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Front-Runners for pharmacotherapeutic correction of the airway ion transport defect in cystic fibrosis

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Summary

Although cystic fibrosis patients display multi organ dysfunction (e.g. pancreas, gut, lung) it is lung disease that is the leading cause of premature death in these patients. Cystic fibrosis lung disease is characterized by persistent pulmonary infection and mucus plugging of the airways initiated by failure of solute transport across the airway epithelium. Many drug therapies aim to alleviate the secondary characteristics of CF lung disease, however, new therapies in development are targeted at correcting the ion transport deficiency of CF. The goal is to hydrate airway surfaces by stimulating secretion (through activation of the cystic fibrosis transmembrane conductance regulator and calcium activated chloride channels), and/or inhibiting absorption (through the epithelial sodium channel) thereby stimulating healthy mucociliary clearance. If mucociliary clearance can be stimulated sufficiently from an early age then there is the possibility that secondary lung infection may be eradicated from the syndrome of CF disease.

Introduction

Currently, the drug development pipeline described by the North American Cystic Fibrosis Foundation lists 33 drugs that are developed or in development for the treatment of cystic fibrosis (CF, <http://www.cff.org/research/DrugDevelopmentPipeline>). Of these drugs, many target the infection and inflammation present in the CF lung, the aim being to ameliorate symptoms and recover lung function rather than correct the basic CF defect. However, a third of the drugs listed in the pipeline focus on correction of the ion transport deficiency of CF, and have the potential to delay or arrest the development of CF lung disease (see Table 1).

In the simplest pathophysiological scenario, the absence of functional CFTR (cystic fibrosis transmembrane conductance regulator) at the apical membrane of ciliated airway epithelial cells, results in 1) a reduced capacity to secrete Cl^- and water to the airway surface and 2) a failure to regulate absorption of Na^+ and water from airway surfaces [1,2]. This imbalance of active ion transport favors the net removal of salt and water from airway surfaces. Loss of water in the periciliary gel layer (PCL) results in a loss of lubrication of the airway surface and increased concentrations of mucin (the secreted glycoproteins) in the mucus layer (mix of glycoproteins, DNA, proteins, water, electrolytes and other components). Dehydrated PCL leads to collapse of cilia, thickening of the mucus layer and the creation of an adhesive mass that ultimately produces mucus plugging and mucus plaques on airway surfaces [3–6] (see

Figure 1). These plaques serve as the nidus for the persistent bacterial infection that characterizes CF, stimulate inflammation, obstruct the airway lumen, and produce the airflow obstruction characteristic of CF patients [7,8]. Thus, pharmacotherapies directed at treating the proximate cause of CF lung disease have recently focused on restoring the hydration of the airway surface and, hence, restoring mucus clearance.

POTENTIAL THERAPEUTIC AGENTS – REHYDRATING AGENTS

A. Osmotic agents

Hypertonic saline (HS)—Inhaled HS acts as an osmotic agent to draw water onto airway surfaces (see Figure 2). Ironically, HS is more active when deposited on CF airway epithelia than on normal airway epithelia. The NaCl concentration gradient formed by aerosol deposition within ASL is dissipated more slowly across a CF airway epithelium. This is because CF airways only have active Na⁺ channels, compared to normal airway epithelia that express active Na⁺ and Cl⁻ channels [9]. For this reason, NaCl remains on CF airway surfaces for longer periods of time and is more osmotically active, drawing more water to airway surfaces.

A number of short-term studies (< 2 weeks, or single doses) performed in the mid-1990's through 2000 measured the immediate effects of aerosolized HS on mucociliary clearance and lung function [10–13]. These studies reported that HS restored defective mucociliary clearance in CF patients, but was accompanied by short term fall in FEV₁ (<5%). Subsequently, in 2006, two papers appeared that strongly supported the hydration mechanism of action of HS and its longer term efficacy in CF. In the first, Donaldson et al. showed that HS alone increased basal mucociliary transport over a two-week interval (7% HS, q.i.d., by PariLCStar) and increased both FEV₁ and FEF_{25–75%} [14]**. Interestingly, pretreatment with amiloride, designed to slow the absorption of Na⁺ from airway surfaces and hence potentiate the hydrating effects of HS, actually blunted the response of CF patients with respect to both mucus clearance and lung function. Subsequent studies suggested that amiloride blocked an apical membrane aquaporin in human airway epithelial cells; likely aquaporin 5, suggesting that indeed, osmotically driven water flow to the surface was the therapeutic mechanism of action for hypertonic saline [15]. In a companion paper to [14], Elkins et al. showed that inhalation of HS (7%, b.i.d., PariLCStar) was associated with a modest but sustained increase in lung function and a dramatic 40–60% reduction in acute infectious exacerbations [16]**. Prolonged HS therapy appeared to be safe and was actually associated with fewer acquisitions of new organisms than vehicle.

HS studies are now being extended in several directions. First, there are studies ongoing designed to deliver HS aerosols to adolescent/adult subjects by more rapid delivery devices, e.g., by the Pari-eFlow. Second, and perhaps most importantly, the potential efficacy of HS in preventing lung disease in infants is being tested. Preliminary short-term studies of HS inhalation in CF infants have shown that this therapy appears to be safe, based on imaging and pulmonary function tests. It is anticipated that a large multi-Center study to test whether HS can prevent CF lung disease/exacerbations will be initiated (3%, Pari Sprint nebulizer, b.i.d.) in CF infants nationwide (USA) by the summer of 2008. Currently, it is estimated that more than 25% of CF patients in the U.S. are using HS therapy.

Bronchitol (inhaled mannitol)—Inhaled mannitol, like hypertonic saline, acts as an osmotic agent. Its higher molecular weight ensures that mannitol gradients in the ASL dissipate slowly via permeation through the pericellular path. Thus, mannitol may have a longer osmotic effect on airway surfaces than HS. However, this advantage is, to some degree, offset by the greater molecular weight of mannitol (~180 MW per one osmole) versus NaCl (53 MW per 2 osmoles). Thus, a large mass of mannitol must be inhaled to produce a significant osmotic driving force. Currently, dry mannitol powder is being administered via a unique dry powder device. To achieve a 420 mg inhaled therapeutic dose, the contents of ~14 capsules (30 mg)

must be inhaled per dosing session (i.e. > b.i.d). Results from Phase I studies suggested that inhaled mannitol is relatively well-tolerated, particularly if pretreatment with a bronchodilator is performed [12]. Results from a one-month Phase II study showed substantial improvement of FEV₁ and FEF_{25–75%}, at values comparable to those observed by Donaldson et al. [14] with hypertonic saline, in CF subjects [17]**. Currently, a large (~360 subject) three-month CF Phase III trial has been fully enrolled in the U.K., Australia, and New Zealand, and there are plans to initiate Phase III studies in the U.S.

B. Alternative Cl[−] channel activators

Denufosol (INS37217)—Aerosolized Denufosol is a UTP analog that was designed to resist metabolism by cell surface ecto-ATPases, and, have greater efficacy by increasing its residence time on airway surfaces. The concept is that INS37217 will chronically activate P2Y₂ receptors, leading to a persistent increase in Ca²⁺-activated Cl[−] channel (CaCC) activity in CF patients and a modest inhibition of the epithelial Na⁺ channel (ENaC). Phase I studies revealed that the compound was safe and well-tolerated by normal and CF subjects [18]. Phase II studies revealed that inhalation of INS37217 over one-month (t.i.d) prevented the typical CF lung disease-induced loss of lung function with time [19]. This effect was most pronounced in patients who had an FEV₁ of > 75% predicted, and no strict dose dependence was observed in doses of 20, 40, and 60 mg (dosed via PariLCStar nebulizer). Interestingly, positive interactions were observed between the use of an enzyme that cleaves DNA, DNase (Pulmonzyme), and INS37217. Currently, the first of two large Phase III cohorts designed to test the efficacy and safety of INS37217 over a six-month efficacy interval and six-month open label safety interval has been fully enrolled (365 subjects;Tiger1). Enrollment in the replicate Tiger2 study is underway.

Moli-1901—(Lantibio/AOP Orphan Pharmaceuticals AG) is currently in Phase II clinical trials in Europe. This 19 residue polycyclic peptide is known to increase free intracellular Ca²⁺ concentrations [20] through release of calcium from endoplasmic reticulum stores. In both normal and CF epithelia, Moli-1901 stimulates a Ca²⁺-dependent increase in short circuit current that is consistent with activation of CaCC, the same conductance activated by P2Y agonists. However, unlike P2Y agonists, there is no proposed mechanism to simultaneously inhibit Na⁺ absorption. Phase I clinical trials have demonstrated that CF nasal potential difference is sensitive to superfusion of Moli-1901. However, the effects were transient (< 2 min) at lower doses and the authors suggested that desensitization during repeated low doses may be an issue [21]. A small but cumulative change in nasal PD was observed at higher doses, with a maximal change (~15 mV) in nasal PD at 3 μM Moli-1901. The half life of the drug is 64 days in rat lung [22] and, therefore, even modest increases in chloride transport may be clinically relevant if the effects are sustained. Lantibio reported that the drug is tolerated well at daily inhaled doses of 2.5 mg, and that in a 28 day period there is an increase in FEV₁ of +2% vs. the −3% for placebo controls [21].

C. Na⁺ channel blockers

The airway epithelial Na⁺ channel (ENaC) is activated by a series of proteolytic steps that occur within the cell, e.g., furin-mediated, and on the cell surface, channel-activating protease (CAP) mediated [3,23]. Thus, there have been two strategies to block the excessive and unregulated Na⁺ transport that characterizes CF airways.

First, there is a program to block what may be the predominant cell surface CAP expressed on airway cells, i.e., prostasin (CAP1). *In vitro* data have indicated that a compound previously studied in Japan for pancreatitis, QAU145 (Novartis), will inhibit short-circuit current mediated by Na⁺ transport in excised guinea pig trachea and increase mucus transport in sheep over

short- and long-term intervals [24]. Phase I studies of QAU145, in the nose for safety, and its ability to inhibit ENaC-mediated Na⁺ transport, have been initiated.

A second approach is to block the Na⁺ channel from the airway surface utilizing an open channel blocker. The classic Na⁺ channel blocker is amiloride [25]. Amiloride has been extensively tested as pharmacotherapy for CF lung disease. The results have been mixed, exhibiting short-term actions to improve mucociliary clearance and, as monotherapy, protecting lung function. However, when amiloride is added to the usual mix of pharmacotherapies for treating the CF patient in the modern era, no therapeutic benefits of amiloride have been detected. A series of pharmacokinetic studies have suggested that part of the reason amiloride may be ineffective is that it is very rapidly absorbed from the airway surface, so full block may not be achieved.

Based on these considerations, a series of extremely potent (>100X amiloride) and longer-acting Na⁺ channel blockers have been developed for aerosol delivery [26]. The first of these third generation amiloride analogs, PS552, was thoroughly tested in a pre-clinical program. PS552 was found to be more potent and selective than amiloride and without pathologic effects in the lung. Because most small molecules inhaled into the lung are ultimately absorbed, a dose-limiting parameter for Na⁺ channel blockers is exposure of the kidney to absorbed drug. PS552 is designed, in contrast to amiloride, to be primarily hepatically excreted to avoid natriuretic and anti-kaluretic effects. Studies in sheep showed durable (>4 hr) effects on mucus clearance from single inhalations of PS552 [27].

In Phase I studies, PS552 was shown to be safe and without detectable natriuretic or anti-kaluretic effects (2 mg, q.d., PariLCStar). Pharmacodynamic Phase IB studies revealed that, as in the sheep, PS552 had a measureable pharmacodynamic enhancement of mucus clearance in normal humans for > 4 hr. In a two-week Phase 2A study, no untoward effects were observed on renal function, and post-hoc analyses revealed trends for protecting against loss of lung function in treated versus vehicle-dosed subjects. Currently, a fourth-generation inhaled Na⁺ channel blocker (GS680) is under development for CF pharmacotherapy as an aerosol by Parion/Gilead Sciences.

D1. Novel therapeutic entities – Correctors

In the last decade, two novel classes of drugs have made progress as potential therapies for CF, correctors and potentiators [28–30]**. Corrector drugs are designed to allow mutated CFTR to bypass the endogenous quality control systems in the cell and reach the apical membrane. Consequently, these drugs may correct the biogenesis problem in CF and promote trafficking of mutated CFTR protein to the plasma membrane, where most mutated proteins, including ΔF508, exhibit partial Cl[−] channel function [31] (Figure 3). If every CF cell could traffic even modest amounts of ΔF508 CFTR to the apical membrane, there could be substantial therapeutic gain [32]*. The corrector 4-phenylbutyrate (transcriptional regulator and chemical chaperone) produces a marginal increase in mature CFTR in the apical membrane [29], whilst the effects of curcumin (plant product with a variety of bioactive properties) are more debatable [33]. However, a recent study with an analog of sildenafil (phosphodiesterase 5 inhibitor, aka Viagra), KM11060, reported that this drug (at 37°C) can traffic mutated CFTR to the apical membrane with an efficiency of ~80% of that produced by reduced temperature [34]. Most of these drugs are still in early development although 4-phenylbutyrate/genistein dual therapy is in recruitment for phase 2 trials.

D2. Novel therapeutic entities – Potentiators

Potentiator drugs have also reached phase 1 and 2 clinical trials. This set of drugs targets mutated CFTR present in the apical membrane and is designed to augment the ion channel

function of these proteins. The CFTR mutations that are especially amenable to this approach are the mutated channels that already reach the membrane but display less functional activity than wild-type. Two such mutations are R117H and G551D. R117H is present in 0.8–2% of the CF population (The Cystic Fibrosis Genetic Analysis Consortium) and results in mutated but mature CFTR protein that demonstrates a lower open probability ($P_O \sim 0.1$) than wild type CFTR [$P_O \sim 0.35$ – 0.40 [35,36]. G551D also reaches the plasma membrane as a mature protein. However, it demonstrates severely diminished open probability, $P_O \sim 0.04$ [37], and is present in 2–6% of CF patients (The Cystic Fibrosis Genetic Analysis Consortium). The plant isoflavone genistein, a phytoestrogen, has been well documented [37–39], at concentrations of $\sim 50 \mu\text{M}$ or greater, to activate mutated CFTR in the epithelium. It is, however, difficult to achieve these concentrations, since genistein bioavailability by oral administration is very low [40].

Consequently, there has been a search to find more potent and specific CFTR potentiators than genistein. Two compounds are in development by Vertex Pharmaceuticals, in collaboration with Cystic Fibrosis Foundation Therapeutics, and they are currently in phase 1 and phase 2 clinical trials. Oral VX-770 is in phase 2 trials in G551D genotype CF patients. VX-809 is currently in phase 1A trials and expected to enter phase 1B trials in mid 2008. *In vitro* patch clamp studies, carried out on CFTR expressed in Fisher Rat Thyroid cells, have demonstrated that VX-770 increases $\Delta F508 P_O$ from 0.11 ± 0.05 to 0.45 ± 0.06 , and G551D P_O from 0.08 ± 0.03 to 0.52 ± 0.19 [41]**. These data suggest that VX-770 can increase $\Delta F508$ and G551D P_O to values in the range reported for wild type CFTR. Chloride secretion across Fisher Rat Thyroid monolayers over-expressing $\Delta F508$ in Ussing chambers in response to VX770 was somewhat less robust, with an increase above a very low basal short circuit current of ~ 2 fold [41]. The data are not surprising, since the quantity of $\Delta F508$ CFTR protein in the membrane is presumably small. However, the increase in G551D current was 14-fold, representing 65% of the current carried by wild type CFTR in this system. Importantly, VX-770 is more potent than genistein, with an EC_{50} of $\sim 600 \text{ nM}$, and is reported to be orally bioavailable [41]. Likely, for $\Delta F508$ CF patients, dual therapy will be required, with corrector to traffic mutated CFTR protein to the apical membrane and potentiators such as VX-770 to stimulate activation.

4. CONCLUSIONS

This is an exciting period for pharmacotherapy of CF in general and CF lung disease in particular. The hard-won scientific work that led to insights into the molecular and lung-specific pathogenesis of CFTR mutations has borne fruit in the context of more specific and, hence, likely effective pharmacotherapies. The correctors, in particular, offer the chance to treat CF systemically and effectively. Because CF lung disease evolves episodically, the development of hydrating agents offers the possibility of arresting the progression of CF lung disease and indeed, in infants, preventing CF lung disease.

However, challenges remain. Because CF lung disease is now a truly chronic disease, the signs that indicate signal efficacy are becoming increasingly difficult to detect in classic two-four week Phase II trials. Thus, there is a great need for biomarkers that are sensitive to the severity of lung disease and signaling efficacy of novel compounds over this time interval. In parallel, the wealth of new drugs has made it difficult to recruit large numbers of subjects for definitive Phase III trials. Further, the apparent activity of HS as an effective osmotic therapy has made the decision to remove patients from this form of therapy to enroll in trials that require control groups off HS therapy difficult for clinical investigators. However, in the broad scheme of CF pharmacotherapy, as compared to the previous era, these are good problems to have.

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Figure 1.

Pathogenesis of CF. Cystic fibrosis remains the most common potentially lethal genetic disease of Caucasians in North America, Europe, and New Zealand and Australia. The median age for survival of CF patients is presently 36 years, and a persistent bacterial bronchitis/bronchiectasis is the most common cause of mortality. The increased life-span to 36 years reflects, in large part, better antimicrobial therapy for pulmonary infections and better attention to nutrition and treatment of pancreatic dysfunction. Cystic fibrosis lung disease results from a failure of innate lung defense mechanisms as a result of airway dehydration. Normal airways (NL, *left panel*) exhibit a periciliary layer (PCL) of $\sim 7 \mu\text{m}$, a height at which cilia can extend fully and beat effectively to propel the overlying mucus blanket. A balance of CFTR-mediated Cl^- secretion and ENaC-mediated Na^+ absorption keeps the periciliary layer sufficiently hydrated to support this mucociliary clearance. (*Middle Panel*) In the absence of CFTR (as in CF), Cl^- secretion is severely diminished. In parallel, ENaC is poorly regulated in the absence of CFTR function and the result is inappropriate rates of Na^+ absorption. This dysregulated absorption causes the PCL to become depleted of liquid and the mucus blanket to become concentrated, which produces adhesion to collapsed cilia and arrest of mucociliary clearance. (*Right panel*) To restore normal mucociliary clearance to CF airways, either or both ion transport defects must be modified to match the normal airway functions, i.e., increase Cl^- secretion and/or decrease Na^+ absorption. Addition of osmolytes to the apical domain (e.g. hypertonic saline, HS) generates an osmotic driving force for liquid transport into the surface compartment because the airway epithelium is very water permeable (low resistance epithelium and abundance of aquaporins). Osmotic therapies directly deposit osmoles on airway surfaces, whereas ion channel modulators add osmoles to the surface by producing net NaCl secretion. Both strategies rehydrate the PCL and dilute mucins in the mucus layer, which restores the effective beat stroke of cilia and mucociliary clearance.

Figure 2.

Summary of the pharmacotherapeutic targets for the treatment of CF lung disease. Of all of the drug therapies in development that are designed to restore airway hydration and promote mucociliary clearance, the osmotic agents are by far the furthest ahead in the development pipeline. Since the airway epithelium is highly water permeable, addition of osmotic agents to the apical surface (1), either using hypertonic saline or mannitol, sets up an osmotic gradient that drives fluid to the apical surface. Small but significant clinical gains in FEV_1 have been reported, but more importantly the frequency of exacerbations are significantly reduced while on this therapy. Phase III clinical trials for hypertonic saline have been completed and this therapy is now available in most CF clinics. In the early 1990s, it was found that apically applied

P2Y₂ receptor agonists (ATP/UTP) elicited a chloride secretory response in both normal and cystic fibrosis airways. The presence of this alternative Ca²⁺ activated Cl⁻ secretory pathway has been recognized as a potential pharmacotherapeutic target (2). Two leading drugs that target this pathway are the P2Y₂ receptor analog Dunufosol (Inspire 37217) and (3) the Ca²⁺-raising agent Moli-1901 (Lantibio). Dunufosol, by activating P2Y₂ receptors, increases the rate of PIP₂ hydrolysis, resulting in an increase in IP₃ and release of Ca₂₊ from stores. Whilst the increase in free intracellular Ca²⁺ activates Cl⁻ secretion through calcium activated chloride channels (CaCC), the drop in PIP₂ levels, as a result of its hydrolysis, leads to a decrease in ENaC activity. The agent Moli-1901, a polycyclic peptide, is known to interact with phospholipids in the plasma and organellar membranes, and elevate intracellular Ca²⁺. This in turn leads to activation of CaCC.

In addition, ENaC-mediated absorption is known to be dysregulated in CF due to the lack of CFTR-mediated inhibition of ENaC. Therefore, this channel has been targeted to reduce the abnormal absorption of Na⁺ in CF airways (4). The amiloride-analogs PS552/P680 (Parion Sciences, Parion/Gilead, respectively) are open channel blockers, whilst QAU145 (Novartis) inhibits the serine proteases (Channel Activating Proteins - CAP inhibitor) that activate ENaC under normal physiological conditions. The strategy of blocking absorption should result in a net secretory activity and improved airway hydration.

For ΔF508 patients, the absence of CFTR protein in the membrane reduces secretion and allows absorption via ENaC to continue unregulated. Corrector drugs (5a) are designed to facilitate trafficking of ΔF508-CFTR to the apical membrane, where it is known that they have residual functional activity. If ΔF508-CFTR can be trafficked to the membrane, potentiator drugs (5b) have been designed to increase mutated CFTR function. In addition, some mutations in CF, namely G551D and R117H, represent mutated proteins that successfully traffick to the membrane but have limited functionality. The potentiator drug VX-770 (Vertex) is currently in clinical trials, and aims to improve the function of G551D mutated CFTR in the airway epithelium. In vitro studies have already confirmed increased functionality of mutated protein using this compound but the clinical gains have yet to be evaluated.

Figure 3.

CFTR mutations and correction/potential of their function. There are more than 1500 mutations in the CFTR gene, but more than 70% of CF chromosomes exhibit a single mutation, i.e., a three base pair deletion that results in an absence of phenylalanine at position 508 of the CFTR protein ($\Delta F508$ CFTR). This mutation, and many others, produces a dysfunction in the biogenesis of functional CFTR protein. Many signals promote the maturation of wild-type CFTR protein, but they are not accessed by mutated CFTR and, hence, mutated proteins do not fold appropriately. Misfolded proteins recognized as being “abnormal” by cells are degraded intracellularly, in part by proteasomes. An important observation is that folding of CFTR is temperature-sensitive, and low temperature allows a small fraction of mutant CFTR to fold appropriately ([42]). If mutant CFTR protein reaches the apical cell membrane, the normal cellular location for CFTR, in response to low temperature, it may exhibit partial Cl^- channel function but a short residency time on the cell surface. Cl^- secretion *via* CFTR is the main tonic pathway mediating normal hydration of airway surfaces. Thus CFTR represents a potential major therapeutic target in the treatment of CF. CF lung disease can result from a spectrum of mutations in the CFTR protein. Normally, wild type CFTR (Panel 1) is trafficked to the apical membrane, where its function is regulated by a number of pathways, primarily by PKC/PKA-activation. The channel displays spontaneous activity, but its open times increase in frequency and duration upon activation. A wild-type CFTR Cl^- channel likely has a mean open probability (P_O) of ~ 0.4 *in situ*. The most frequent and deleterious mutation of CFTR is the deletion of phenylalanine at position 508 ($\Delta F508$). This results in misfolding of the protein and degradation of the protein before it matures and traffics to the plasma membrane (Panel 2), i.e., mutated protein is recognized and broken down within the cell. Thus $\Delta F508$ -CFTR is very scarce/absent in the plasma membrane. Under low temperature conditions, a small fraction of $\Delta F508$ -CFTR can traffic to the cell membrane in some cell types and displays residual Cl^- transport capabilities. However, its function is limited both by its low open probability ($P_O < 0.1$) and the rapid turnover of $\Delta F508$ CFTR in the apical membrane. G551D-CFTR (Panel 3) does mature/traffic properly and is found in the apical membrane, but its functional activity is severely reduced by its very low open probability ($P_O < 0.04$). This defect results in an

epithelium with a low Cl^- secretory capacity. Another mutation that results in mature protein at the apical membrane is R117H-CFTR (Panel 4). This protein exhibits flickery single channel kinetics and a reduced open probability ($P_O < 0.1$) compared to wild type CFTR, but it does exhibit sufficient Cl^- secretory capacity to delay the onset of severe clinical signs of CF, e.g., the prognosis for $\Delta\text{F508/R117H}$ heterozygotes is significantly better than for ΔF508 homozygotes. To target mutated CFTR pharmacotherapeutically requires that mutated CFTR be present in the membrane, e.g., as is the case for G551D and R117H. For ΔF508 mutations, the mutated protein must be trafficked to the membrane first (drugs designed to do this are termed correctors), and secondly, the function of the mutated channel must be improved (drugs designed to increase channel function are termed potentiators).

Table 1

Summary of the leading drug therapies for the correction of ion transport deficiency in cystic fibrosis.

Mechanism of Action	Drug	Company	Clinical Trial Phase	Ref
CFTR	Vertex Corrector	Vertex	Pre-clinical	[43]
correction – trafficks mutated protein to the membrane	UCSF Corrector	UCSF	Research	[44]
CFTR	VX-770	Vertex	Phase II	[28,41]
potentiation – improves mutated CFTR function	VX-809	Vertex	Phase Ia	
Alternative Cl⁻	Denufosal	Inspire	Phase III	[19]
secretion	Moli-1901	Lantibio	Phase II	[21]
Na⁺ absorption	P-552	Parion	Phase II	[26,27]
Inhibitor	P-680	Parion/Gilead	Pre-clinical	
	QAU145	Novartis	Phase II	[24]
Osmolytes	Hypertonic NaCl		Available	[14,16]
	Bronchitol	Pharmaxis	Phase III	[12,17]