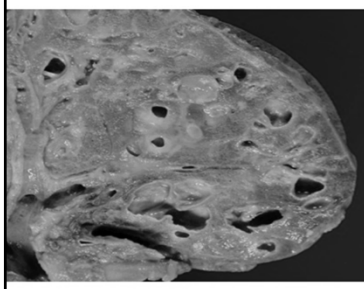

Cystic fibrosis: hitting the target

Heartland Collaborative Annual Meeting
Friday, October 5, 2012
Thomas Ferkol MD

Cystic fibrosis: a historical timeline

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Cystic fibrosis: epidemiology

Population	Epidemiologic	Newborn screening
Caucasian (US)	1 in 1,900-3,700	1 in 3,400-3,800
Caucasian (Great Britain)	1 in 2,400-3,000	1 in 2,200-3,200
Hispanic	1 in 8,000-9,000	--
African American	1 in 15,300	--
Native American	1 in 40,000	--
Asian (US, England)	1 in 10,000	--
Israel	1 in 5,000	--
Southern Europe	1 in 2,000-4,000	--

Cystic fibrosis: clinical presentations

Gastrointestinal
- meconium ileus
- meconium plug syndrome
- distal intestinal obstruction syndrome
- rectal prolapse
- neonatal hyperbilirubinemia
- failure to thrive
- hypoproteinemic edema
- hypovitaminosis
- recurrent pancreatitis
- biliary cirrhosis and portal hypertension

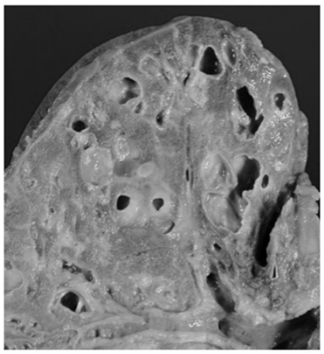
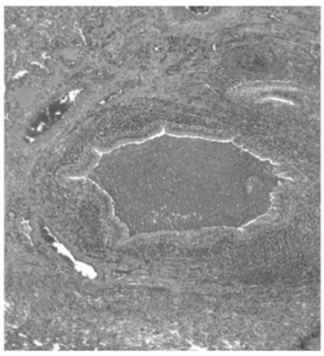
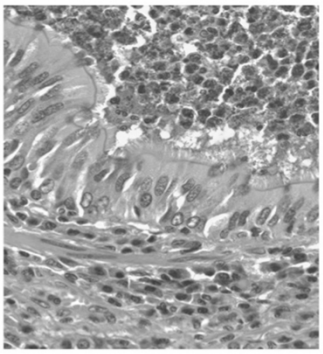
Endocrine
- diabetes

Genitourinary
- male infertility

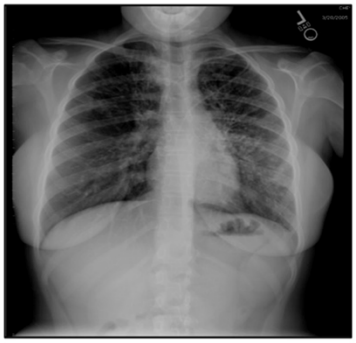
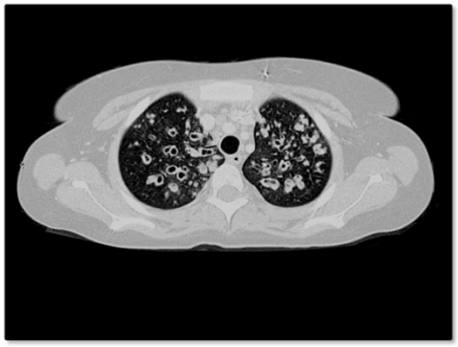
Sweat Gland Dysfunction
- hypochloremic, hyponatremic alkalosis

Respiratory
- chronic cough
- recurrent sinopulmonary infections
- bronchiolitis/asthma
- nasal polyposis
- *Staphylococcus aureus* pneumonia
- *Pseudomonas aeruginosa* endobronchitis

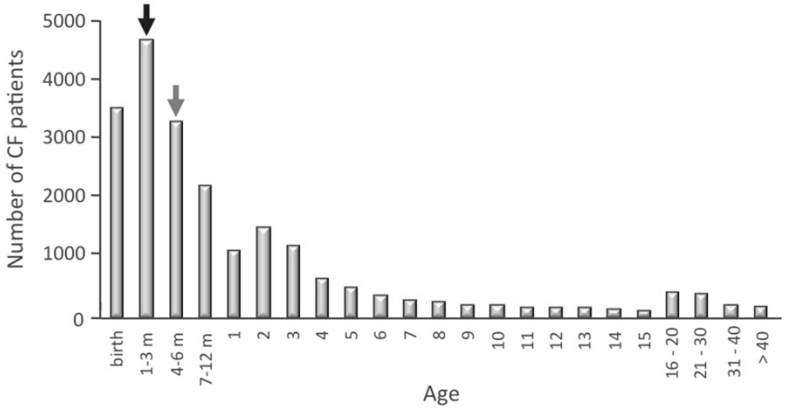
Cystic fibrosis: pathology

Cystic fibrosis: radiological findings

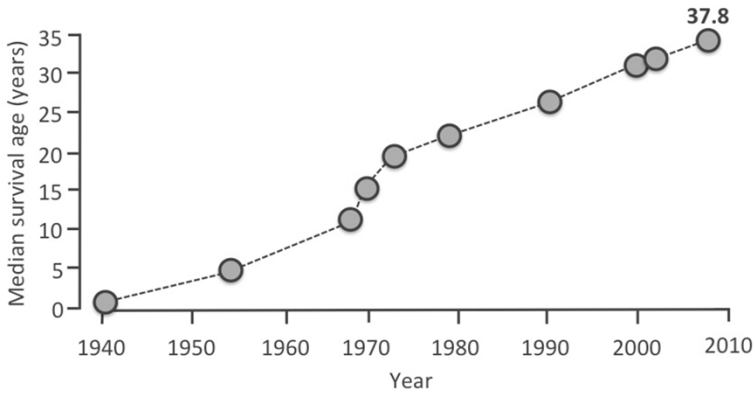



Age at diagnosis of cystic fibrosis patients



Cystic Fibrosis Foundation Registry, 2007.

Cystic fibrosis: median survival age, 1940-2007



Cystic Fibrosis Foundation Registry, 2007.

Cystic fibrosis: prognosis

Involvement of the respiratory tract typically dominates the clinical picture and determines the fate of the patient.

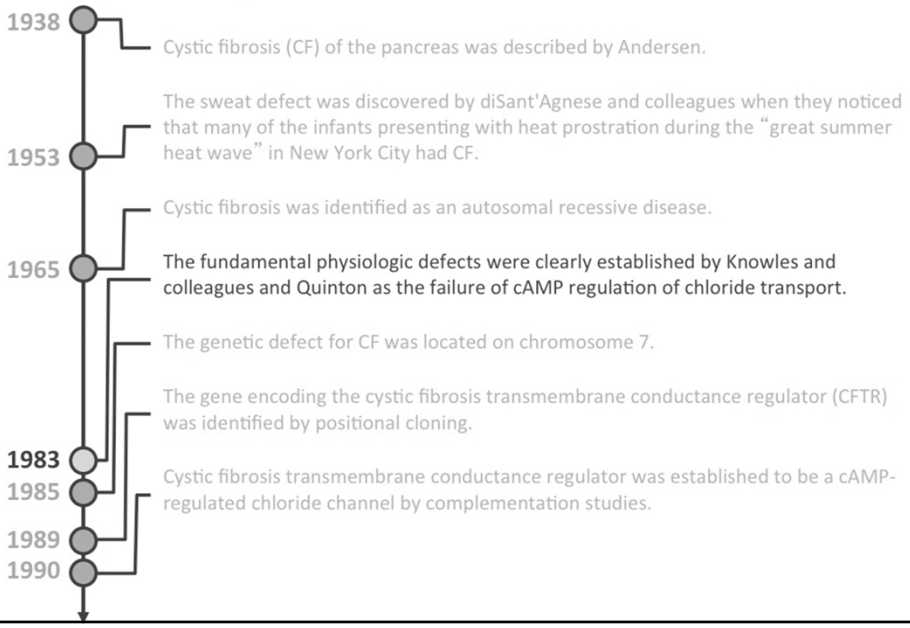
Pancreatic function is a strong determinant of outcome.

Natural variation in severity of the pulmonary involvement is important in determining the severity of the clinical course.

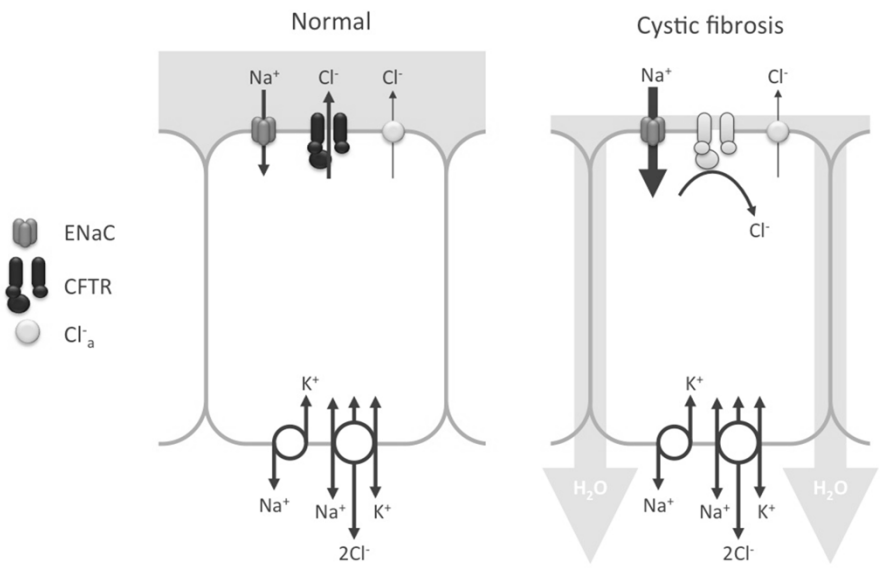
Patients who are nutritionally replete have less morbidity and mortality.

Early diagnosis and treatment is effective in prolonging the lives of affected individuals.

Cystic fibrosis: a historical timeline



Cystic fibrosis: airway inflammation



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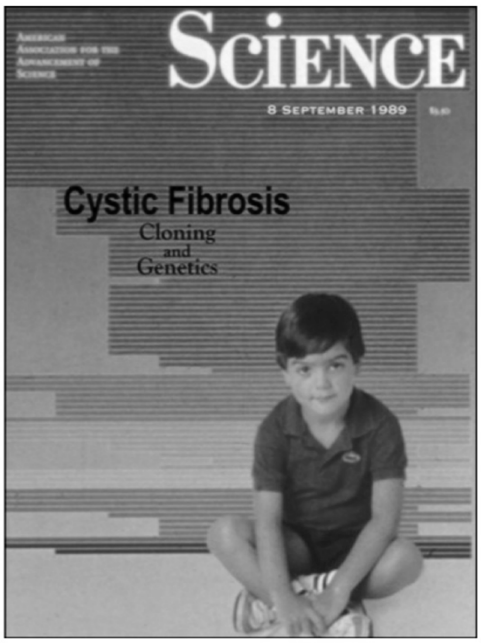
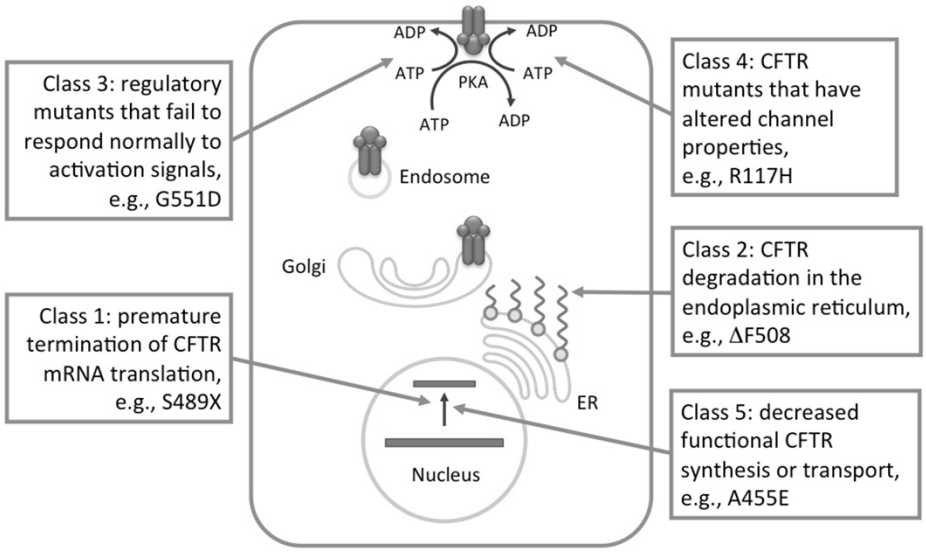
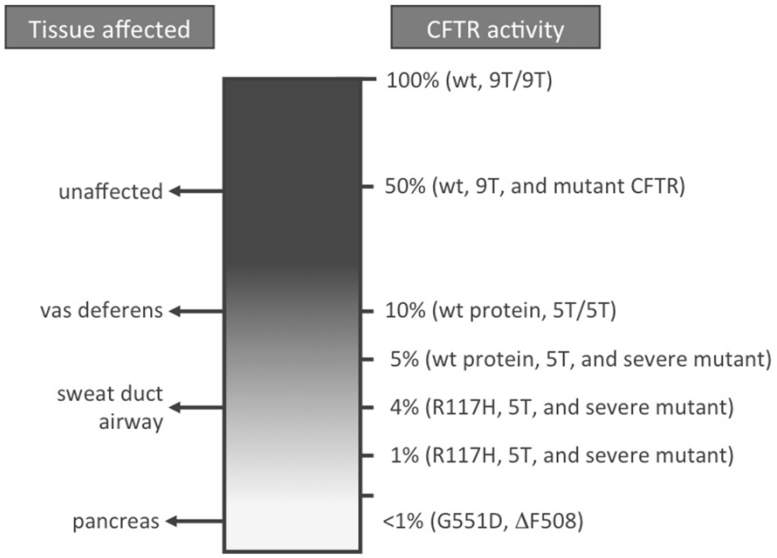


Classes of cystic fibrosis-causing mutations



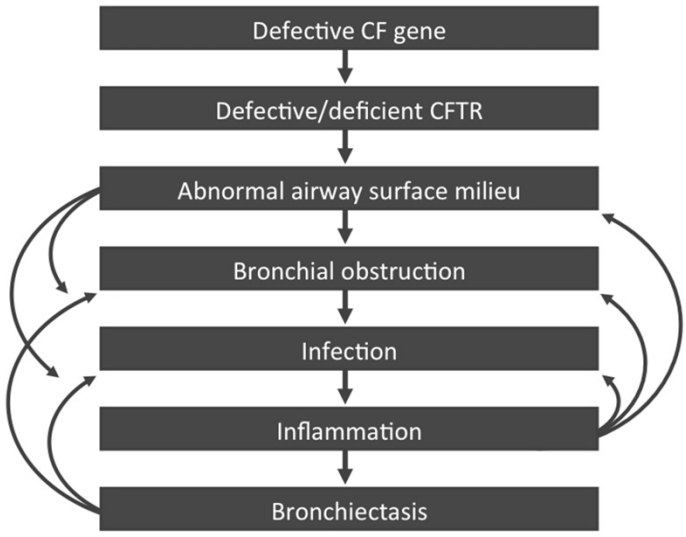
Prospects for correcting cystic fibrosis: level of correction

Chillon M, *et al. N Engl J Med*. 1996; 332:1475.

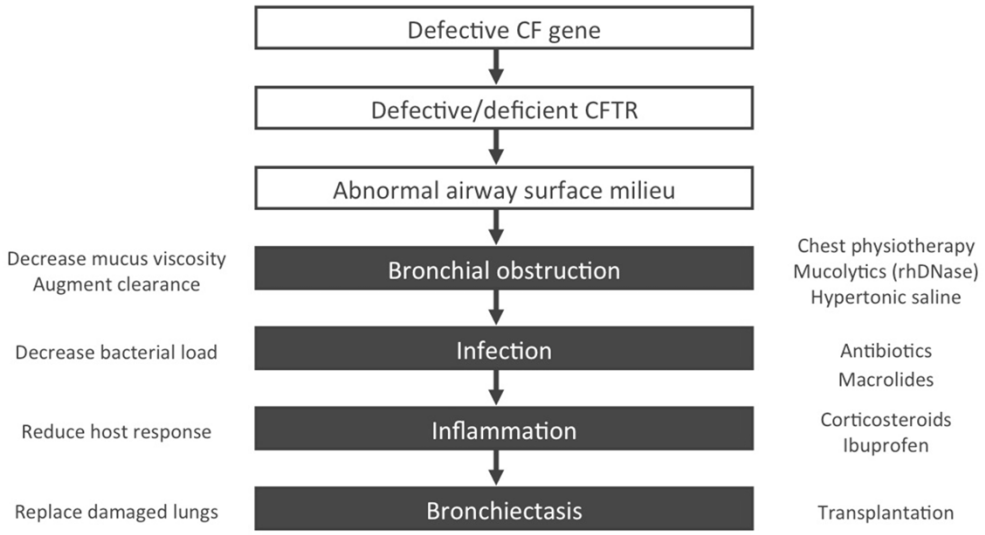


Pathogenesis of lung disease in cystic fibrosis

Davis PB, *et al. J Respir Crit Care Med*. 1996;154:1229.



Treatment of cystic fibrosis lung disease



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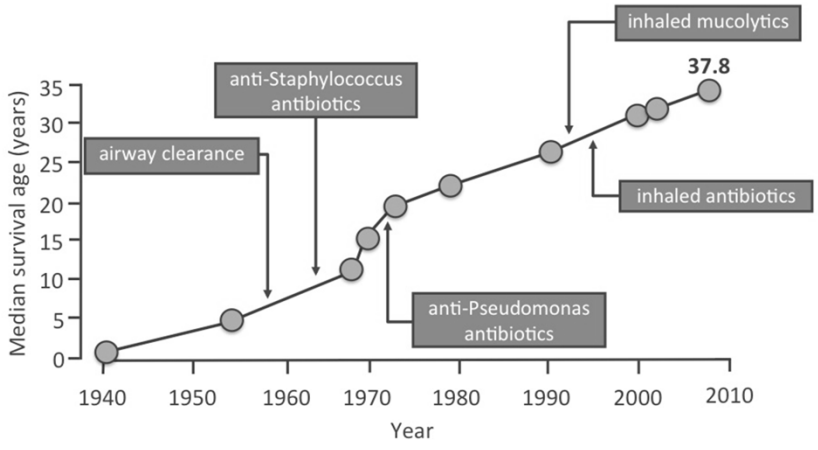
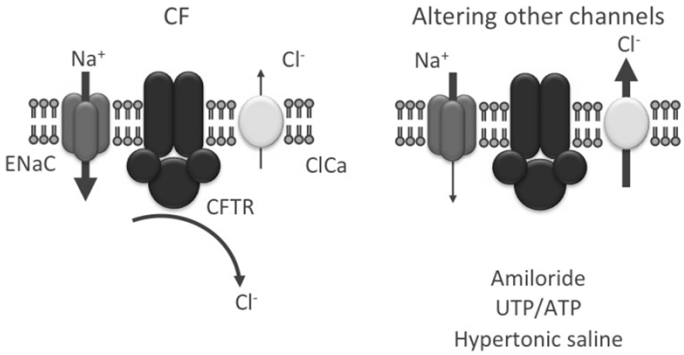


Cystic Fibrosis Foundation Registry, 2007.

Treatment of cystic fibrosis lung disease

	Defective CF gene	
	↓	
	Defective/deficient CFTR	
	↓	
Block Na^+ uptake Increase Cl^- efflux	Abnormal airway surface milieu	Amiloride UTP/ATP Hypertonic saline
	↓	
Decrease mucus viscosity Augment clearance	Bronchial obstruction	Mucolytics (rhDNase) Chest physiotherapy
	↓	
Decrease bacterial load	Infection	Antibiotics Macrolides
	↓	
Reduce host response	Inflammation	Corticosteroids Ibuprofen
	↓	
Replace damaged lungs	Bronchiectasis	Transplantation

Cystic fibrosis: alternative therapies to effect bioelectric properties of the respiratory epithelium



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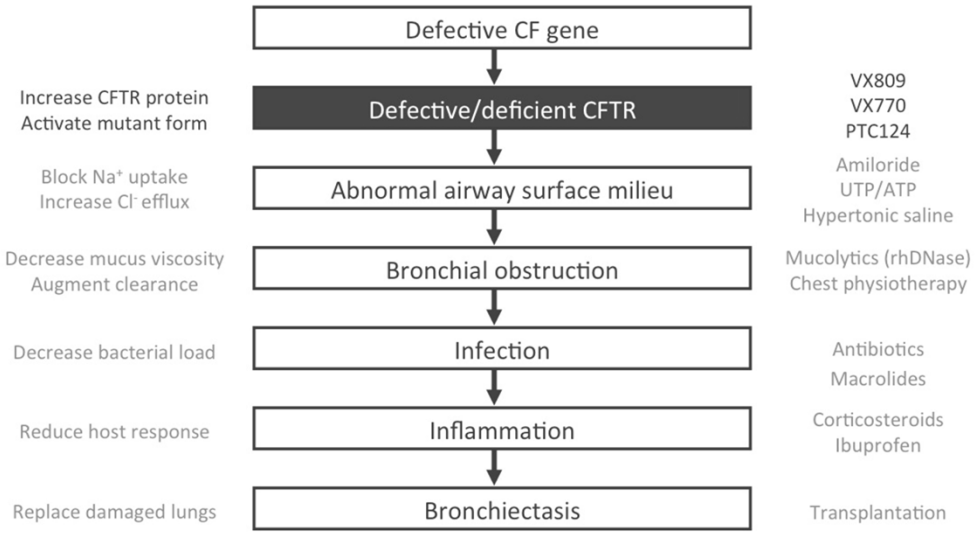
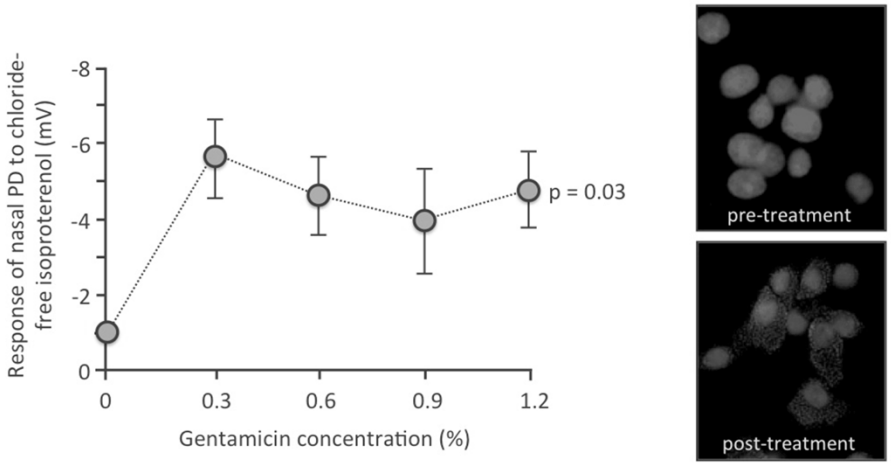


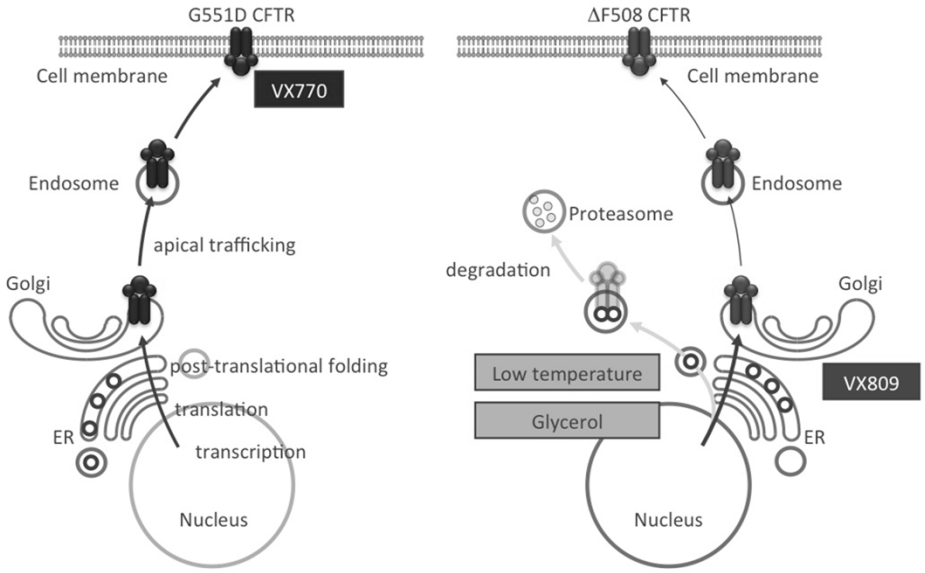
Gentamicin-induced correction of CFTR function in patients with cystic fibrosis and *CFTR* stop mutations

Wilschanski M. *N Engl J Med*. 2003; 349:1433.



Cystic fibrosis: correcting CFTR dysfunction

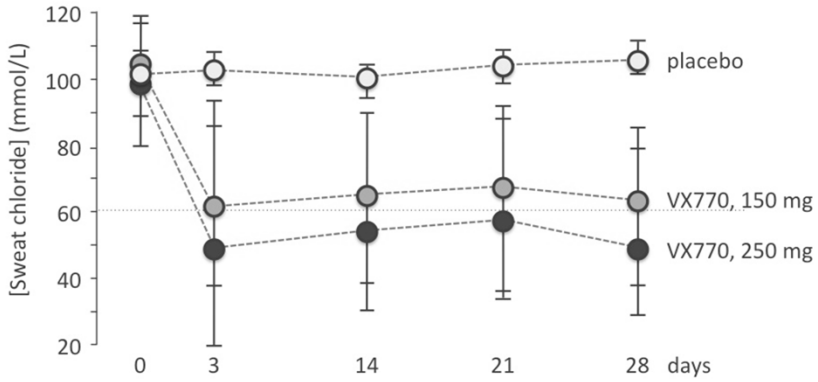
Zeitlin P. *N Engl J Med*. 2004;351:606



Cystic fibrosis: correcting G551D CFTR dysfunction

Accurso FJ, *et al. N Engl J Med*. 2010;363:1991.

A four-week, randomized placebo-controlled trial that compared the effect of regular treatment with VX770 with placebo in CF patients with G551D mutation.



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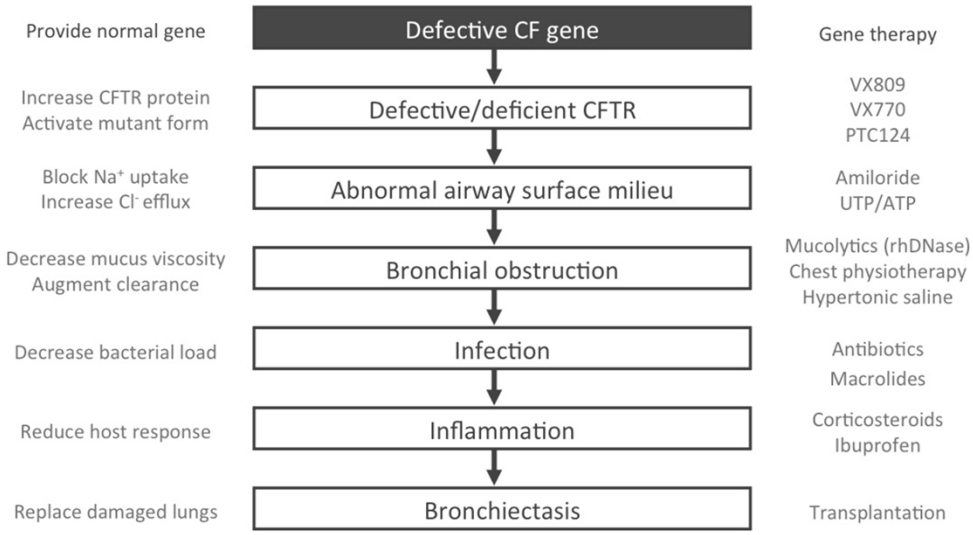

Active or completed human gene therapy protocols

Infectious diseases (40)
- Human immunodeficiency virus (37)
- Other viral diseases (3)

Monogenic diseases (58)
- Alpha1-antitrysin deficiency (2)
- Chronic granulomatous disease (3)
- **Cystic fibrosis (23)**
- Familial hypercholesterolemia (1)
- Fanconi anemia (4)
- Gaucher disease (3)
- Hunter syndrome (1)
- Ornithine transcarbamylase deficiency (1)
- Purine nucleoside phosphorylase deficiency (1)
- Severe combined immunodeficiency disease (6)
- Leukocyte adhesion deficiency (1)
- Canavan disease (3)
- Hemophilia (5)
- Muscular dystrophy (1)
- Amyotrophic lateral sclerosis (1)
- Junctional epidermolysis bullosa (1)
- Neuronal ceroid lipofuscinosis (1)

Cancer (405)

Other diseases(66)
- Peripheral artery disease (24)
- Arthritis (4)
- Arterial restenosis (3)
- Congestive heart failure (1)
- Coronary artery disease (21)
- Alzheimer disease (2)
- Ulcer (3)
- Bone fracture (1)
- Peripheral neuropathy (1)
- Parkinson disease (2)
- Eye disorders (4)
- Erectile dysfunction (1)
- Intractable pain (1)

Cystic fibrosis: hitting the target

Conclusions

Children with cystic fibrosis are being identified much earlier.

The diagnosis of cystic fibrosis is based on newborn screening, clinical features, and abnormal sweat chloride concentrations

Airway clearance techniques, inhaled mucolytic agents, antibiotics and pancreatic enzyme replacement therapy are still the cornerstones of cystic fibrosis care.

Newer mutation-specific therapies are changing the disease trajectory for some patients.

Treatment options for patients with cystic fibrosis will be increasingly defined by the patient's mutant CFTR alleles.