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The therapeutic potential of CFTR modulators for COPD and other airway diseases

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Abstract

Airways diseases, especially chronic obstructive pulmonary disease (COPD) and asthma, are common causes of morbidity and mortality worldwide. There is an ongoing unmet need for novel and effective therapies. There is an established pathophysiological link and phenotypic similarity between the chronic bronchitis phenotype of COPD and cystic fibrosis (CF). New evidence suggests that CFTR dysfunction may play a role in other common airways diseases such as COPD, non-atopic asthma and non-CF bronchiectasis. Newly approved and investigational drugs that target both mutant and wild type CFTR channels have provided a new treatment opportunity addressing the mucus defect in pulmonary diseases that share the same pathophysiology with CF.

Introduction

Airways diseases, especially chronic obstructive pulmonary disease (COPD) and asthma, are a major international health concern; COPD is the now the third leading cause of death in the U.S. Most cases are linked to cigarette smoking, although other environmental exposures can also cause disease. One predominant clinical phenotype is chronic bronchitis [1–3].

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Conflict of Interest Statement

G.M.S. has served on CF-related advisory boards for Bayer and Electromed. He has served as site PI for contracted CF clinical trials sponsored by Nivalis, Vertex, Pro-QR, and UAB received compensation for J.F.C. and L.F. in a sponsored research agreement with DiscoveryBioMed, Inc S.M.R. UAB received compensation for S.M.R. role as a consultant for Vertex Pharmaceuticals, Novartis, and Galapagos for the design of CF clinical trials and sponsored research agreements S.M.R. also served as PI for CF Clinical Trials sponsored by Vertex Pharmaceuticals and Novartis conducted at UAB. He has received COPD-related grant funding from NHLBI. The funders had no role in decision to publish or preparation of the manuscript.

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Chronic bronchitis is particularly troubling as it can often dominate symptoms, is associated with pulmonary exacerbations, and presently has few treatment options. Chronic bronchitis, asthma, and non-CF bronchiectasis (NCFBE) share many clinical and pathologic features with cystic fibrosis (CF), a model obstructive lung disease caused by gene mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). This overlap motivates investigators to explore CFTR dysfunction as a central disease mechanism and provides a possible joint therapeutic target. The discovery of CFTR potentiators, including the recently FDA-approved agent ivacaftor that can also potentiate even wild type forms of CFTR, may therefore represent a new therapeutic strategy. Here we review the potential element of acquired CFTR dysfunction, with an emphasis on COPD, and the possibility of CFTR-specific treatment in other airway diseases.

Acquired CFTR Dysfunction in Smoking-Related Diseases

There is a longstanding interest in the effects of cigarette smoking on epithelial ion transport. The prior literature of CFTR dysfunction in response to cigarette-smoke exposure was previously reviewed [4].

More recently, multiple prospective studies have established that acquired smoking-induced CFTR dysfunction affects the health of COPD smokers and correlates with disease severity and clinical symptoms. Cigarette smokers and COPD patients exhibited reduced CFTR function by nasal potential difference (NPD) measurements, and these differences were accompanied by reduced CFTR mRNA levels from the nares [5–7]. This was also confirmed in the lower airways [7]. In these studies, CFTR dysfunction was tightly associated with symptoms of chronic bronchitis [5,7], and was positively correlated with reduced forced expiratory volume (FEV₁) in the lungs of patients with COPD [8].

While reduced CFTR activity in the airways was supported by previous studies in the epithelial cells, deficient CFTR function was also found to be present systemically in the sweat glands and gastrointestinal tract, indicating that systemic therapy for CFTR may be most appropriate [9]. Each of these studies excluded patients that harbor one or more genetic mutations in CFTR, indicating inheritance was not a factor in these diseases. Sweat rate studies demonstrated that CFTR-dependent sweat secretion increases when smokers quit smoking for 2 weeks, indicating CFTR function is compromised upon smoking but has the potential to recover [10].

Current evidence implicates acrolein and cadmium as cigarette-smoke constituents that block CFTR function *in vitro* and can also reach detectable levels in humans [11,12]. These toxic ingredients are also present in other forms of indoor and outdoor air pollution, and can themselves activate redox pathways [13] that have also been implicated in acquired CFTR dysfunction [14]. In addition, unpublished data indicates that electronic cigarettes may cause acquire CFTR dysfunction *in vitro*. These agents may be potentially amenable to therapeutic intervention. Certainly, the chronic use of electronic cigarettes is now a considered a concern in lung disease [15].

The mechanistic basis of acquired CFTR dysfunction on a molecular level includes reduced CFTR mRNA expression, diminished protein stability, and reduced channel gating. *In vitro* and *in vivo* studies have shown cigarette smoke affects CFTR mRNA level [5,16]. Since smoking also increases mucus expression and reduces cilia beat frequency and impairs ciliogenesis [17], even small decrements in CFTR function are likely to impose marked effects on airway physiology and mucus clearance. Given the variety of pathophysiological mechanisms for CFTR dysfunction, numerous therapeutic interventions may be possible. These pathways are summarized in Figure 1.

CFTR Dysfunction in Non-Smoking Related COPD

Although less is known about the pathophysiology of COPD unrelated to smoking, especially regarding the role of CFTR, similar mechanisms might be at play. Although patients with COPD due to alpha-1-antitrypsin deficiency alone would not be expected to have the deleterious effects of cigarette smoking, redox-induced injury might be involved [7], and neutrophil elastase itself may degrade CFTR channels [18]. Understanding the differences among these COPD populations warrants further study to assess the relationship to CFTR.

Acquired CFTR dysfunction in asthma and Non-CF Bronchiectasis (NCFBE)

Asthma is an episodic airways disease characterized by recruitment of various inflammatory cells to the airways which are exploited to treat some phenotypes of asthma [19]. Persistence of this inflammatory process drives epithelial surface and glandular mucus metaplasia that characterizes the airway remodeling present in asthmatics. The resultant mucus is pathologically distinct from normal subjects, particularly during status asthmaticus [20]. The abnormal mucus in asthmatics shares properties of CF mucus including increased mucin density, high plasma protein concentrations, and distinctly high protease levels (e.g., neutrophil elastase)[20,21]. Notably, many of these features are present in patients with clinically severe asthma at the onset of neutrophil-associated inflammation [22].

In asthma, airway metaplasia and pathological alteration of mucus are associated with airway plugging [23] due to impaired mucus clearance. These processes cause episodic mucus plugging during acute exacerbations that complicate severe asthma [23]. In its most severe and chronic form, asthma that is affected by bronchiectasis has particularly poor outcomes that include increased infectious burden, exacerbation frequency, and poor treatment response, which is reminiscent of a mild form of CF [24].

While there is a large body of literature that has examined the link between genetic abnormalities of the CFTR gene and the propensity for asthma [25], it is unclear if the general asthma patient population has CFTR dysfunction [26,27]. However, more recent evidence has suggested a link between neutrophilic bronchitis-type asthma and Phe508del-heterozygosity [25,28], suggesting a need to further phenotype patients for CFTR defects.

Other studies have examined whether asthmatic inflammation may induce altered CFTR function in the absence of genetic mutations. While IL-13 may reduce CFTR in isolated cell models[29], chronic IL-4 and IL-13 exposure enhances CFTR activity in mature human

airway monolayers [30,31]. This was confirmed in *in vivo* mice tracheal studies and in a mouse fungal-exposure model [32]. Thus, typical allergic pathways positively affect CFTR dysfunction [33]. However, new evidence links non-allergic asthma with CFTR dysfunction in human nares [34], but the mechanism is unknown. Thus, whether non-allergic (possibly neutrophilic) or exacerbating asthma are conditions of CFTR dysfunction remains open to future investigation.

Non-CF Bronchiectasis (NCFBE) is a disorder characterized by neutrophilic inflammation and cyclical infection and mucus obstruction, much like CF and chronic bronchitis [35,36]. There is evidence that bronchiectasis may represent a spectrum of CFTR-related disorders as there are increased frequencies of CFTR mutations in patients in various studies [37]. In addition to the associations of CFTR mutant alleles in bronchiectasis, CFTR functional defects have been discovered in patients harboring no-CFTR mutant alleles using sweat chloride and nasal potential difference measurements [38]. Thus, while the mechanisms of CFTR dysfunction in asthma and NCFBE are not as well understood, there is evidence that certain subsets of patients demonstrate CFTR dysfunction. The association of CFTR dysfunction with complications of these diseases, however, is unknown.

Therapy Challenges in COPD

Although COPD is among the most common causes of death worldwide, no current pharmacologic treatments alter its natural history [39,40]. Therapies including bronchodilators and inhaled corticosteroids do not reduce mortality in the COPD [41–43]. Additionally, inhaled steroids in COPD are associated with an increased risk of pneumonia and do not alter mucus obstruction or its clearance [41,44,45]. Mucolytic therapy for COPD has yielded marginal benefits thus far [46–48]. Due to the lack of efficacy of currently available agents, poor bioavailability, and failure to deliver the drug to the distal airways to affect mucus obstruction, an improved approach that targets the small airways (with a potent and orally available agent) could be expected to overcome these limitations. This type of therapy would be expected to improve mucus stasis, an important cause of residual airway obstruction in COPD not addressed by current therapies. Furthermore, these types of therapies are necessary even after tobacco cessation because COPD patients have continued lung function decline and increased mortality after tobacco cessation [49].

CF Therapies in Non-CF Lung Diseases

Since there is shared pathophysiology between CF and other airway diseases, several trials have looked at previously approved CF therapies for other lung diseases. Although not all efforts have been successful, including randomized trials for dornase alfa in COPD and non-CF bronchiectasis [34], there are shared benefits of intravenous corticosteroids during exacerbations [50], chest physiotherapy [51], and, most recently, the chronic administration of azithromycin to reduce acute exacerbations [52,53]. This experience suggests that some agents effective in CF may also be efficacious in COPD and other airways diseases.

CFTR Modulator Therapy in CF

“CFTR potentiators” are a class of agents developed to correct the underlying gating defects of CFTR that is transported to cell surface [54,55]. The archetype agent ivacaftor (formerly VX-770) potentiates multiple CFTR forms, including WT, G551D (a class III mutation), and other mutations with residual expression or function (Class III, IV, and V) in primary airway epithelial monolayers, but only if there is a sufficient cell surface number of channels [56]. Ivacaftor is now FDA approved for treatment of CF with 33 different CFTR mutations. CF Patients treated with ivacaftor demonstrate improved CFTR function, mucociliary clearance (MCC), pulmonary function, and exacerbation frequency [57].

While CFTR potentiators were originally developed to restore activity to mutant CFTR, other CFTR potentiators increase wild type CFTR activity [5,58]. For example, both ivacaftor and other CFTR potentiators activate wild type CFTR by augmenting open channel probability [59–61]. Because CFTR regulates airway surface liquid (ASL) depth [62] which in turn determines mucociliary clearance (MCC) [63–65], potentiation of CFTR anion secretion may result in augmented mucus transport compared to resting conditions [66]. A recent study examined the role of ivacaftor in primary human bronchial epithelial (HBE) cells and human bronchi that were exposed to cigarette smoke extract [66]. Although it was known that cigarette smoking was linked to acquired CFTR dysfunction, its impact on mucociliary transport was less characterized. In this study, Raju et al. demonstrated that cigarette smoke extract (CSE) reduced CFTR-dependent currents within minutes, and had reduced airway surface liquid depth and reduced ciliary beat frequency within 60 minutes of exposure [56]. Chronic exposure also decreased CFTR protein levels, but more importantly, the channel gating and open probability were decreased ~75% rapidly following CSE exposure (Figure 2) [56]. Moreover, the effects of CSE were reversed by coadministration with ivacaftor, illustrating the importance of this potentiator in mucociliary clearance.

CFTR Modulators in the Treatment of Chronic Bronchitis

Recent *in vitro* work demonstrating that ivacaftor can reduce CFTR dysfunction and restore ASL and mucus transport in smoke-exposed human tissue [5,12] has set the stage for larger trials of ivacaftor in COPD with chronic bronchitis. As ivacaftor actively augments channel gating, which is affected in COPD due to smoking [12], to restore ASL depth and mucociliary transport acutely [67], this represents a logical approach to addressing the pathway.

In a recent study, 12 active or former smokers with COPD and chronic bronchitis were enrolled in a pilot evaluation of ivacaftor treatment [68]. Ivacaftor-treated patients had non-significant improvements in CFTR function compared with those receiving placebo, as detected by an improved sweat chloride concentration and nasal potential differences. Ivacaftor patients also had non-significant improvements in symptoms as detected by changes in the Breathlessness, Cough and Sputum Scale (BCSS) that exceeded the minimally clinical important difference of 1 unit. The patients with the largest improvement in sweat chloride also had the greatest improvement in BCSS and the highest sweat chloride concentration at baseline, indicating more severe CFTR dysfunction that was partially

reversible. Pharmacokinetic analysis revealed stable ivacaftor concentrations, with an area under the curve that mirrored the experiences of patients with cystic fibrosis. Although this pilot trial was underpowered and potentially too brief to detect definitive changes in lung function, there were improvements in CFTR activity and respiratory symptoms. These results set the stage for longer trials to identify the effects of CFTR potentiation on clinical outcomes in patients with chronic bronchitis with a substantial degree of acquired CFTR dysfunction at baseline.

These trials also emphasize the importance of delineating the most appropriate patient phenotypes for future studies that involve differentiation based on baseline CFTR functional status (and/or CFTR genotype), severity of lung disease, smoking status, and level of concomitant emphysema and bronchiectasis [4,69].

In addition to improving channel gating, we also speculate that next generation potentiators (in development by Novartis and Galapagos Pharmaceuticals) may represent future targets for the CFTR gating defect. In addition, CFTR correctors, which restore and/or enhance cell surface-localized numbers of channels may be explored in future research.

PDE-4 Inhibition to Treat CFTR Dysfunction

In addition to direct stimulation of CFTR activity with potentiators, new therapies may offer promise for alternative means to activate wild-type CFTR. Roflumilast is a phosphodiesterase-4 (PDE-4) inhibitor approved for the treatment of frequent exacerbations in COPD patients with chronic bronchitis [70]. Though originally intended to treat inflammation in COPD across the disease spectrum, it was only shown to be effective in patients with chronic bronchitis [71]. Roflumilast activates CFTR by augmenting its phosphorylation in a manner that is competitive with cAMP-dependent stimuli, a distinction from CFTR potentiators [72]. Roflumilast also restored CFTR function in human bronchial epithelial cells exposed to cigarette smoke [73]. Downstream of CFTR augmentation, roflumilast augmented ASL depth, including cells affected by cigarette smoking [72,73]. The effect of roflumilast on CFTR expression has not been reported.

The activity of roflumilast on CFTR may partially explain its therapeutic benefit in COPD patients with chronic bronchitis and frequent exacerbations since this phenotype is associated with an increased prevalence of CFTR dysfunction [7,12]; this also adds additional credence to the hypothesis that CFTR potentiation may be beneficial in COPD. CFTR activation and fluid secretion in the intestine was also shown to occur with roflumilast, perhaps explaining the adverse event of diarrhea observed after administration [72]. One implication of this is that COPD patients also commonly use beta-adrenergic agonists, which increase intracellular cAMP; whether CFTR activators that operate by this general mechanism, such as roflumilast, are disadvantaged as compared to other cAMP-independent CFTR modulators, such as CFTR potentiators, warrants further study.

Conclusions

Many airways diseases demonstrate mucus obstruction as a common pathophysiological mechanism. Data in COPD, especially the chronic bronchitis phenotype, indicates that this

mechanism may be due to decreased CFTR function in addition to other causes of compromised mucus transport. The promise of CFTR modulators brings interest in the treatment of acquired CFTR dysfunction in COPD. Recently, the CFTR potentiator ivacaftor was tested for safety and early efficacy with positive outcomes in COPD patients with chronic bronchitis [68]. Given the increasing evidence for CFTR dysfunction in asthma and CFTR, there is reason to consider expanding the investigation of CFTR modulators to these disorders.

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References and recommended reading

Papers of particular interest, published within the period of the review, have been highlighted as

* of special interest

** of outstanding interest

- Kim V, Han MK, Vance GB, Make BJ, Newell JD, Hokanson JE, Hersh CP, Stinson D, Silverman EK, Criner GJ. Investigators CO. The chronic bronchitic phenotype of copd: An analysis of the copdgene study. *Chest*. 2011; 140(3):626–633. [PubMed: 21474571]
- Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013; 187(3):228–237. [PubMed: 23204254]
- Kim V, Sternberg AL, Washko G, Make BJ, Han MK, Martinez F, Criner GJ. National Emphysema Treatment Trial Research G. Severe chronic bronchitis in advanced emphysema increases mortality and hospitalizations. *COPD*. 2013; 10(6):667–678. [PubMed: 23978192]
- 4**. Raju SV, Solomon GM, Dransfield MT, Rowe SM. Acquired cystic fibrosis transmembrane conductance regulator dysfunction in chronic bronchitis and other diseases of mucus clearance. *Clin Chest Med*. 2016; 37(1):147–158. Review that describes the mechanistic basis for acquired CFTR dysfunction in chronic bronchitis. [PubMed: 26857776]
5. Sloane PA, Shastry S, Wilhelm A, Courville C, Tang LP, Backer K, Levin E, Raju SV, Li Y, Mazur M, Byan-Parker S, et al. A pharmacologic approach to acquired cystic fibrosis transmembrane conductance regulator dysfunction in smoking related lung disease. *PloS one*. 2012; 7(6):e39809. [PubMed: 22768130]
- 6*. Cantin AM, Hanrahan JW, Bilodeau G, Ellis L, Dupuis A, Liao J, Zielenski J, Durie P. Cystic fibrosis transmembrane conductance regulator function is suppressed in cigarette smokers. *Am J Respir Crit Care Med*. 2006; 173(10):1139–1144. First evidence that CFTR expression was decreased by exposure to cigarette smoke *in vitro* and *in vivo*. They showed that acquired CFTR deficiency occurs in the nasal respiratory epithelium of cigarette smokers and suggested that CFTR deficiency contributed to cigarette-induced diseases such as chronic bronchitis. [PubMed: 16497995]
- 7**. Dransfield MT, Wilhelm AM, Flanagan B, Courville C, Tidwell SL, Raju SV, Gaggar A, Steele C, Tang LP, Liu B, Rowe SM. Acquired cystic fibrosis transmembrane conductance regulator dysfunction in the lower airways in copd. *Chest*. 2013; 144(2):498–506. This important study compared lower airway CFTR activity in current and former smokers with COPD, current smokers without COPD, and nonsmokers and found that smokers with and without COPD had reduced lower airway activity compared with nonsmokers and suggested that CFTR dysfunction contributed to COPD pathogenesis. [PubMed: 23538783]

8. Zhao R, Liang X, Zhao M, Liu SL, Huang Y, Idell S, Li X, Ji HL. Correlation of apical fluid-regulating channel proteins with lung function in human copd lungs. *PLoS One*. 2014; 9(10):e109725. [PubMed: 25329998]
9. Courville CA, Tidwell S, Liu B, Accurso FJ, Dransfield MT, Rowe SM. Acquired defects in cfr-dependent beta-adrenergic sweat secretion in chronic obstructive pulmonary disease. *Respir Res*. 2014; 15(25)
10. Courville CA, Raju SV, Liu B, Accurso FJ, Dransfield MT, Rowe SM. Recovery of acquired cystic fibrosis transmembrane conductance regulator (cfr) dysfunction following smoking cessation. *American Journal of Respiratory & Critical Care Medicine*. 2015 In press.
11. Rennolds J, Butler S, Maloney K, Boyaka PN, Davis IC, Knoell DL, Parinandi NL, Cormet-Boyaka E. Cadmium regulates the expression of the cfr chloride channel in human airway epithelial cells. *Toxicol Sci*. 2010; 116(1):349–358. [PubMed: 20363832]
- 12*. Raju SV, Jackson PL, Courville CA, McNicholas CM, Sloane PA, Sabbatini G, Tidwell S, Tang LP, Liu B, Fortenberry JA, Jones CW, et al. Cigarette smoke induces systemic defects in cystic fibrosis transmembrane conductance regulator function. *Am J Respir Crit Care Med*. 2013; 188(11):1321–1330. This significant paper illustrated that cigarette smoke affected other organ systems such as intestinal epithelium and showed that acrolein, a component of cigarette smoke, was higher in smokers and inhibited CFTR channel gating, and that a scavenger of acrolein, N-acetylcysteine, could reverse these effects. [PubMed: 24040746]
13. Bodas M, Van Westphal C, Carpenter-Thompson R, DKM, Vij N. Nicotine exposure induces bronchial epithelial cell apoptosis and senescence via ros mediated autophagy-impairment. *Free Radic Biol Med*. 2016; 97:441–453. [PubMed: 27394171]
14. Rasmussen JE, Sheridan JT, Polk W, Davies CM, Tarran R. Cigarette smoke-induced ca2+ release leads to cystic fibrosis transmembrane conductance regulator (cfr) dysfunction. *J Biol Chem*. 2014; 289(11):7671–7681. [PubMed: 24448802]
15. Rowell TR, Tarran R. Will chronic e-cigarette use cause lung disease? *Am J Physiol Lung Cell Mol Physiol*. 2015; 309(12):L1398–1409. [PubMed: 26408554]
- 16*. Clunes LA, Davies CM, Coakley RD, Aleksandrov AA, Henderson AG, Zeman KL, Worthington EN, Gentzsch M, Kreda SM, Cholon D, Bennett WD, et al. Cigarette smoke exposure induces cfr internalization and insolubility, leading to airway surface liquid dehydration. *Faseb J*. 2012; 26(2):533–545. In this mechanistic study, the authors demonstrate that cigarette exposure directly leads to loss of CFTR from the cell surface and results in airway surface dehydration, leading to mucus stasis, and suggested that strategies for rehydrating the surface could provide a therapy for chronic bronchitis. [PubMed: 21990373]
17. Leopold PL, O'Mahony MJ, Lian XJ, Tilley AE, Harvey BG, Crystal RG. Smoking is associated with shortened airway cilia. *PLoS One*. 2009; 4(12):e8157. [PubMed: 20016779]
- 18*. Le Gars M, Descamps D, Roussel D, Sausseureau E, Guillot L, Ruffin M, Tabary O, Hong SS, Boulanger P, Paulais M, Malleret L, et al. Neutrophil elastase degrades cystic fibrosis transmembrane conductance regulator via calpains and disables channel function in vitro and in vivo. *Am J Respir Crit Care Med*. 2013; 187(2):170–179. This manuscript provides a novel link between neutrophil elastase-calpain activation and CFTR loss of function in bacterial lung infections relevant to CF. They demonstrate that neutrophil elastase degrades CFTR through activation of intracellular calpains. [PubMed: 23220915]
19. Robinson DS, Hamid Q, Ying S, Tsicopoulos A, Barkans J, Bentley AM, Corrigan C, Durham SR, Kay AB. Predominant th2-like bronchoalveolar t-lymphocyte population in atopic asthma. *N Engl J Med*. 1992; 326(5):298–304. [PubMed: 1530827]
20. Sheehan JK, Richardson PS, Fung DC, Howard M, Thornton DJ. Analysis of respiratory mucus glycoproteins in asthma: A detailed study from a patient who died in status asthmaticus. *Am J Respir Cell Mol Biol*. 1995; 13(6):748–756. [PubMed: 7576713]
21. Fahy JV, Dickey BF. Airway mucus function and dysfunction. *N Engl J Med*. 2010; 363(23):2233–2247. [PubMed: 21121836]
22. Nakagome K, Matsushita S, Nagata M. Neutrophilic inflammation in severe asthma. *Int Arch Allergy Immunol*. 2012; 158(Suppl 1):96–102. [PubMed: 22627375]
23. Evans CM, Kim K, Tuvim MJ, Dickey BF. Mucus hypersecretion in asthma: Causes and effects. *Curr Opin Pulm Med*. 2009; 15(1):4–11. [PubMed: 19077699]

24. Oguzulgen IK, Kervan F, Ozis T, Turktaş H. The impact of bronchiectasis in clinical presentation of asthma. *South Med J*. 2007; 100(5):468–471. [PubMed: 17534081]
25. Sandford A. The role of cftr mutations in asthma. *Can Respir J*. 2012; 19(1):44–45. [PubMed: 22332134]
26. Maurya N, Awasthi S, Dixit P. Association of cftr gene mutation with bronchial asthma. *Indian J Med Res*. 2012; 135(4):469–478. [PubMed: 22664493]
27. Noone PG, Knowles MR. 'Cftr-opathies': Disease phenotypes associated with cystic fibrosis transmembrane regulator gene mutations. *Respir Res*. 2001; 2(6):328–332. [PubMed: 11737931]
28. Goodwin J, Spitale N, Yaghi A, Dolovich M, Nair P. Cystic fibrosis transmembrane conductance regulator gene abnormalities in patients with asthma and recurrent neutrophilic bronchitis. *Can Respir J*. 2012; 19(1):46–48. [PubMed: 22332135]
29. Skowron-zwarg M, Boland S, Caruso N, Coraux C, Marano F, Tournier F. Interleukin-13 interferes with cftr and aqp5 expression and localization during human airway epithelial cell differentiation. *Exp Cell Res*. 2007; 313(12):2695–2702. [PubMed: 17553491]
30. Danahay H, Atherton H, Jones G, Bridges RJ, Poll CT. Interleukin-13 induces a hypersecretory ion transport phenotype in human bronchial epithelial cells. *Am J Physiol Lung Cell Mol Physiol*. 2002; 282(2):L226–236. [PubMed: 11792627]
31. Galletta LJ, Pagesy P, Folli C, Caci E, Romio L, Costes B, Nicolis E, Cabrini G, Goossens M, Ravazzolo R, Zegarra-Moran O. Il-4 is a potent modulator of ion transport in the human bronchial epithelium in vitro. *J Immunol*. 2002; 168(2):839–845. [PubMed: 11777980]
32. Anagnostopoulou P, Dai L, Schatterny J, Hirtz S, Duerr J, Mall MA. Allergic airway inflammation induces a pro-secretory epithelial ion transport phenotype in mice. *Eur Respir J*. 2010; 36(6):1436–1447. [PubMed: 20413543]
33. Schulz A, Tummeler B. Non-allergic asthma as a cftr-related disorder. *J Cyst Fibros*. 2016; 15(5):641–644. [PubMed: 26526220]
34. Hillas G, Nikolakopoulou S, Hussain S, Vassilakopoulos T. Antioxidants and mucolytics in copd management: When (if ever) and in whom? *Curr Drug Targets*. 2013; 14(2):225–234. [PubMed: 23256719]
35. Morrissey BM. Pathogenesis of bronchiectasis. *Clin Chest Med*. 2007; 28(2):289–296. [PubMed: 17467548]
36. Russell DW, Gaggari A, Solomon GM. Neutrophil fates in bronchiectasis and alpha-1 antitrypsin deficiency. *Ann Am Thorac Soc*. 2016; 13(Suppl 2):S123–129. [PubMed: 27115946]
37. Bergounoux A, Viart V, Miro J, Bommart S, Molinari N, des Georges M, Claustres M, Chiron R, Taulan-Cadars M. Should diffuse bronchiectasis still be considered a cftr-related disorder? *J Cyst Fibros*. 2015; 14(5):646–653. [PubMed: 25797027]
38. Bienvenu T, Sermet-Gaudelus I, Burgel PR, Hubert D, Crestani B, Bassinet L, Dusser D, Fajac I. Cystic fibrosis transmembrane conductance regulator channel dysfunction in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med*. 2010; 181(10):1078–1084. [PubMed: 20167849]
39. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: Gold executive summary. *American journal of respiratory and critical care medicine*. 2007; 176(6):532–555. [PubMed: 17507545]
40. Mannino DM. Copd: Epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest*. 2002; 121(5 Suppl):121S–126S. [PubMed: 12010839]
41. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Jama*. 2008; 300(20):2407–2416. [PubMed: 19033591]
42. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007; 356(8):775–789. [PubMed: 17314337]
43. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008; 359(15):1543–1554. [PubMed: 18836213]

44. Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Willits LR, Yates JC, Vestbo J. Pneumonia risk in copd patients receiving inhaled corticosteroids alone or in combination: Torch study results. *Eur Respir J*. 2009; 34(3):641–647. [PubMed: 19443528]
45. Singh S, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease: A critical review and update. *Curr Opin Pulm Med*. 2009
46. Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, van Schayck CP, Olivieri D, Del Donno M, De Backer W, Lankhorst I, et al. Effects of n-acetylcysteine on outcomes in chronic obstructive pulmonary disease (bronchitis randomized on nac cost-utility study, broncus): A randomised placebo-controlled trial. *Lancet*. 2005; 365(9470): 1552–1560. [PubMed: 15866309]
47. Zheng JP, Kang J, Huang SG, Chen P, Yao WZ, Yang L, Bai CX, Wang CZ, Wang C, Chen BY, Shi Y, et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (peace study): A randomised placebo-controlled study. *Lancet*. 2008; 371(9629):2013–2018. [PubMed: 18555912]
48. Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006; 3:CD001287.
49. Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the united states: Data from the national health and nutrition examination survey, 1988–1994. *Arch Intern Med*. 2000; 160(11):1683–1689. [PubMed: 10847262]
50. Dovey M, Aitken ML, Emerson J, McNamara S, Waltz DA, Gibson RL. Oral corticosteroid therapy in cystic fibrosis patients hospitalized for pulmonary exacerbation: A pilot study. *Chest*. 2007; 132(4):1212–1218. [PubMed: 17646219]
51. Chakravorty I, Chahal K, Austin G. A pilot study of the impact of high-frequency chest wall oscillation in chronic obstructive pulmonary disease patients with mucus hypersecretion. *Int J Chron Obstruct Pulmon Dis*. 2011; 6:693–699. [PubMed: 22259246]
52. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW 3rd. Azithromycin in patients with cystic fibrosis chronically infected with *pseudomonas aeruginosa*: A randomized controlled trial. *JAMA: the journal of the American Medical Association*. 2003; 290(13):1749–1756. [PubMed: 14519709]
53. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, Make B, et al. Azithromycin for prevention of exacerbations of copd. *The New England journal of medicine*. 2011; 365(8):689–698. [PubMed: 21864166]
54. Tummler B. treatment of cystic fibrosis with cftr modulators. *Pneumologie*. 2016; 70(5):301–313. [PubMed: 26894479]
55. Solomon GM, Marshall SG, Ramsey BW, Rowe SM. Breakthrough therapies: Cystic fibrosis (cf) potentiators and correctors. *Pediatr Pulmonol*. 2015; 50(Suppl 40):S3–S13. [PubMed: 26097168]
- 56**. Raju SV, Lin VY, Liu L, McNicholas CM, Karki S, Sloane PA, Tang L, Jackson PL, Wang W, Wilson L, Macon KJ, et al. The cystic fibrosis transmembrane conductance regulator potentiator ivacaftor augments mucociliary clearance abrogating cystic fibrosis transmembrane conductance regulator inhibition by cigarette smoke. *Am J Respir Cell Mol Biol*. 2017; 56(1):99–108. In this study, the investigators show that cigarette smoke extract reduces CFTR-dependent current in human bronchial epithelial cells and human bronchi within minutes of exposure and the mechanism involved was reduction of CFTR gating. They showed that cigarette smoke extract treatment of purified CFTR resulted in acrolein modifications in amino acid residues likely to disrupt CFTR gating. Importantly, they also demonstrated that cigarette smoke extract reduced airway surface liquid depth and ciliary beat frequency and these effects could be blocked with ivacaftor coadministration *in vitro*. [PubMed: 27585394]
- 57**. Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, Sagel SD, Khan U, Mayer-Hamblett N, Van Dalfsen JM, Joseloff E, et al. Clinical mechanism of the cftr potentiator ivacaftor in g551d-mediated cystic fibrosis. *American journal of respiratory and critical care medicine*. 2014 This clinical study evaluated ivacaftor in a postapproval setting to determine mechanism of action and the response of clinically relevant markers. The results indicated that the treated patients improved in lung function, body mass index, their hospitalization rate, and in *Pseudomonas aeruginosa* burden, all of which illustrated the therapeutic benefit of ivacaftor.

- 58**. Van Goor F, Hadida S, Grootenhuys PD, Burton B, Cao D, Neuberger T, Turnbull A, Singh A, Joubran J, Hazlewood A, Zhou J, et al. Rescue of cf airway epithelial cell function in vitro by a cftr potentiator, vx-770. *Proc Natl Acad Sci U S A*. 2009; 106(44):18825–18830. Original manuscript describing the mechanistic basis of CFTR potentiation by Vx-770 (ivacaftor). [PubMed: 19846789]
- 59*. Van Goor F, Yu H, Burton B, Hoffman BJ. Effect of ivacaftor on cftr forms with missense mutations associated with defects in protein processing or function. *Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society*. 2014; 13(1):29–36. In this important study, the investigators show that ivacaftor, a drug effective in patients 6 years and older who have the G551D-CFTR gating mutation, is also effective other mutant forms of CFTR. This study emphasized that this drug could provide clinical benefit for a much larger spectrum of CF patients with mild defects in either CFTR processing or in channel conductance. [PubMed: 23891399]
60. Ren HY, Grove DE, De La Rosa O, Houck SA, Sopha P, Van Goor F, Hoffman BJ, Cyr DM. Vx-809 corrects folding defects in cystic fibrosis transmembrane conductance regulator protein through action on membrane-spanning domain 1. *Mol Biol Cell*. 2013; 24(19):3016–3024. [PubMed: 23924900]
61. Pedemonte N, Tomati V, Sondo E, Galletta LJ. Influence of cell background on pharmacological rescue of mutant cftr. *Am J Physiol Cell Physiol*.
62. Tarran R, Loewen ME, Paradiso AM, Olsen JC, Gray MA, Argent BE, Boucher RC, Gabriel SE. Regulation of murine airway surface liquid volume by cftr and ca2+-activated cl- conductances. *J Gen Physiol*. 2002; 120(3):407–418. [PubMed: 12198094]
63. Tarran R. Regulation of airway surface liquid volume and mucus transport by active ion transport. *Proc Am Thorac Soc*. 2004; 1(1):42–46. [PubMed: 16113411]
64. Roomans GM, Kozlova I, Nilsson H, Vanthanouvong V, Button B, Tarran R. Measurements of airway surface liquid height and mucus transport by fluorescence microscopy, and of ion composition by x-ray microanalysis. *Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society*. 2004; 3(Suppl 2):135–139.
65. Matsui H, Randell SH, Peretti SW, Davis CW, Boucher RC. Coordinated clearance of periciliary liquid and mucus from airway surfaces. *Journal of Clinical Investigation*. 1998; 102(6):1125–1131. [PubMed: 9739046]
66. Donaldson SH, Corcoran TE, Laube BL, Bennett WD. Mucociliary clearance as an outcome measure for cystic fibrosis clinical research. *Proc Am Thorac Soc*. 2007; 4(4):399–405. [PubMed: 17652507]
67. Raju SV, Lin VY, Liu L, McNicholas CM, Karki S, Sloane PA, Tang L, Jackson PL, Wang W, Wilson L, Macon KJ, et al. The cftr potentiator ivacaftor augments mucociliary clearance abrogating cftr inhibition by cigarette smoke. *Am J Respir Cell Mol Biol*. 2016
- 68**. Solomon GM, Hathorne H, Liu B, Raju SV, Reeves G, Acosta EP, Dransfield MT, Rowe SM. Pilot evaluation of ivacaftor for chronic bronchitis. *Lancet Respir Med*. 2016; 4(6):e32–33. First Clinical description of Ivacaftor administration in COPD patients with the chronic bronchitis phenotype. While this study was primarily intended to demonstrate safety, early efficacy in patients with reduced CFTR function was observed in markers of CFTR function and symptoms scores. [PubMed: 27185048]
69. Solomon GM, Raju SV, Dransfield MT, Rowe SM. Therapeutic approaches to acquired cystic fibrosis transmembrane conductance regulator dysfunction in chronic bronchitis. *Ann Am Thorac Soc*. 2016; 13(Suppl 2):S169–176. [PubMed: 27115953]
70. Rennard SI, Calverley PM, Goehring UM, Bredenbroeker D, Martinez FJ. Reduction of exacerbations by the pde4 inhibitor roflumilast—the importance of defining different subsets of patients with copd. *Respiratory research*. 2011; 12:18. [PubMed: 21272339]
71. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, Rabe KF. M, groups Ms. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: Two randomised clinical trials. *Lancet*. 2009; 374(9691):695–703. [PubMed: 19716961]

72. Lambert JA, Raju SV, Tang LP, McNicholas CM, Li Y, Courville CW, Faris RF, Coricor GE, Smoot LH, Mazur MM, Dransfield MT, et al. Cfr activation by roflumilast contributes to therapeutic benefit in chronic bronchitis. *Am J Respir Cell Mol Biol*. 2013
73. Tyrrell J, Qian X, Freire J, Tarran R. Roflumilast combined with adenosine increases mucosal hydration in human airway epithelial cultures after cigarette smoke exposure. *American journal of physiology Lung cellular and molecular physiology*. 2015; 308(10):L1068–1077. [PubMed: 25795727]

Highlights

- Common airway diseases including COPD, asthma and non-CF bronchiectasis (NCFBE) share the common pathophysiologic feature of mucus obstruction
- Acquired CFTR dysfunction is a potential overlapping mechanism to explain abnormal mucus clearance in these diseases
- CFTR modulators have shown promise in CF and thus should be tested in diseases with CFTR dysfunction
- Early studies indicate safety and promise efficacy for the CFTR potentiator ivacaftor in COPD with chronic bronchitis

Figure 1. Schematic depicting the known pathways resulting in CFTR dysfunction and delayed mucus clearance in COPD and chronic bronchitis

Also depicted are known and potential therapeutic interventions to restore CFTR function in cigarette-smoke exposed CFTR dysfunction.

Figure 2. Cigarette smoke extract acutely reduces CFTR-dependent channel opening

A. Representative recording from macropatch of HEK293 cells expressing wild-type CFTR then exposed to low dose PKA inhibitor (PKI, 40U/ml) to ascertain phosphorylation status) then CSE (1%). CFTR_{inh}-172 (10 μM) was added to confirm CFTR dependence. Holding potential was −50 mV. **B.** Summary data of that shown in A. *P<0.05, N=4–6/condition. **C.** Unitary conductance tracing of inside-out patch derived from wild-type CFTR expressing HEK293 cells showing significant and immediate inhibition of CFTR channel opening upon addition of CSE (1%). Holding potential was −50 mV. Experiment performed in presence of 1mM MgATP plus 40U/ml of the catalytic subunit of PKA. Insets i and ii show individual channel openings at higher time resolution as demarked on the condensed continuous recording. *P<0.05, N=4. Dotted line represents zero current level. Adapted from Raju, SV et al, *Am J Respir Cell Mol Biol.* 2017 Jan;56(1):99–108 with permission.