envolve™
Pharmacy Solutions

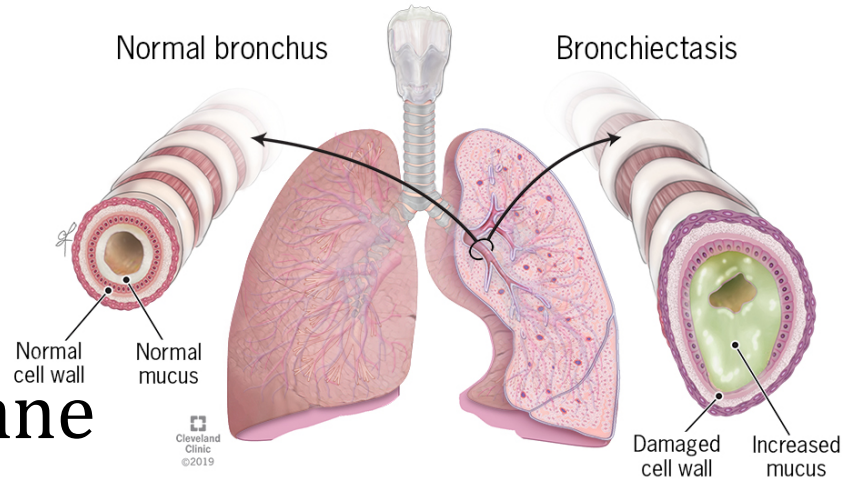
Cystic Fibrosis

Shabrin Murshed, Doctorate of Pharmacy Candidate
University of the Pacific School of Pharmacy Class of 2021

OBJECTIVES

- Define Cystic Fibrosis
- Understand Epidemiology, Risk Factors and Symptoms
- Discuss Pathogenesis and Diagnosis
- Review Cystic Fibrosis Guidelines
- Discuss Current and Future Therapies
- What Does Cystic Fibrosis Look Like Now?

WHAT IS CYSTIC FIBROSIS?

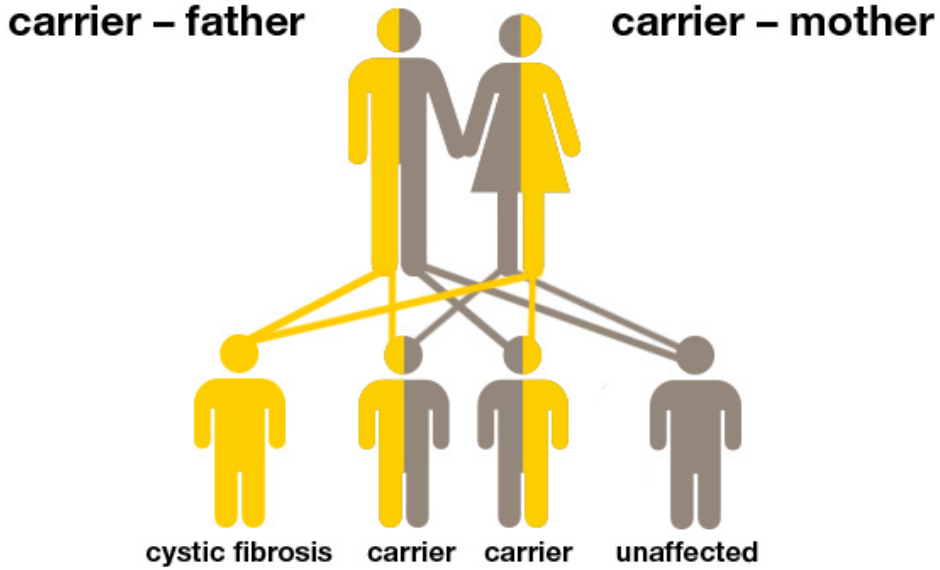


- A progressive, genetic disease
- Mutations in cystic fibrosis transmembrane conductance regulator (CFTR) gene (dysfunction in gene)
- Unable to move chloride and water to cell surface
- Results in thick and sticky mucus
- Mucus causes difficulty breathing and persistent lung infections
- Mucus causes intestinal blockages and pancreatic insufficiency

EPIDEMIOLOGY AND RISK FACTORS

- Carrier: a person with 1 defective CF gene
- People with 2 defective genes have a 25% chance of having CF
- There are 1700 mutations that can affect the CF gene
- Common in people of north European ancestry

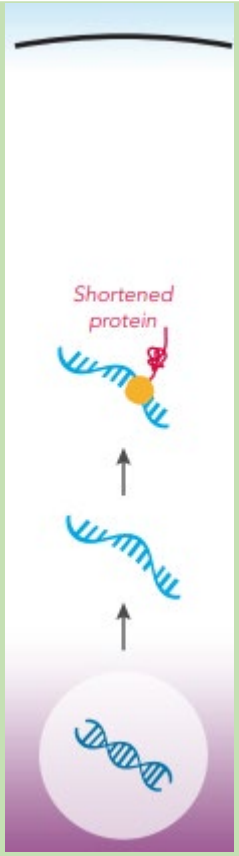
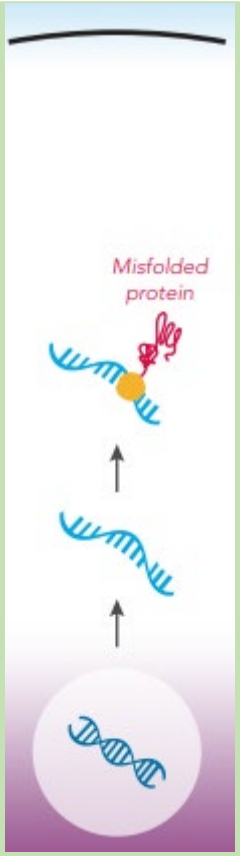
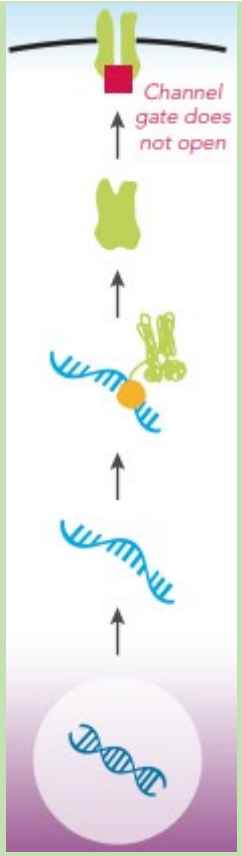
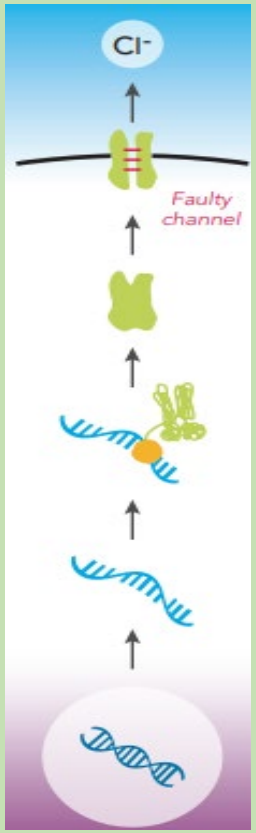
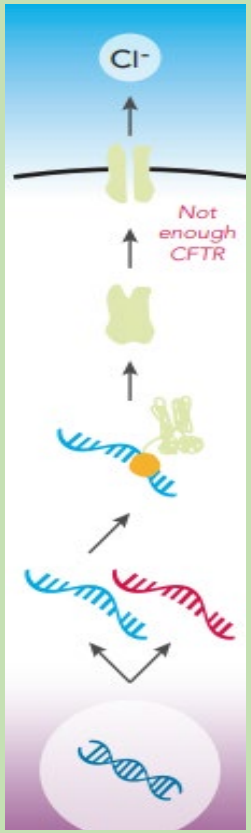
Prevalence of Cystic Fibrosis	
United States	30,000
Worldwide	70,000
Caucasian-Americans	1 in 3,500 births
Hispanic-Americans	1 in 7,000 births
African-Americans	1 in 17,000 births
Asian-Americans	1 in 90,000 births



PATHOPHYSIOLOGY

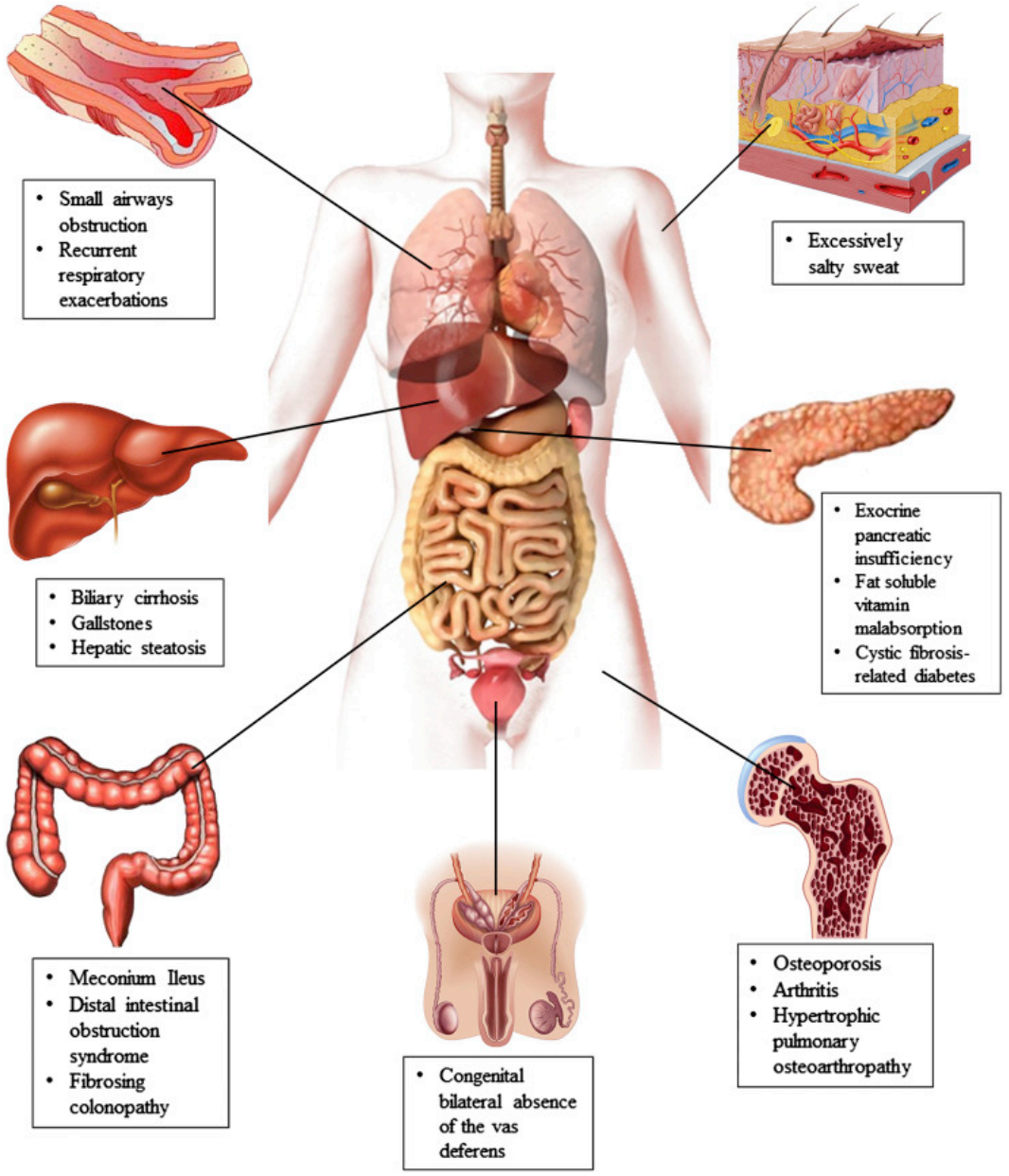
- Defective CFTR protein leads to thick and sticky mucus
- Serious lung infections from bacteria being trapped in the mucus
- Lung tissue destruction from elastase release
- Mucus blocks the pancreas canaliculi and gallbladder duct leading to malabsorption
- Distal Intestinal Obstruction Syndrome (DIOS) from thickening of stool
- Imbalance of minerals in blood leading to complications: dehydration, arrhythmias, fatigue

CFTR MUTATION CLASSES

	CLASS I	CLASS II	CLASS III	CLASS IV	CLASS V
	No functional CFTR is created	CFTR is created but misfolds keep it from moving to cell surface	CFTR is created and moves to cell surface, but channel gate does not open properly	CFTR is created and moves to cell surface, but the function of the channel is faulty	Normal CFTR is created and moves to cell surface, but in insufficient quantities
% of CF patients with at least one mutation in the class	22%	88%	6%	6%	5%
What's happening inside the cell					

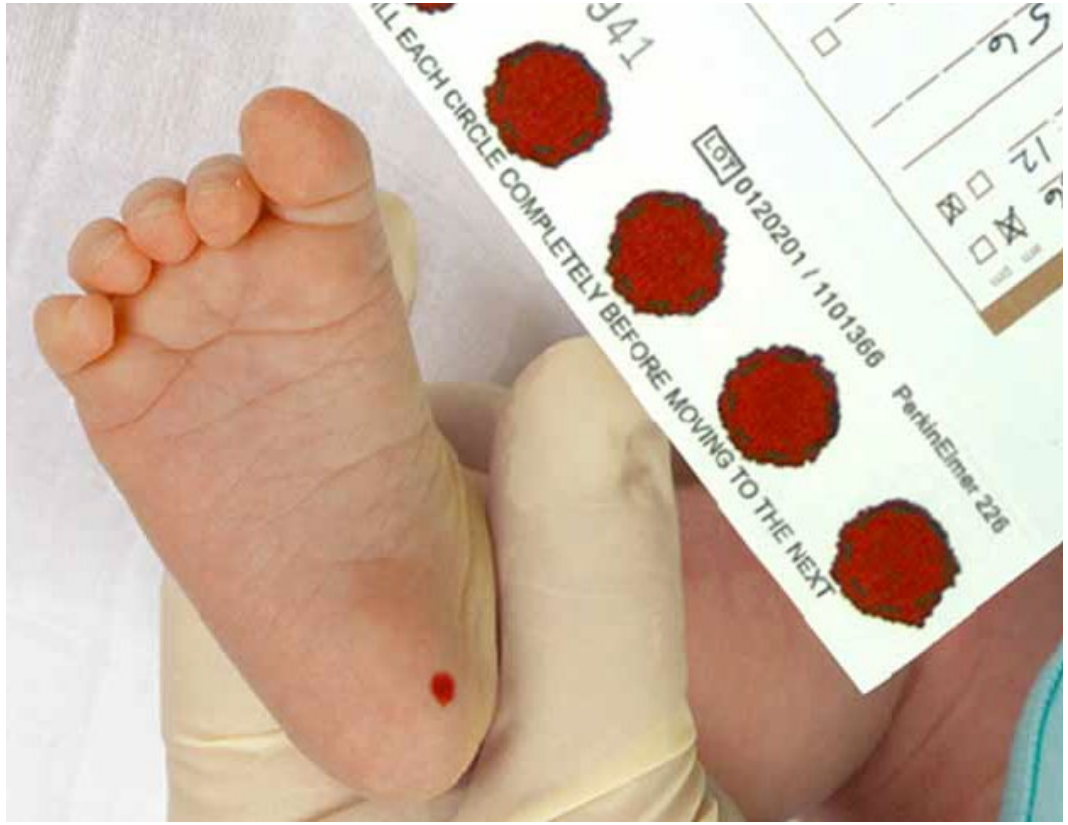
SYMPTOMS

- Salty-tasting skin
- Persistent coughing, with phlegm
- Frequent lung infections
- Wheezing
- Poor growth or weight gain
- Greasy, bulky stools/difficulty with bowel movements
- Male infertility



DIAGNOSIS

- Newborn screening (NBS): screens for different genetic and congenital disorders
- Sweat chloride test: ≥60 mmol/L, must be confirmed with genetic test
- Genetic/carrier test: determines if a carrier has the most common types of mutations with a blood sample or cheek swab

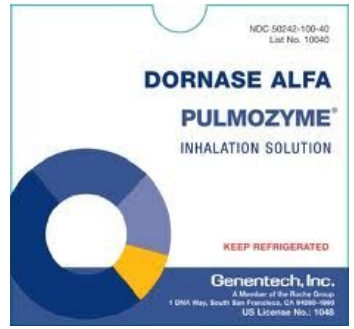


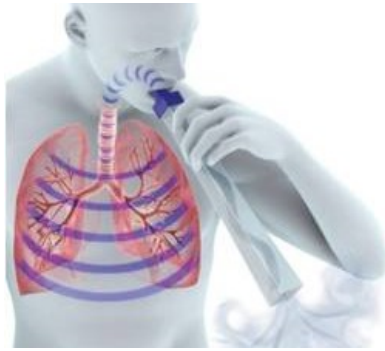
COMPLICATIONS OF CYSTIC FIBROSIS

RESPIRATORY	GASTROINTESTINAL	OTHER
Infection	Bowel problems: gallstones, intestinal blockage, rectal prolapse	Depression
Chronic respiratory failure	Malnutrition	Anxiety
	Electrolyte abnormalities	Infertility
	CFRD: Cystic Fibrosis-Related Diabetes	

Management of Respiratory Complications

1. Bronchodilators: helps widen airways by relaxing the muscles in the airway walls → albuterol
2. Mucus thinners (mucolytics)
    - Hypertonic saline: increases the amount of salt in the airways, which attract water and thins the mucus, making it easier to cough out
    - Dornase alfa: inhaled medication that thins the mucus. Cuts up the long DNA strands in white blood cells, which helps break up the thick, sticky mucus that leads to lung infections
3. Airway clearance techniques: involves coughing or huffing to help mucus out of small airways
4. Antibiotics (prevention and controlling lung infections)
    - Inhaled tobramycin and aztreonam: taken every other month for 28 days or alternate both every 28 days
    - Oral antibiotics (ciprofloxacin, cephalexin, amoxicillin, doxycycline): May be taken daily for acute or chronic therapy
    - IV antibiotics: for lung exacerbations
5. Control of airway inflammation: NSAIDs, inhaled and systemic steroids and cromolyn
6. Lung transplantation: receiving new lungs from a donor which can extend and improve the quality of life





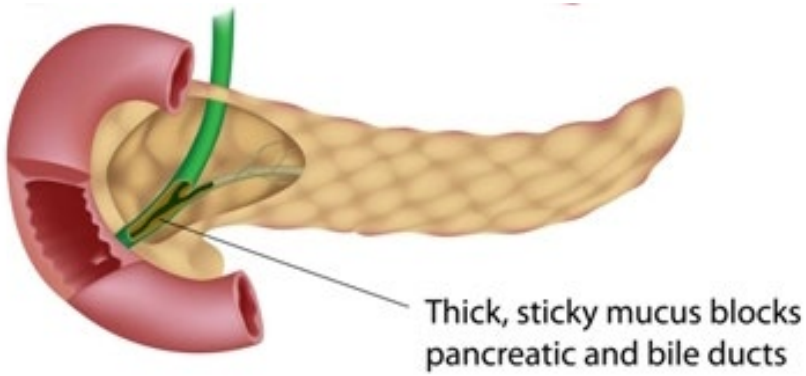
Management of GI Complications

Constipation treatment (partial or full blockage/DIOS):

- Oral rehydration, osmotic laxatives, hyperosmolar contrast enemas
- A balanced electrolyte intestinal lavage solution or enema
- To prevent recurrence, regular administration of oral polyethylene glycol 3350 may be given for 6 months– 1 year

Pancreatic insufficiency:

- Pancreatic enzyme replacement therapy (PERT) containing multiple combinations of proteases, lipases and amylases



Gastroesophageal reflux disease (GERD) or acid reflux:

- Proton pump inhibitors (PPI): omeprazole, lansoprazole, etc.
- H2 blockers: ranitidine, famotidine
- Antacids: Mylanta®, Maalox®

Cystic Fibrosis-Related Diabetes (CFRD): shares features with both Type 1 and 2 DM

Management of Nutrition and Electrolytes

- The energy needs of CF patients are 1.5-2x higher than healthy patients
- The goal is to gain weight and maintain a healthy BMI
  - Adult women: BMI of 22+
  - Adult men: BMI of 23+
- Patients are encouraged to intake an additional 500 calories/day in addition to a well-balanced diet
- Supplemental vitamins ADEK and minerals including fluoride and zinc are recommended
- Sodium chloride supplementation is based on patient's age and environmental conditions

Management of Depression/Anxiety

- CF patients and caregivers of CF patients are more likely to experience depression and anxiety
- Anxiety stems from making time for daily treatments, remembering to take medications, missing out on activities, and being hospitalized frequently

Untreated mental health problems can lead to

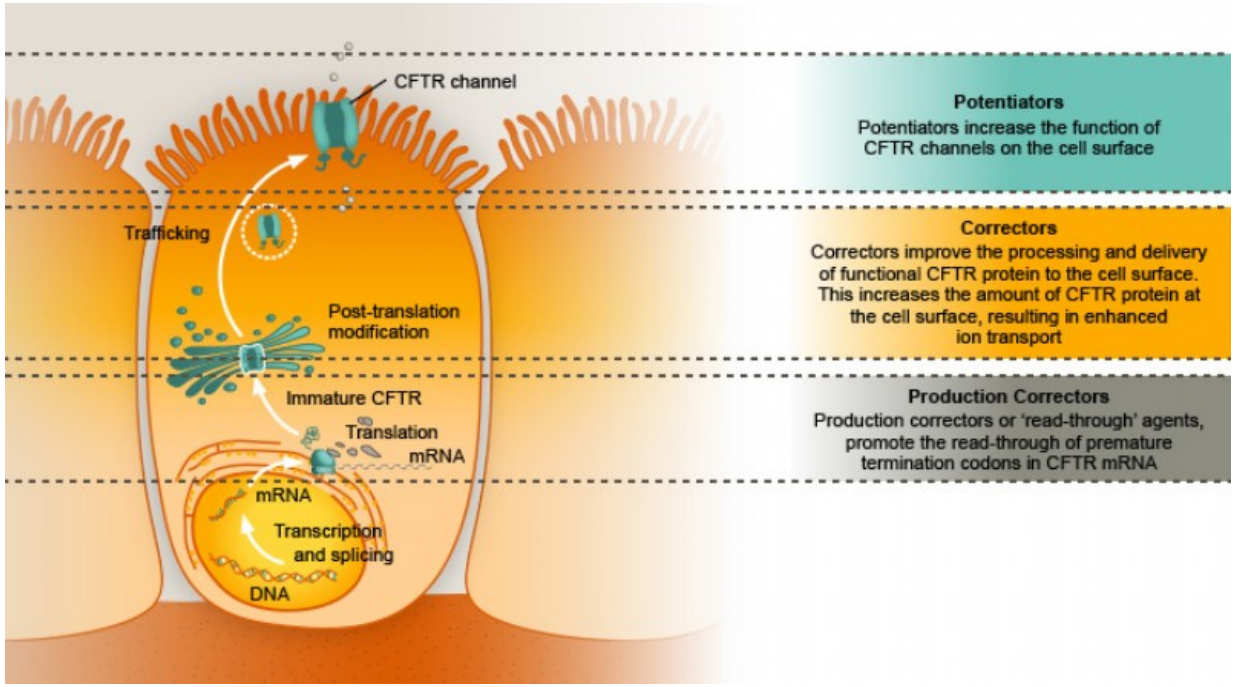
- Less adherence to treatment plans
- Worse lung function
- Lower BMI
- More hospitalizations
- Higher health care costs
- Lower quality of life

CFTR MODULATOR THERAPY CARE GUIDELINES

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

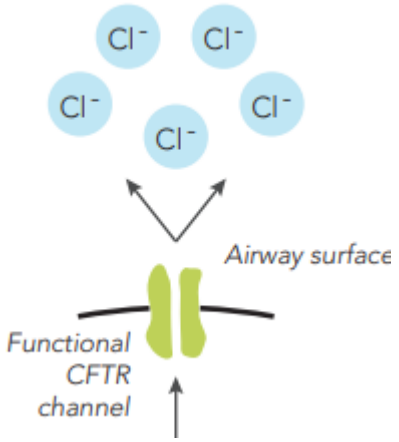
3 types of CFTR modulators

1. Potentiators
2. Correctors
3. Amplifiers (not available yet)



Potentiators

Hold the CFTR protein tunnel gate open to allow chloride to flow through the cell membrane and regulate the amount of fluids at the cell surface. This helps reduce symptoms of CF by decreasing the stickiness of the mucus.

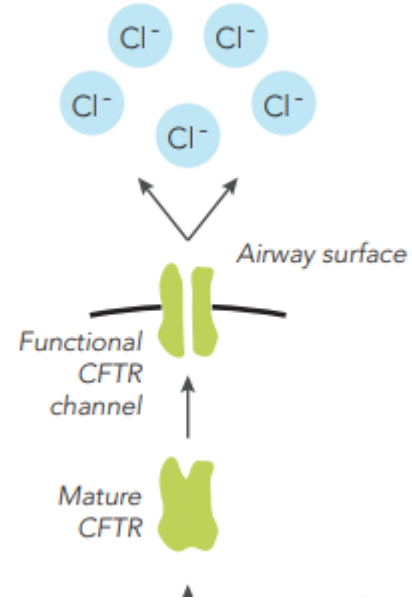


Ivacaftor (Kalydeco®)

- Approved for ages 6 months and up
- Binds to defective protein at cell's surface
- Hold the chloride channel gate open allowing chloride to flow through
- Regulates the amount of fluids at the cell surface
- Medication shows improvement in lung function (FEV_1, FVC, BMI, and QOL (STRIVE, ENVISION trials, GOAL study)

Correctors

Help the proteins form the correct 3D shape, move to the cell surface, and stay there longer. Correctors are used in combination with potentiators to correct the protein conformation then hold the gate open to allow chloride flow.



Treatment Options

- Lumacaftor/Ivacaftor= Orkambi®
- Tezacaftor/Ivacaftor= Symdeko®
- Elexacaftor (corrector)/Tezacaftor (corrector)/Ivacaftor (potentiator)= Trikafta®

ADVANCES IN CYSTIC FIBROSIS TREATMENT

Restore CFTR Function: PHASE 2

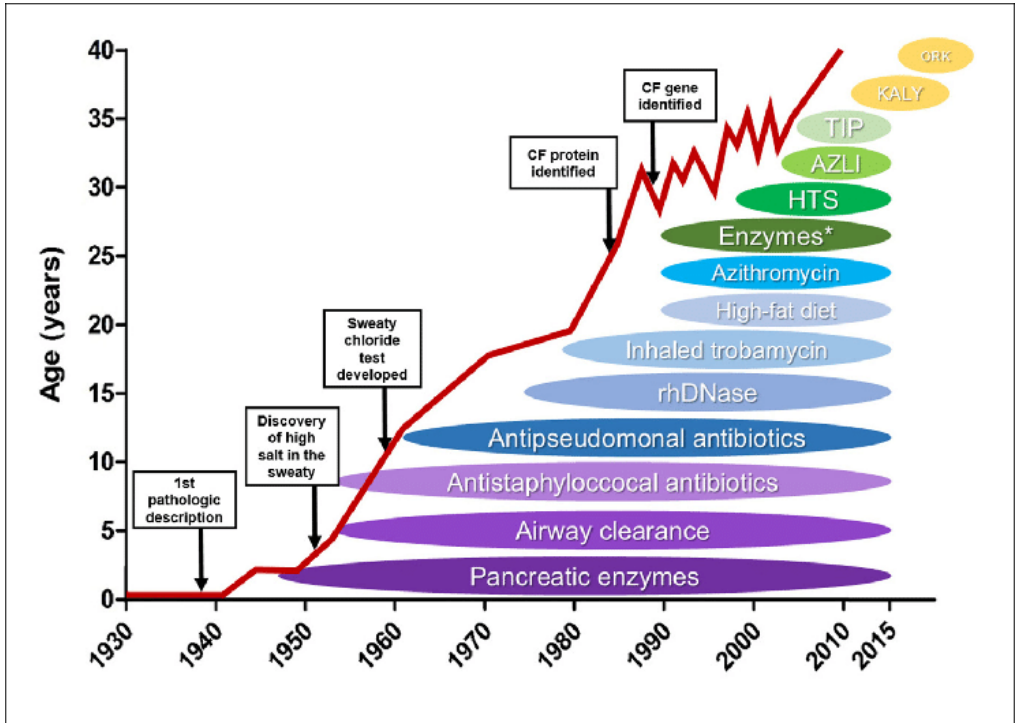
- ABBV-2222: corrector (Abbvie)
  - Studied for patients who have two copies of F508del CFTR mutation
  - Studied for combination therapy with ABBV-3067 (potentiator)
- ABBV-3067: potentiator (Abbvie)
  - Studied for monotherapy and in combination with ABBV-2222 (corrector)
- ELX-02: restore CFTR function in patients with nonsense mutations (Eloxx Pharmaceuticals)
  - Studied for patients who have at least one copy of G542X CFTR mutation
- PTI-428 (amplifier) + PTI-801 (corrector) + PTI-808 (potentiator) (Proteostasis Therapeutics)
  - Studied for monotherapy and in combination with each other
- VX-121: corrector (Vertex Pharmaceuticals)
  - Studied in combination with tezacaftor (corrector) and VX-561 (potentiator)
- VX-561: potentiator (altered form of Kalydeco®) (Vertex Pharmaceuticals)
  - Studied in patients with CFTR gating mutation

DRUG	INDICATION	DOSING	ADR/DDI	MONITORING
Kalydeco® (ivacaftor)	Ages 6months+: mutations in G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R. **Not effective in patients with homozygous F508del mutation**	Ages 6 months – <6 years: • 5-7kg: 25mg granule packet q12h • 7-<14kg: 50mg granule packet q12h • ≥14kg: 75mg granule packet q12h Mix entire packet of granules with 5ml of soft food or liquid at or below room temperature. Must be completely consumed within 1 hour. Ages 6+: 150mg q12h with fat-containing food **Reduce dose in moderate/severe hepatic impairment and when co-administering with moderate/strong CYP3A inhibitors**	**ADRs** • Headache (17%) • URTI, nasal congestion (16%) • Nausea, rash (10%) • Rhinitis (6%) • Dizziness, arthralgia, bacteria in sputum (5%) **DDI** CYP3A inhibitors: • reduce Kalydeco dose to one tablet/packet twice a week with strong inhibitors • Reduce to one tablet/packet once daily with moderate inhibitors Avoid grapefruit or Seville oranges	• AST/ALT • FEV_1 • Ophthalmological exams (pediatric patients)
Orkambi® (lumacaftor + ivacaftor)	Ages 2+ with homozygous F508del mutation in CFTR gene **Not studied in patients with other mutations**	Ages ≥2-5: • <14kg: lumacaftor 100mg/ivacaftor 125mg granule packet q12h • ≥14kg: lumacaftor 150mg/ivacaftor 188mg granule packet q12h Ages 6-11: • Two tablets (lumacaftor 100mg/ivacaftor 125mg) q12h Ages 12+: • Two tablets (lumacaftor 200mg/ivacaftor 125mg) q12h **Reduce dose in patients with moderate/severe hepatic impairment** **When initiating Orkambi in patients taking strong CYP3A inhibitors, reduce Orkambi dose for 1st week of treatment**	**ADRs** • Dyspnea, nasopharyngitis, nausea (13%) • Diarrhea (12%) • URTI (10%) • Fatigue, abnormal respiration (9%) **DDI** • CYP3A inhibitors, inducers, substrates • CYP2B6, CYP2C, digoxin, p-gp substrates, anti-allergies, systemic corticosteroids, antibiotics, antifungals, anti-inflammatories, antidepressants, hormonal contraceptives, oral hypoglycemic, PPIs, H2RAs, antacids, warfarin	• Blood pressure • Ophthalmological exams • AST, ALT, bilirubin • s/sx of respiratory effects

DRUG	INDICATION	DOSING	ADR/DDI	MONITORING
Symdeko® (tezacaftor + ivacaftor)	Ages 6+ with homozygous F508del mutations or at least one mutations in CFTR gene that response to tezacaftor/ ivacaftor	Ages 6–<12 years (<30kg): • Morning dose: one tablet with tezacaftor 50mg/ivacaftor 75 mg • Evening dose: one tablet with ivacaftor 75mg Take ~12 hours apart Ages 6–<12 (≥30kg) and ages 12+: • Morning dose: one tablet with tezacaftor 100mg/ivacaftor 150mg • Evening dose: one tablet with ivacaftor 150mg Take ~12 hours apart **Reduce in patients with moderate/severe hepatic impairment** **Reduce when co-administered with drugs that are moderate/strong CYP3A inhibitors**	**ADRs** • Headache (15%) • Nausea (9%) • Sinus congestion, dizziness (4%) **DDI** • CYP3A inhibitors: reduce Symdeko when co-administered with strong/moderate CYP3A inhibitors • Avoid food containing grapefruit or Seville oranges	• AST/ALT • Ophthalmological exams (pediatric patients)
Trikafta® (elexacaftor + tezacaftor + ivacaftor)	Ages 12+ with at least one F508del mutation in the CFTR gene	Ages 12+: • Morning dose: two elexacaftor 100mg, tezacaftor 50mg, ivacaftor 75mg tablets • Evening dose: one ivacaftor 150mg tablet Takes ~12 hours apart with fat-containing food **Not recommended in patients with severe hepatic impairment** **Reduce dose in moderate hepatic impairment (risk-benefit)** **Reduce dose when co-administered with moderate/strong CYP3A inhibitors**	**ADRs** • Headache (17%) • URTI (16%) • Abdominal pain (14%) • Diarrhea (13%) • Rash, increased ALT (10%) **DDI** • Strong CYP3A inducers: avoid • Strong/moderate CYP3A inhibitors: reduce Trikafta dose • Avoid grapefruit food/drink	• LFTs • Ophthalmological exams (pediatric patients)

WHAT DOES CF LOOK LIKE NOW?

- Goal of CF treatment: minimize s/sx of condition
- Early identification and management can allow patients to live longer lives than before
- Predicted life span for a CF patient born between 2014-2018 is about 44 years (average 16 years in 1970)
- Frequent hospitalizations and complications of disease
- Progressive respiratory insufficiency is a major cause of mortality
- Median survival post lung transplant is 8.3 years



KEY TAKEAWAYS

- CF is a rare genetic disease that affects several body systems including lungs, pancreas, liver and skin
- Patients are tested for CF at birth
- There are many complications from CF that require management and supportive care
- CFTR modulator therapies attempt to restore CFTR function
- There have been many advances in CF treatment, leading to longer life expectancies and better QOL for patients

REFERENCES

1. “About Cystic Fibrosis.” *Cystic Fibrosis Foundation*, www.cff.org/What-is-CF/About-Cystic-Fibrosis/.
2. “Anxiety” *Cystic Fibrosis Foundation,*https://www.cff.org/Life-With-CF/Daily-Life/Emotional-Wellness/Anxiety-and-CF/.
3. “Carrier Testing” *Cystic Fibrosis Foundation,* https://www.cff.org/What-is-CF/Testing/Carrier-Testing-for-Cystic-Fibrosis/.
4. “CFTR Modulator Therapies” *Cystic Fibrosis Foundation,* https://www.cff.org/Life-With-CF/Treatments-and-Therapies/Medications/CFTR-Modulator-Therapies/.
5. “CFTR Modulator Types” *Cystic Fibrosis Foundation,* https://www.cff.org/Research/Developing-New-Treatments/CFTR-Modulator-Types/.
6. “Conditions Cystic Fibrosis.” *Newborn Screening Information for Cystic Fibrosis | Baby's First Test | Newborn Screening | Baby Health*, www.babysfirsttest.org/newborn-screening/conditions/cystic-fibrosis-cf .
7. “Cystic Fibrosis” *Medline Plus,* https://medlineplus.gov/ency/article/000107.htm.
8. “Depression” *Cystic Fibrosis Foundation,* https://www.cff.org/Life-With-CF/Daily-Life/Emotional-Wellness/Depression-and-CF/.
9. “Distal Intestinal Obstruction Syndrome (DIOS) *Cystic Fibrosis Canada* https://www.cysticfibrosis.ca/distal-intestinal-obstruction-syndrome-dios.
10. “Drug Development” *Cystic Fibrosis Foundation,* https://www.cff.org/trials/pipeline.
11. “Fertility in Men with Cystic Fibrosis” *Cystic Fibrosis Foundation,* https://www.cff.org/Life-With-CF/Transitions/Reproductive-Health-and-Fertility/CF-and-the-Male-Reproductive-System/Fertility-in-Men-With-CF/#:~:text=Most%20men%20with%20CF%20(97,fertilize%20an%20egg%20through%20intercourse.
“Kalydeco Prescribing Information” *Vertex Pharmaceuticals Incorporated,* https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203188s022l_207925s003lbl.pdf .
12. LeGrys VA, Yankaskas JR, Quittell LM, Marshall BC, Mogayzel PJ, Cystic Fibrosis Foundation. Diagnostic Sweat Testing: The Cystic Fibrosis Foundation Guidelines. *J Pediatr*. 2007 Jul;151(1):85-9.PMID: 17586196.
13. Lynch, J. P., 3rd, Sayah, D. M., Belperio, J. A., & Weigt, S. S. (2015). Lung transplantation for cystic fibrosis: results, indications, complications, and controversies. *Seminars in respiratory and critical care medicine*, *36*(2), 299–320. https://doi.org/10.1055/s-0035-1547347.
14. “NBS Disorders Detectable” *California Department of Public Health*, https://www.cdph.ca.gov/Programs/CFH/DGDS/Pages/nbs/NBS-Disorders-Detectable.aspx.
15. “Newborn Screening for CF.” *CF Foundation*, www.cff.org/What-is-CF/Testing/Newborn-Screening-for-CF/.
16. “Newborn Screening for CF” *Cystic Fibrosis Foundation,* https://www.cff.org/What-is-CF/Testing/Newborn-Screening-for-CF/#:~:text=The%20Importance%20of%20Early%20Diagnosis%20of%20CF&text=Research%20shows%20that%20children%20who,Improve%20growth.
17. “Orkambi Prescribing Information” *Vertex Pharmaceuticals Incorporated,* https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206038Orig1s000lbl.pdf.
18. Rafeeq MM, Murad HAS. Cystic fibrosis: current therapeutic targets and future approaches. J Transl Med. 2017 Apr 27;15(1):84. doi: 10.1186/s12967-017-1193-9. PMID: 28449677; PMCID: PMC5408469.
19. “Restore CFTR Function” *Cystic Fibrosis Foundation,* https://www.cff.org/Research/Research-Into-the-Disease/Restore-CFTR-Function/.
20. “Sweat Test Clinical Care Guidelines” *Cystic Fibrosis Foundation* https://www.cff.org/Care/Clinical-Care-Guidelines/Diagnosis-Clinical-Care-Guidelines/Sweat-Test-Clinical-Care-Guidelines/.
21. “Symdeko Prescribing Information” *Vertex Pharmaceuticals Incorporated,* https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210491lbl.pdf.
22. “Trikafta Prescribing Information” *Vertex Pharmaceuticals Incorporated,* https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212273s000lbl.pdf.
23. “Types of CFTR Mutations” *Cystic Fibrosis Foundation* https://www.cff.org/What-is-CF/Genetics/Types-of-CFTR-Mutations/.

THANK YOU FOR YOUR ATTENTION!