Emerging Cystic Fibrosis Therapies: CFTR modulation

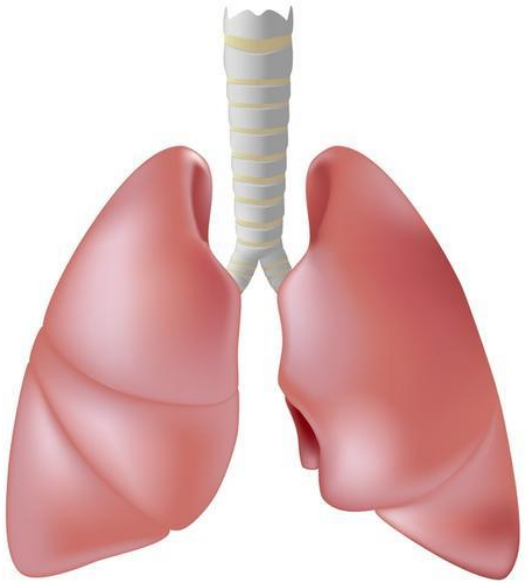


Image: https://s3.amazonaws.com/healthtap-public/ht-staging/user_answer/reference_image/2535/large/Cystic_Fibrosis.jpeg?1349133889

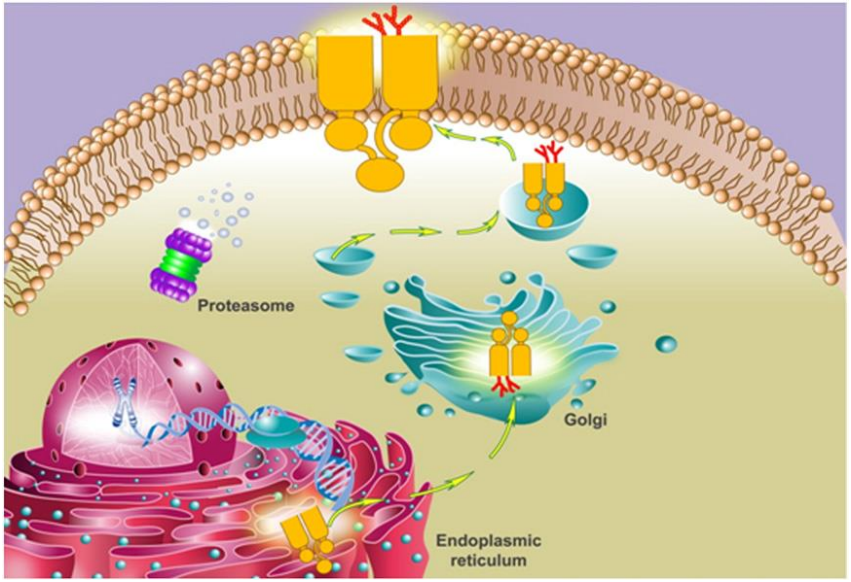
Goals

- Normal CFTR structure and function
- Clinical manifestations of CF
- CFTR modulators in the drug pipeline

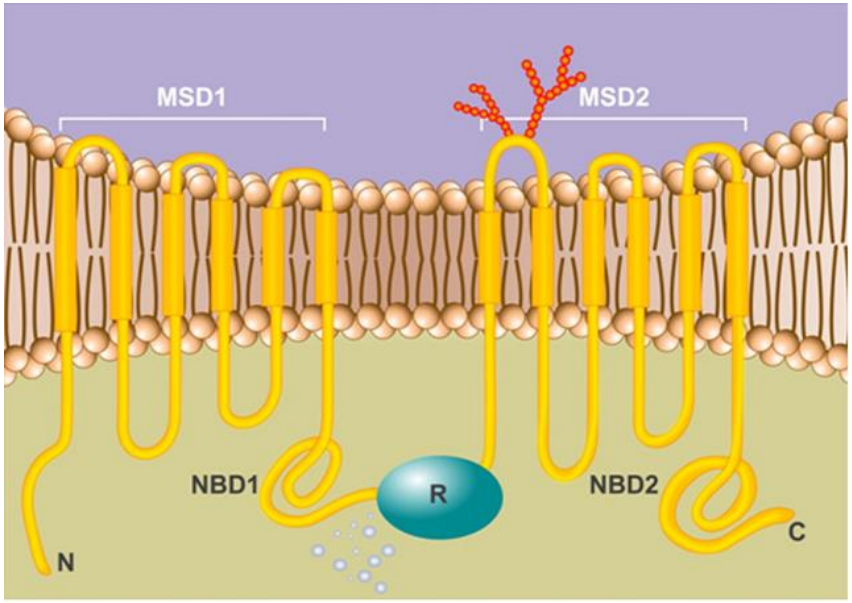
Case Report

- 11 month old male infant
- FTT, greasy stools, productive cough
- NBS: elevated immunoreactive trypsinogen
- Chloride sweat test: elevated Cl-
- Genetic testing: F508del/G551D

CFTR structure and function



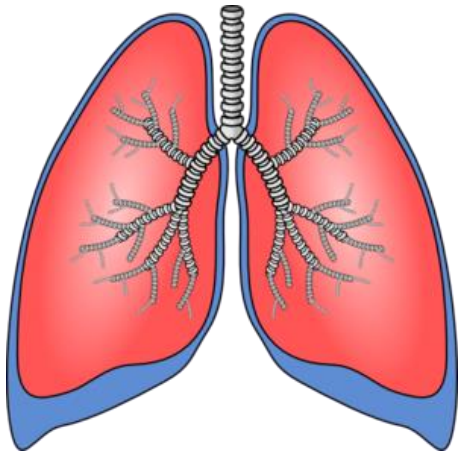
Normal CFTR biosynthesis



Normal CFTR Structure

Lubamba, Bob, Barbara Dhooghe, Sabrina Noel, and Teresinha Leal. "Cystic Fibrosis: Insight into CFTR Pathophysiology and Pharmacotherapy." *Clinical Biochemistry* 45(2012): 1132-1144.

Clinical Correlates of CFTR dysfunction



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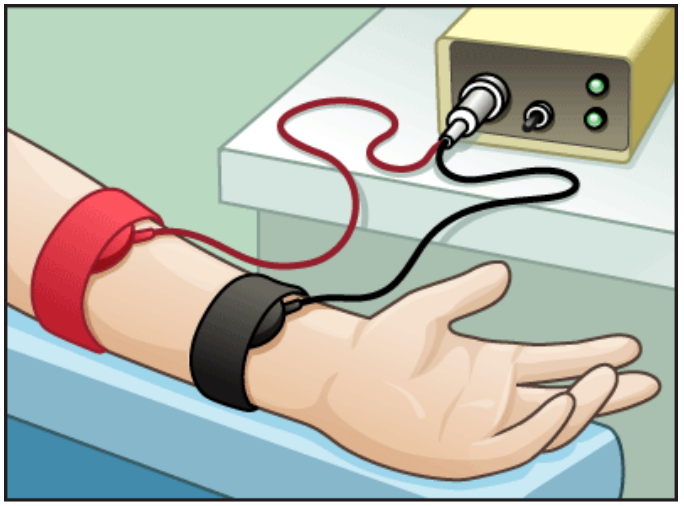

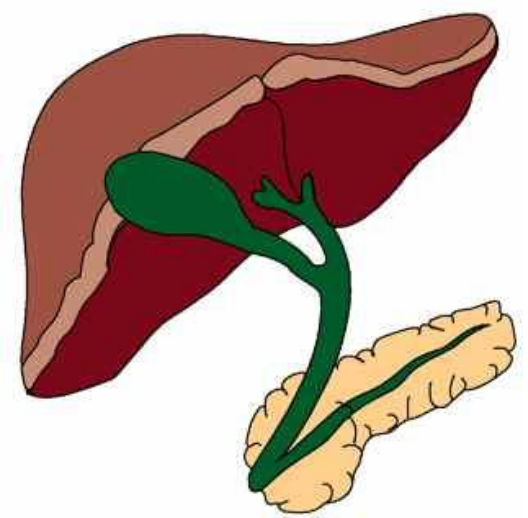

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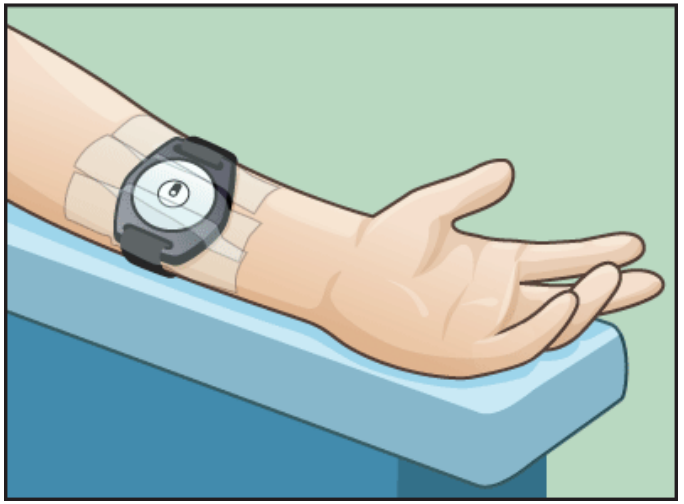
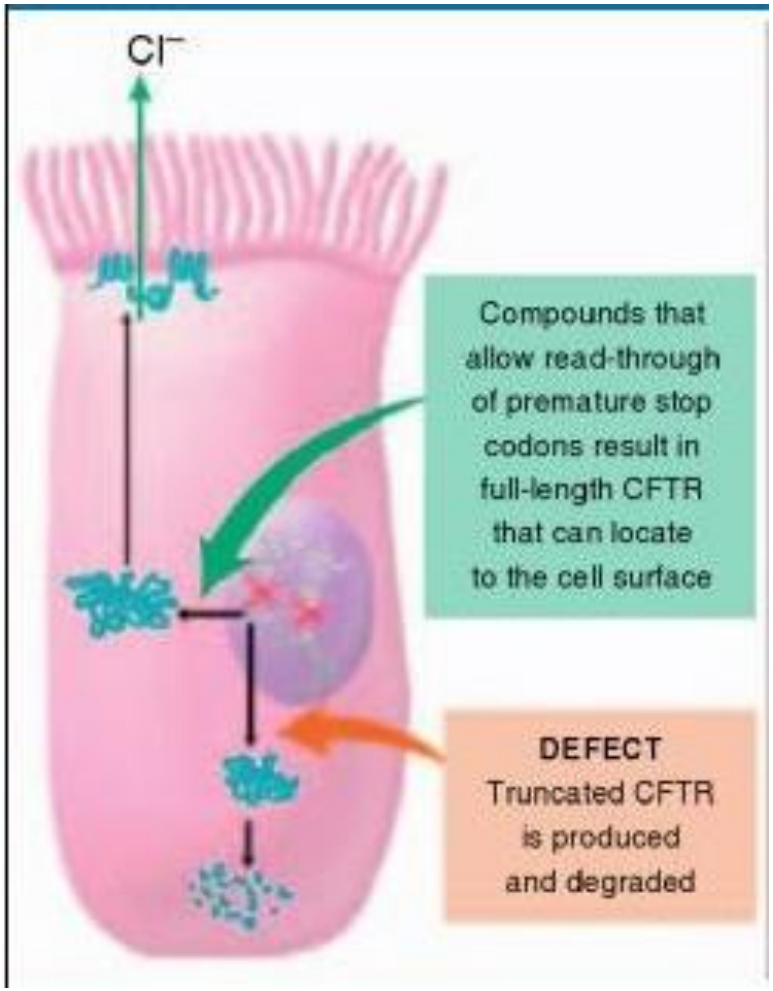


http://www.childrenscolorado.org/imgs/KidsHealth/image/ial/images/879/879_image.gif

Class I *CFTR* mutation



http://www.medscape.com/viewarticle/727395_4

- CFTR not synthesized due to **premature stop** or splicing defect
- About **5-10%** of CF
- Ataluren (PTC 124) **induces read-through** of premature stop codons

Lubamba, Bob, Barbara Dhooghe, Sabrina Noel, and Teresinha Leal. "Cystic Fibrosis: Insight into CFTR Pathophysiology and Pharmacotherapy." *Clinical Biochemistry* 45(2012): 1132-1144.

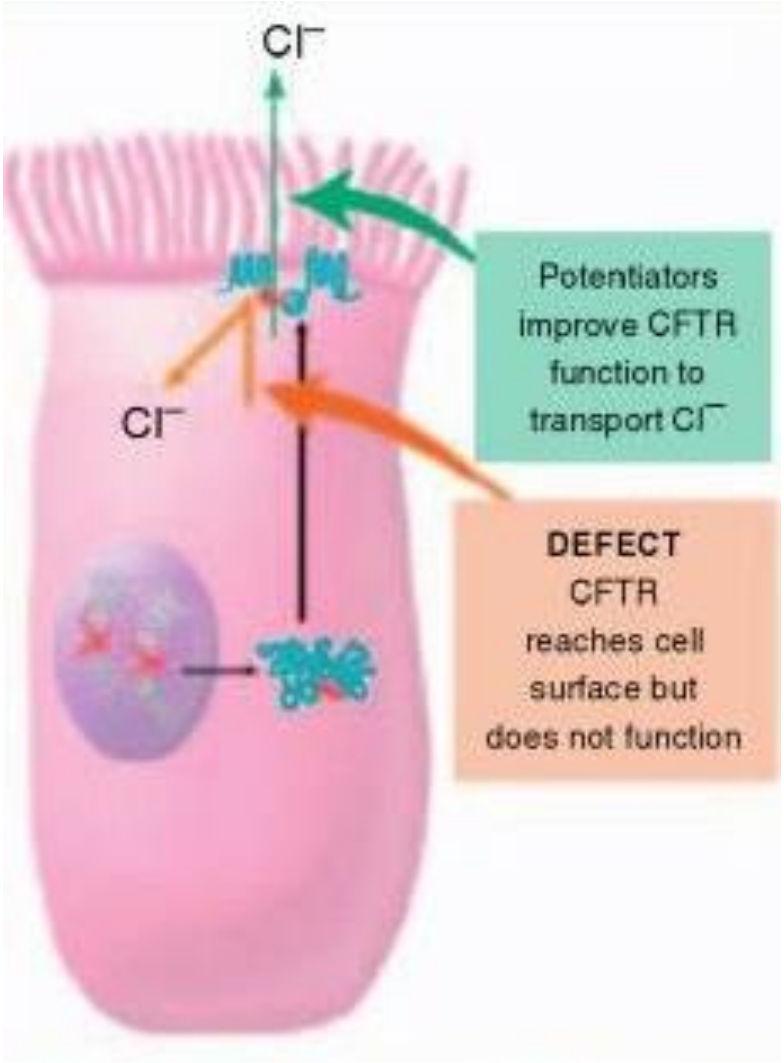
Ataluren (PTC 124)

- Completed phase 3
- Primary endpoint: change in FEV1 at 48 weeks
- Secondary endpoint: rate of exacerbations
- Results: not statistically significant
- Next: Ongoing Open Label Extension Study

"Drug Development Pipeline." *Cystic Fibrosis Foundation*. Web. 17 Feb. 2013. <http://www.cff.org/treatments/Pipeline/>.

Class III and IV *CFTR* mutations

- Class III: **Defective gating**
- Class IV: Reduced Cl- conduction (milder)
- Prototype: **G551D**
- **2-3%** of CF cases
- Ivacaftor (VX-770) a **potentiator** that restores cAMP-dependent activity of CFTR



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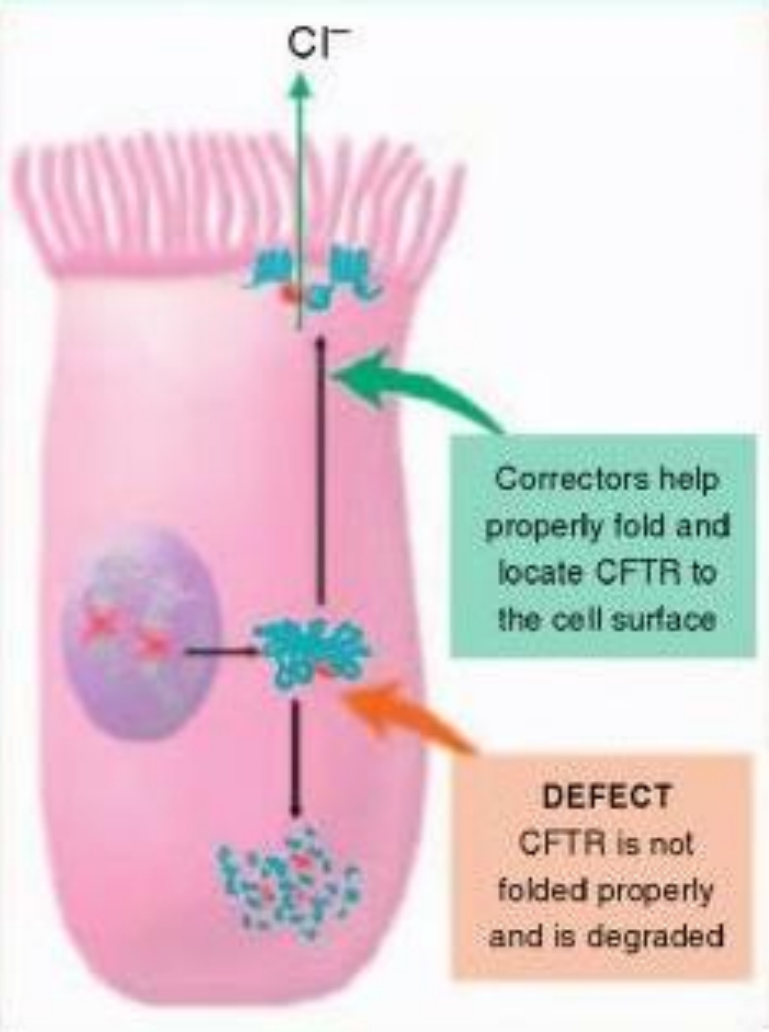
Ivacaftor (VX-770)

- FDA approved in January 2012
- Endpoints
  - Primary: improved lung function
  - Secondary: reduced exacerbations, increase in weight & increase in QOL measures
- 10% Improvement in lung function

"Drug Development Pipeline." *Cystic Fibrosis Foundation*. Web. 17 Feb. 2013. <http://www.cff.org/treatments/Pipeline/>.

Class II *CFTR* mutation



http://www.medscape.com/viewarticle/727395_4

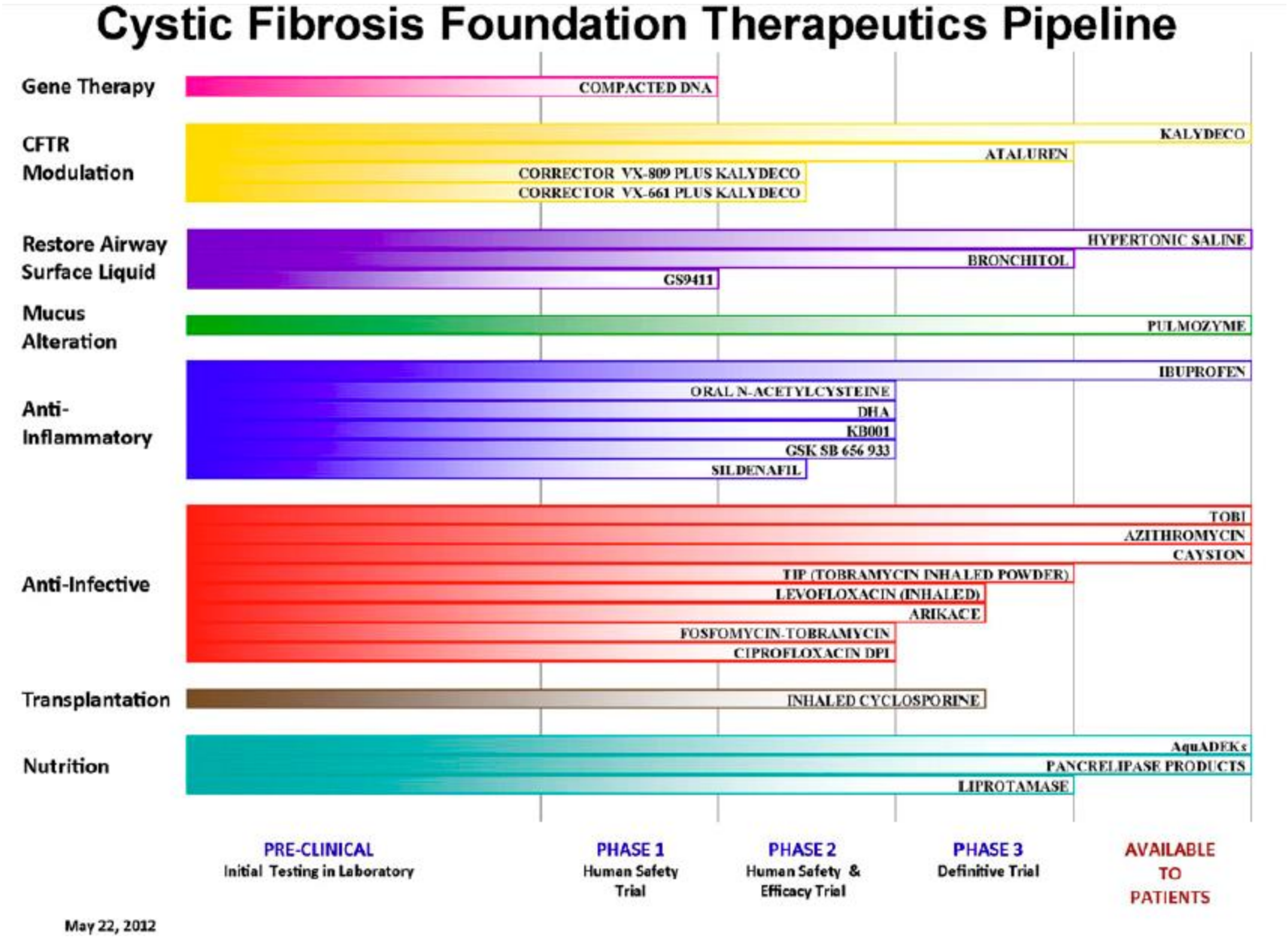
- CFTR does **not reach the cell membrane**
- Prototype: **F508del**
- About **70%** of CF
- VTX-809 and VX-661 are **correctors** of CFTR that enhance trafficking to cell membrane

Lubamba, Bob, Barbara Dhooghe, Sabrina Noel, and Teresinha Leal. "Cystic Fibrosis: Insight into CFTR Pathophysiology and Pharmacotherapy." *Clinical Biochemistry* 45(2012): 1132-1144.

Lumacaftor (VX-809) + Kalydeco

- Phase 2 study completed
- Significant improvements in lung function in F508del homozygous
- Smaller improvements for F508del heterozygous
- Next: Phase 3 trial in F508del homozygous patients

"Drug Development Pipeline." *Cystic Fibrosis Foundation*. Web. 17 Feb. 2013. <http://www.cff.org/treatments/Pipeline/>.



http://journal.publications.chestnet.org.libproxy.lib.unc.edu/data/Journals/CHEST/926155/chest_143_1_207.pdf

Case Report Continued

Patient's new treatment regimen:

- Chest PT 20 minutes twice daily
- High calorie and high fat diet
- Vitamin once daily
- Enzymes with every meal and snack
- TOBI nebulizer twice daily based on culture
- Pulmicort nebulizer twice daily
- Albuterol as needed
- PPI once daily