Cystic Fibrosis is a disorder of ion transport
Cystic fibrosis (CF) is an autosomal recessive disorder that affects over 70,000 individuals worldwide. Variations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been found to be cause of CF. The CFTR gene was first cloned in 1989 by Lap-Chee Tsui. Current National Institutes of Health Director Francis Collins was an author on the paper that published the sequence and proposed structure.¹

Clinical findings associated with CF
One of the most debilitating consequences of CF is abnormally viscous secretions in the airways of the lungs, however many organ systems that contain epithelial cells are also affected. Over 1000 different CFTR mutations have been identified in patients with cystic fibrosis. The CFTR protein is an ion channel that allows chloride ions to cross cell membranes. When this ion transport is disrupted in CF, water transport is also affected due to changes in the osmotic forces, leading to most of the dysfunction associated with CF.

CFTR mutations can have varying consequences
Depending on the type and location of the mutation within the CFTR gene, it can have deleterious effects on the function of the protein or on the quantity of functional protein produced. The most common mutation, F508del, is a folding mutation that affects the quantity of the protein that gets inserted into the cell membrane while the G551D mutation affects the activation of the channel opening.

The F508del mutation of CFTR
The nucleotide sequence of the normal gene in this region is: "CAUCUUUGGUG". While you might assume that the F508 mutation is "UUU" in fact it is "CUU". The "CUU" deletion changes the sequence to "CAUGGUG". To put this in words, the 3rd position of codon 508 becomes the 3rd position of codon 507. And since both AUC and AUU both encode Isoleucine (I) – this 3base deletion results in a clean deletion of F508, with no other change in amino9 acid sequence.

Structure of CFTR
CFTR is a large (1480 amino acids) transmembrane protein that functions as a chloride channel. As a member of the family of multidrug ABC transporter proteins, it is composed of two symmetrical halves, each with a bundle of six transmembrane alpha helices and an intracellular nucleotide binding domain. A regulatory domain (colored red) contributes to the opening and closing of the channel.

Ivacaftor is the first FDA-approved CFTR potentiator for G551D
Ivacaftor is a small molecule that has been shown to increase chloride transport in patients with the G551D mutation, acting as a “potentiator” of channel activity. It binds to CFTR and somehow increases the amount of time that it is open and allows chloride ions to pass through.

Combination therapy for F508del
Because of the exciting therapeutic benefits of seen with ivacaftor, there is great interest in finding a suitable therapy for the most common CFTR variant, F508del. A new small molecule, lumicaftor, has shown promise in allowing more CFTR to be expressed in the cell membrane. Ivacaftor has been shown to increase the activity of the F508del mutant. By using a combination of both molecules, it is thought that both the quantity available and its activity will be increased so that chloride transport will approach therapeutic levels.

References