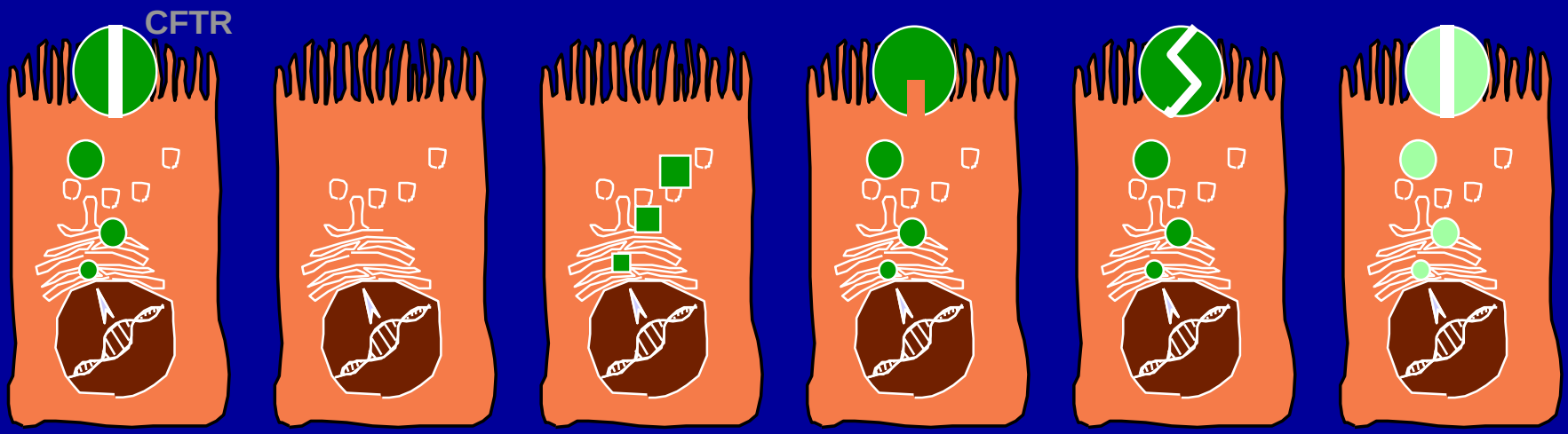

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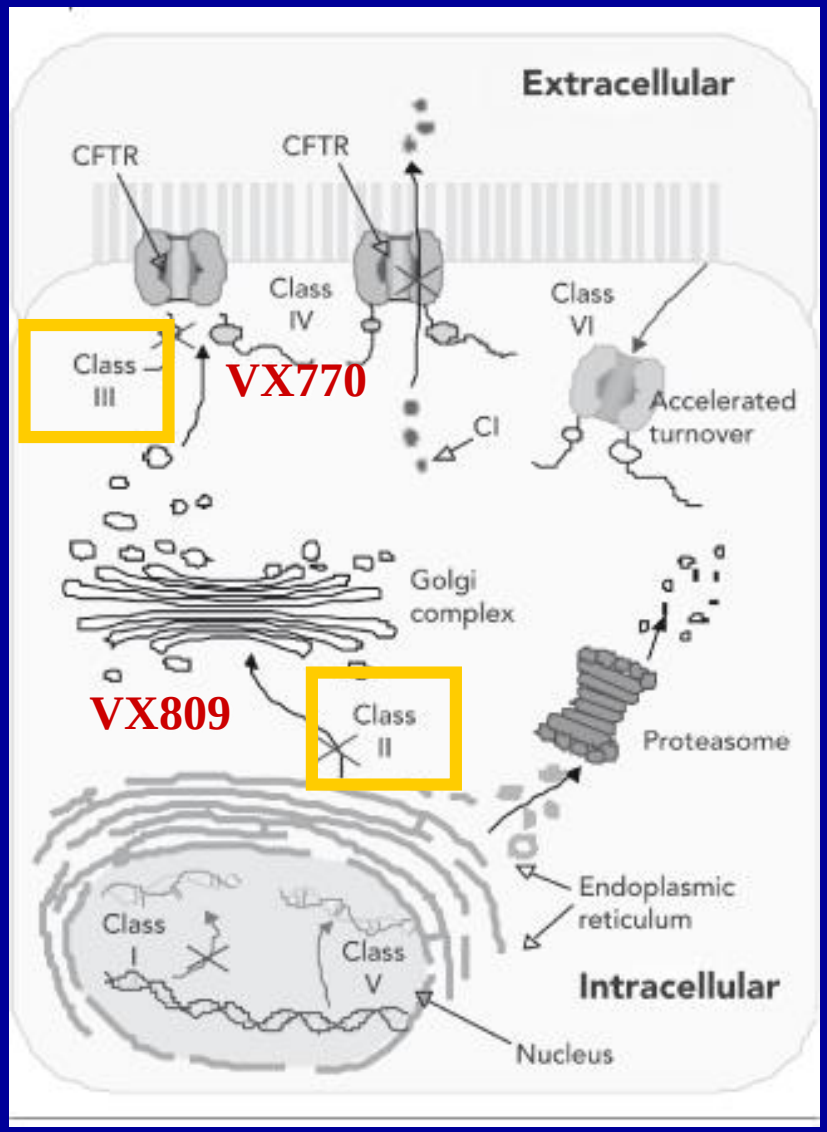
VX809 for DF508

- Considered to restore function to faulty CFTR channel (ΔF508)
- In cell layer experiments using Ussing chamber – functional increase of 15% for chloride transport
- Phase II trial has completed enrolment in ΔF508/ΔF508 pts (N=80)
- Disappointing results



What if we combine the two agents?

- Added kalydeco (VX770) and lumicaftor (VX809)
- Clinical trial:
  - Small improvement in FEV1 (around 3 – 5%)
  - No change in sweat test results
  - Some reduction in chest exacerbations

  Licensed as a drug but not yet approved by NICE in the UK
- Called Orkambi
- Very expensive

Vertex Number	Chemical name	Combination	Trade Name
Vx 770	Ivacaftor		Kalydeco
Vx 809	Lumacaftor	plus Ivacaftor	Orkambi
Vx 661	Tezacaftor	plus Ivacaftor	Symdeko
Vx 659		plus Teza and Iva	
Vx 445		plus Teza and Iva	
Vx 152		plus Teza and Iva	
Vx 440		plus Teza and Iva	

Still in clinical trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

VX-445–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles

Dominic Keating, M.D., Gautham Marigowda, M.D., Lucy Burr, Ph.D., Cori Daines, M.D., Marcus A. Mall, M.D., Edward F. McKone, M.D., Bonnie W. Ramsey, M.D., Steven M. Rowe, M.D., M.S.P.H., Laura A. Sass, M.D., Elizabeth Tullis, M.D., Charlotte M. McKee, M.D., Samuel M. Moskowitz, M.D., Sarah Robertson, Pharm.D., Jessica Savage, M.D., Christopher Simard, M.D., Fredrick Van Goor, Ph.D., David Waltz, M.D., Fengjuan Xuan, Ph.D., Tim Young, Ph.D., and Jennifer L. Taylor-Cousar, M.D., M.S.C.S., for the VX16-445-001 Study Group*

VX445-Tezacaftor-Ivacaftor

Hypothesis

Combine correctors such as VX 659 (or 445) with corrector tezacaftor will increase CFTR and improve function with ivacaftor

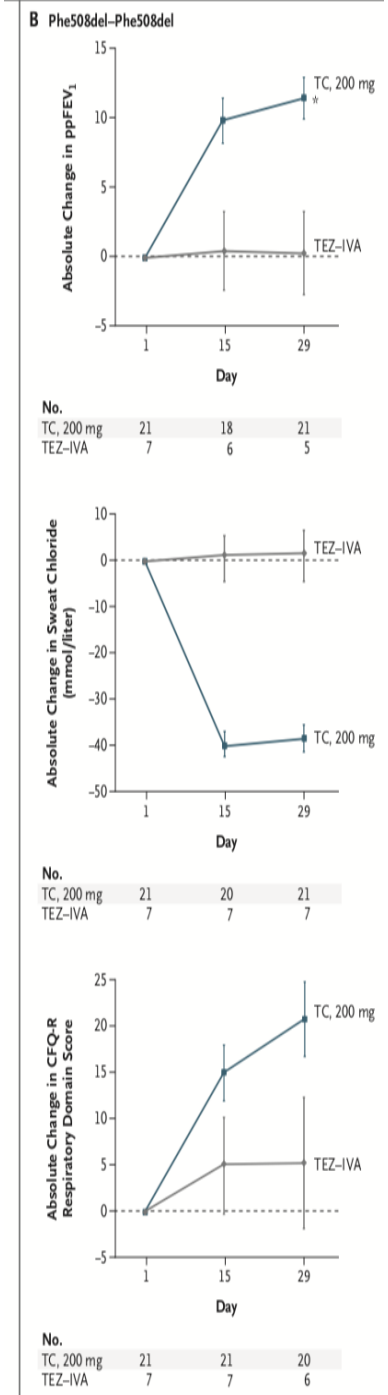


Figure 3 (facing page). Absolute Change from Baseline in the Percentage of Predicted FEV_1, Sweat Chloride Concentration, and CFQ-R Respiratory Domain Score.

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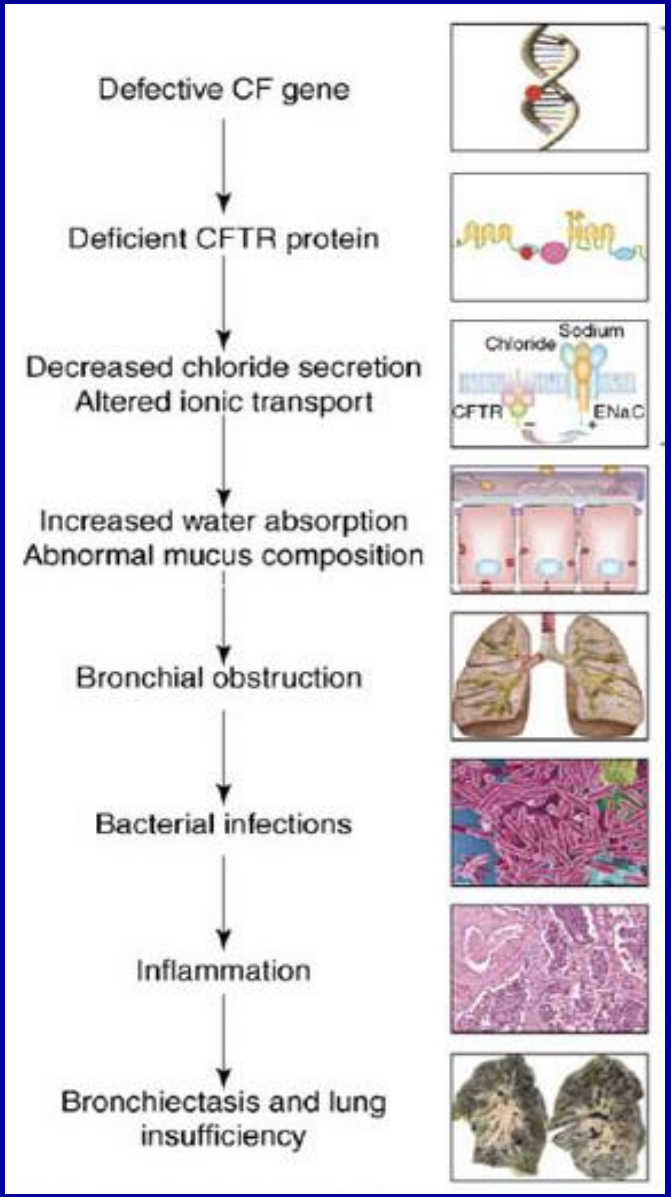
Disease Timeline



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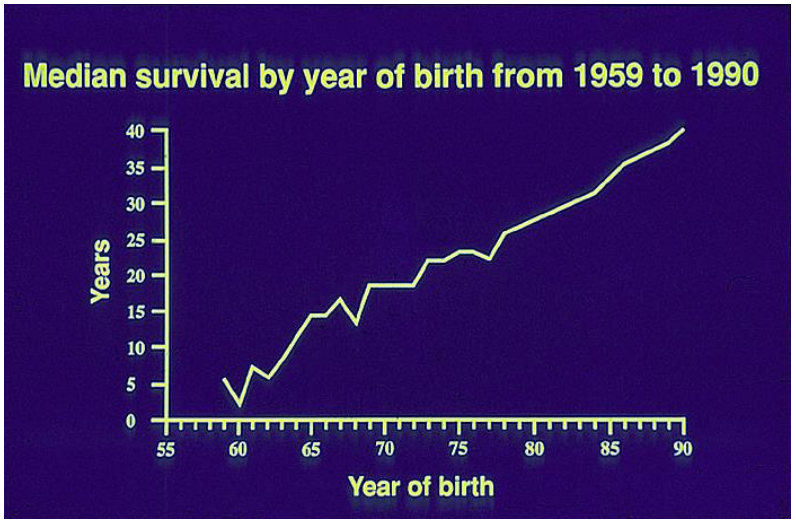

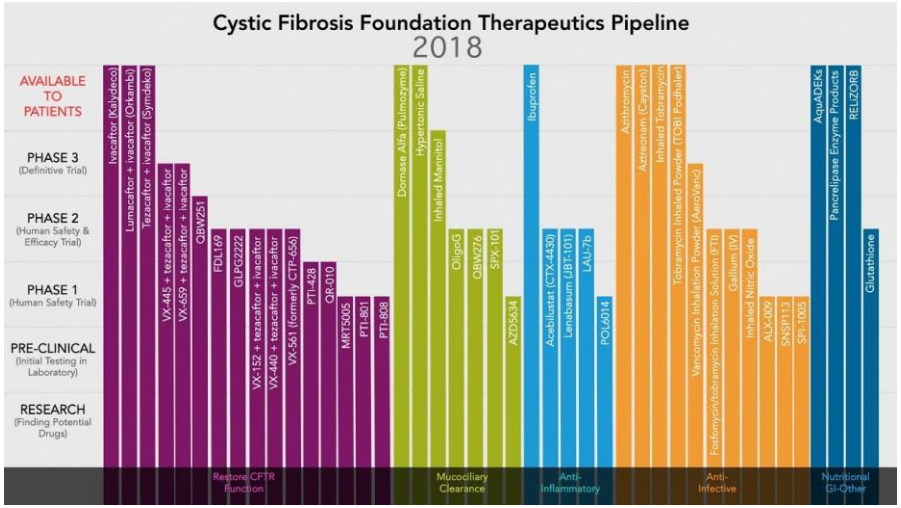

Thank you for your attention