Emerging pharmaceutical therapies for COPD

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Abstract: COPD, for which cigarette smoking is the major risk factor, remains a worldwide burden. Current therapies provide only limited short-term benefit and fail to halt progression. A variety of potential therapeutic targets are currently being investigated, including COPD-related proinflammatory mediators and signaling pathways. Other investigational compounds target specific aspects or complications of COPD such as mucus hypersecretion and pulmonary hypertension. Although many candidate therapies have shown no significant effects, other emerging therapies have improved lung function, pulmonary hypertension, glucocorticoid sensitivity, and/or the frequency of exacerbations. Among these are compounds that inhibit the CXCR2 receptor, mitogen-activated protein kinase Src kinase, myristoylated alanine-rich C kinase substrate, selectins, and the endothelin receptor. Activation of certain transcription factors may also be relevant, as a large retrospective cohort study of COPD patients with diabetes found that the peroxisome proliferator-activated receptor γ (PPARγ) agonists rosiglitazone and pioglitazone were associated with reduced COPD exacerbation rate. Notably, several therapies have shown efficacy only in identifiable subgroups of COPD patients, suggesting that subgroup identification may become more important in future treatment strategies. This review summarizes the status of emerging therapeutic pharmaceuticals for COPD and highlights those that appear most promising.

Keywords: pulmonary, PPAR, phosphodiesterase, emphysema, cigarette, mucus

Introduction
COPD affects ~200 million people worldwide¹ and is the third leading cause of death in the US, claiming ~150,000 lives in 2013.² Approximately 6.3% of US adults aged ≥18 years have COPD,³ and its combined indirect and direct costs in 2010 surpassed $52 billion. More effective treatments for COPD are needed to address this serious health problem. This review summarizes the status of potential therapies currently or recently in clinical trials and highlights those that appear most promising.

COPD pathology
COPD, a complex and heterogeneous chronic progressive inflammatory disease of the distal airways characterized by persistent airflow limitations, typically results from inhaling noxious gases and particles, especially cigarette smoke.⁴ The resulting inflammatory response involves increased numbers of neutrophils, macrophages, B cells, and CD4⁺ and CD8⁺ T lymphocytes in the airways.⁷ Histopathological changes include edema, loss of alveoli, and tissue remodeling involving smooth muscle hypertrophy and fibrosis, which are associated with bronchoconstriction and airway mucus secretion exacerbated by reduced clearance.⁵-⁸ The accompanying systemic inflammation and increased reactive oxygen species (ROS) in patients may contribute to such manifestations as cardiovascular complications, loss of skeletal muscle, osteoporosis, and psychosocial effects.
COPD exacerbations
COPD exacerbations can significantly accelerate lung function decline and overall health. In patients with severe COPD, acute exacerbations requiring hospitalization account for up to 50% of COPD health care costs. Exacerbation risk appears to be associated with serum eosinophilia: in patients with clinical COPD and serum eosinophils above 0.34 x 10⁹ cells/L, risk of severe and moderate exacerbations were increased compared to those in patients with fewer eosinophils. Causes of COPD exacerbations appear multifactorial and elusive but may include bacterial or viral infections, exposure to environmental pollutants, and unidentified factors. Exacerbations are accompanied by a rapid rise of proinflammatory cytokines and chemokines that trigger and sustain rapid influx of neutrophils and their products such as neutrophil elastase into the airways. Reduction in the frequency of COPD exacerbation is a primary or secondary end point of several current clinical trials of emerging therapies.

Treatment of stable COPD
The American Thoracic Society and other leading pulmonary disease organizations recommend that COPD patients cease smoking and use one or more inhaled bronchodilators. The wide choice of inhaled bronchodilators includes short-acting beta₂-agonists (SABA) and long-acting beta₂-agonists (LABA), short-acting muscarinic antagonists (SAMA) and long-acting muscarinic antagonists (LAMA), and combinations of β-agonists and antimuscarinic agents. Inhaled corticosteroids (ICS) and combinations of corticosteroids with other agents may also be used. Oral medications, including methylxanthines and a phosphodiesterase 4 (PDE4) inhibitor, may also be used as adjunctive agents or, in the case of systemic corticosteroids, for acute exacerbations.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recently categorized COPD patients into four groups, in which the familiar spirometry-based grades (GOLD I–IV) are supplemented by patients’ symptom burden (assessed by the modified British Medical Research Council questionnaire or COPD Assessment Test) and exacerbation history: spirometry and exacerbation history are jointly used to determine the risk of adverse health events. Groups A and C have relatively mild symptoms, while Groups A and B have relatively low risk. GOLD recommends that Groups A and B receive SABA, LABA, SAMA, or LAMA bronchodilators. It recommends that Groups C and D also receive ICS or possibly the PDE4 inhibitor roflumilast. Despite symptomatic relief and reduced rates of exacerbations with current medications, long-term studies of exacerbations with COPD patients suggest that medications do not halt the decline of lung function and resulting mortality, although there is limited evidence that fluticasone and/or salmeterol may slow the rate of decline. Several groups are pursuing identification of biomarkers for COPD subgroups based on either the etiological agent/event triggering the exacerbation or the physiological targets that may indicate response to a given therapy. For example, COPD patients with higher levels of exhaled nitric oxide (FeNO) had a greater probability of the enhanced eosinophilic infiltration that is associated with a greater response to corticosteroids. These studies carry significant implications both for current treatment and for the development of novel therapies that may be targeted to specific groups of patients.

Inflammation in COPD
Smoke, from cigarettes, biomass fuel, or air pollution, is a common inducer of inflammation in COPD. The inhaled irritants provoke significant oxidative stress and activate inflammatory cells. Excess neutrophils and macrophages, along with T cells, B cells, and dendritic cells, infiltrate the peripheral airways, concurrent with the narrowing or obliteration of small bronchioles. A number of inflammatory markers are significantly elevated in the serum of patients with COPD, notably including CD40 ligand, epidermal growth factor (EGF), brain-derived neurotrophic factor (BDNF), a variety of acute-phase proteins, and neutrophil-associated proteins. These molecules may represent targets for future COPD therapeutics.

Glucocorticoid (GC) resistance
COPD is relatively resistant to modulation by corticosteroids, as even high doses of GCs do not delay or inhibit COPD progression. Histological analysis of lung tissue removed during lung volume reduction surgery of COPD patients indicated that GC treatment significantly reduced the number of airways with lymphoid follicles but had no long-term effect on luminal occlusion or airway wall thickening.
genes, and recruitment of coactivators such as CREB-binding protein, with consequent transcriptional activation. GC-mediated gene repression requires histone deacetylase 2 (HDAC2) at two distinct steps. First, this acetyl group must be removed by HDAC2 to allow binding to proinflammatory transcription factors such as nuclear factor-κB (NF-κB). Second, activated GR recruits HDAC2, which then deacetylates histones and thus inactivates transcription. Alveolar macrophages (AMs), lungs, and bronchi of COPD patients express lower levels of HDAC2 than those in healthy controls, however, and theophylline treatment, which enhances HDAC activity in AMs, also restores AM GC sensitivity. These effects may underlie the reported ability of theophylline treatment (200–400 mg/day, depending on weight), added to the LABA formoterol and the GC budesonide in a 50-patient (study completion) single-blind, placebo-controlled study, to improve 6-minute walk distance and forced expiratory volume in 1 second (FEV1). However, a double-blind, placebo-controlled study in 46 per-protocol patients found no effect of low-dose (100 mg bid) theophylline added to fluticasone plus salmeterol on HDAC activity, inflammatory biomarkers, or frequency of exacerbation.

Observed COPD-associated reductions in HDAC2 are believed to result from oxidative and nitrosative stress, and levels of the antioxidant transcription factor NF-E2–related factor 2 (Nrf2) are similarly reduced in AMs of COPD patients. Treatment with the Nrf2 activator sulforaphane, similar to theophylline treatment, increases HDAC2 activity and restores GC sensitivity. A number of other mechanisms of GC resistance have also been suggested. Among these may be increased expression of the translationally inactive GRβ, although this remains controversial and GR expression has been found to be reduced in lungs of healthy smokers and COPD patients. Another possibility is posttranslational modifications of GRα by phosphorylation or nitrosylation. Such phosphorylation may be due to p38 mitogen-activated protein kinase (MAPK) activation, and p38 MAPK inhibitors have been shown to reduce the GC resistance seen in some patients with severe asthma.

Restoration of GC sensitivity is an attractive strategy for the development of novel pharmaceutical therapies. As previously noted, the ability of theophylline treatment to accomplish this is controversial. However, roflumilast has been shown ex vivo to improve GC sensitivity of neutrophils from COPD patients, and subgroup analysis of two clinical trials showed that patients receiving ICS were among those particularly likely to experience a reduction of exacerbations in roflumilast treatment. A subsequent 1-year trial showed that roflumilast treatment reduced exacerbations in patients also receiving ICS and LABA.

### Proinflammatory cytokines and chemokines

Numerous proinflammatory cytokines and chemokines are significantly higher in COPD patients than in healthy controls, and multiple biologics and small molecules that target these mediators are under investigation (Tables 1 and 2). Chemokines significantly contribute to inflammation.

### Table I: Developmental status of chemokine receptor inhibitors for COPD

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Role in COPD</th>
<th>Drug</th>
<th>Clinical development</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR1</td>
<td>Receptor for CCL3 (MIP-1α) and chemoattractant for inflammatory cells. CCR1 is also among receptors binding CCL5 and CCL7.</td>
<td>AZD4818</td>
<td>AZD4818 (4-week treatment) provided no significant benefit to COPD patients (NCT00629239).</td>
<td>46</td>
</tr>
<tr>
<td>CCR2</td>
<td>Receptor for CCL2 (MCP-1), which recruits inflammatory cells to lungs in COPD. Increases synthesis of MUC5AC and MUC5B.</td>
<td>AZD2423</td>
<td>AZD2423 (28-day treatment) in DBPCRT (NCT01215279); study has completed but statistical analysis not released.</td>
<td>47, 48</td>
</tr>
<tr>
<td>CXCR2 (IL8RB)</td>
<td>Activated by CXCL8 (IL-8), which is higher in BAL and sputum of COPD patients. CXCL8 is chemotactic for neutrophils.</td>
<td>Navarixin (MK-7123); AZD5069</td>
<td>MK-7123 (navarixin; 6-month treatment) in DBPCRT showed statistically significant improvement in postbronchodilator FEV1 (NCT01006616 and NCT00441701). AZD5069 (4-week treatment) in DBPCRT in patients with moderate-to-severe COPD reduced blood neutrophil counts with no increased infection (NCT01233222).</td>
<td>44, 45</td>
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</table>

**Abbreviations:** DBPCRT, double-blind, placebo-controlled, randomized trial; IL-8, interleukin 8.
IL-1 is largely produced by eosinophils and is therefore low in typical COPD. A subset of COPD patients have elevated eosinophil numbers and IL-5 levels in their blood and airways; these patients are at increased risk for acute exacerbations.9,51 Two MAbs targeted to IL-5 have been investigated for their ability to reduce exacerbation rate in COPD patients, but one showed no evidence of efficacy and results for the other are not yet available (Table 2).

Secretion of IL-17A is a canonical marker of T helper 17 (Th17) lymphocytes, which are distinct from Th1 and Th2 cells. However, most of the cells secreting IL-17 in patients with very severe COPD were identified as mast...
cells. This study also found that levels of IL-17A in lungs of COPD patients correlated with functional decline, with elevations becoming significant in patients with severe and very severe disease. Another study found that the numbers of CD4+IL-17+ cells in the alveolar walls and small airways of COPD patients and CD4+IL-17+ numbers in small airways positively correlated with airflow limitations. These results are compatible with the finding that Th17 cells were present in the lungs of patients with emphysema but not normal controls and that IL-17A-induced secretion of the elastin-degrading enzyme matrix metalloprotease 12 by lung macrophages.

The levels of IL-17A were also elevated in the sputum of patients with acute COPD exacerbations associated with Haemophilus influenzae infection but not other acute exacerbations. Other studies have not similarly distinguished among causes of acute exacerbations, likely accounting for findings that the ratio of regulatory T cells to IL-17 levels in peripheral blood was similar in COPD patients with and without current acute exacerbations, although exacerbations significantly increased levels of transforming growth factor β (TGF-β). Indeed, one study was unable to detect IL-17 in sputum or serum of COPD patients with or without exacerbations. Another study found that the sputum of patients with severe COPD had significantly higher levels of IL-8 but 4.8-fold lower levels of IL-17 compared to that of patients with mild COPD and healthy controls. T cells from many COPD patients have also been reported to produce less IL-17A and IL-22 (also a signature cytokine of Th17 cells) than those of most normal smokers. These complex and apparently contradictory findings underline the uncertainty of the role of IL-17 in COPD. Nevertheless, an IL-17 modulator is currently in clinical trials for COPD.

Based on an IL-18-overexpressing transgenic mouse model that develops emphysema and airway remodeling, Kang et al and Nakajima and Owen proposed that IL-18 is a master regulator of lung pathology in COPD. A phase I safety and tolerability clinical trial (NCT01322594) of the MAb bimosiamose reduced inflammation in COPD patients and its specific inhibitor in COPD patients. Whether modulators of specific cytokines or chemokines can provide improved efficacy in a subgroup of patients is a possibility and warrants further investigation.

### Signaling molecules

Multiple signaling molecules help regulate inflammation and airway remodeling and represent plausible targets for the development of therapeutic candidates. Candidate drugs include inhibitors of p38 MAPK and related kinases, phosphoinositide kinase δ (PI3Kδ), leukotriene B4, selectins, and vasoactive intestinal peptide (Table 3). Although several oral and inhaled p38 MAPK inhibitors have been discontinued, the inhibited narrow spectrum kinase (p38α + Src family) inhibitor JNJ49095397 (previously RV568) shows promising activity in COPD patients; conference presentations have indicated that RV568 significantly increased FEV1 and inhibited IL-1β (90% at 800 μg dose) and CXCL8 expression (73%). However, a recent conference report performed in over 200 COPD patients (half placebo, half 400 μg dose) showed no benefit with RV568 on lung function or EXACT-PRO. PI3Kδ participates in many functions of lymphoid and myeloid cells: B-cell development, migration and activation of natural killer (NK) cells and T cells, neutrophil oxidative burst, macrophage activation triggered by immune complexes, and degranulation and maturation of mast cells. Specific PI3Kδ inhibitors are being developed and studies on the effects of such inhibitors in COPD are in progress. Efficacy data remain limited, however (Table 3). Selectins are essential for migration of inflammatory cells from the bloodstream into pulmonary tissue; the selectin modulator bimosiamose reduced inflammation in COPD patients and thus warrants further testing (Table 3).

Similar to the glucocorticoid receptor, peroxisome proliferator-activated receptor γ (PPARγ), also a member of the nuclear hormone receptor superfamily, exerts potent antioxidant and anti-inflammatory effects via multiple mechanisms, including downregulation of NF-κB and other proinflammatory transcription factors. Lung tissue and bronchial epithelial cells from COPD patients express significantly lower levels of PPARγ than those of nonsmoking controls. In vitro treatment of COPD patient and control bronchial epithelial cells binds TNF-α, was not superior to prednisone in COPD exacerbations and in fact was less effective among patients with eosinophilia (Table 2).

Taken together, these data show that an increased level of a specific cytokine or chemokine during COPD exacerbations or stable COPD does not necessarily predict the efficacy of its specific inhibitor in COPD patients. Whether modulators of specific cytokines or chemokines can provide improved efficacy in a subgroup of patients is a possibility and warrants further investigation.
Table 3 Developmental status of proinflammatory signaling pathway inhibitors for COPD

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Role in COPD</th>
<th>Drug</th>
<th>Clinical development</th>
<th>References</th>
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<tbody>
<tr>
<td>MAPK (p38 mitogen-activated protein kinase)</td>
<td>Higher MAPK in lungs activates proinflammatory response in AMs and lymphocytes.</td>
<td>Acumapimod, dilmapimod (SB-681323), losmapimod, PH-797804, GSK-610677, AZD-7624</td>
<td>Acumapimod (BCT197A2201) reportedly remains in active development, although phase II results have not been reported and there are no current clinical trials. Dilmapiomod (SB-681323) significantly reduced TNF-α production in COPD (NCT00144859) but its development was discontinued. Losmapimod did not induce a significant improvement in exercise tolerance or lung function (NCT01218126) and was discontinued. PH-797804 (6-week treatment) (NCT00559910) significantly improved lung function and dyspnea in moderate-to-severe COPD in DBPCRT but was discontinued. Development of GSK-610677 was discontinued following an unreported phase I trial (NCT00694902). Results of a phase II study of AZD-7624 (NCT02238483) have not been reported.</td>
<td>64, 106–109</td>
</tr>
<tr>
<td>Narrow spectrum kinase inhibitors</td>
<td>p38α and Src family kinases such as Hck are involved in the production of proinflammatory cytokines from macrophages, smooth muscle cells, and human airway epithelial cells. Cigarette smoke activates c-Src and augments airway inflammation and destruction of lung tissue.</td>
<td>JNJ49095397/RV568</td>
<td>RV568 (14-day inhaled treatment) significantly increased FEV₁ and reduced sputum malondialdehyde and serum myeloperoxidase in COPD patients. A recent conference report, however, in over 200 COPD patients showed no benefit with RV568 for 12 weeks with respect to lung function or EXACT-PRO (NCT01867762, NCT01475292, and NCT01661244).</td>
<td>64, 66, 110</td>
</tr>
<tr>
<td>PI3Kδ (phosphoinositide-3-kinase δ)</td>
<td>Involved in maturation and effector functions of B cells and other leukocytes.</td>
<td>GSK2269557, RV1729</td>
<td>GSK2269557 (treatment up to 84 days in NCT02522299 or 28 days in NCT02294734) DBPCRTs in patients with acute exacerbations of COPD in progress. RV1729 (treatment up to 28 days) is being tested in NCT02140346 with limited efficacy data being gathered in a predominantly phase I study. IMD-1041 in DBPCRT (NCT00883584) has no follow-up information posted since April 2009; unclear whether study was performed.</td>
<td>66, 67</td>
</tr>
<tr>
<td>IKK (inhibitor of nuclear factor kappa-B kinase)</td>
<td>IKK is an upstream activator of the proinflammatory transcription factor NF-κB. IKKα and IKKβ activity is elevated in patients with COPD.</td>
<td>IMD-1041, an IKKβ inhibitor</td>
<td>IMD-1041 in DBPCRT (NCT00883584) has no follow-up information posted since April 2009; unclear whether study was performed.</td>
<td>111</td>
</tr>
<tr>
<td>LTB₄ receptor</td>
<td>LTB₄ levels are elevated in sputum, breath, and BAL of COPD patients; highest LTB₄ levels seen in exacerbations. LTB₄ is chemotactic for neutrophils and T cells. AMs bearing the BLT1 receptor are more common in COPD patients.</td>
<td>BILL 284</td>
<td>BILL 284 (12-week treatment) was assessed for effects on lung function, exercise endurance, sputum, and safety in COPD patients (NCT02249247); a 14-day study assessed effects on biomarkers (NCT02249338) – results of neither study have yet been published. Other LTB₄ receptor antagonists have not demonstrated beneficial results.</td>
<td>4, 112</td>
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(Continued)
with PPARγ agonists including 10-nitro-oleic acid (a possible endogenous ligand) or rosiglitazone (a thiazolidinedione) blocked cigarette smoke-induced production of cytokines, chemokines, and ROS, and accompanying suppression of HDAC2 levels.69 The PPARγ agonist rosiglitazone dose dependently inhibited LPS-induced production of TNF-α and CCL5 by AMs of COPD patients, smokers, and never-smokers, shifting them toward an anti-inflammatory M2 phenotype, while both rosiglitazone and pioglitazone attenuated pulmonary inflammation in a tobacco smoke mouse model.70 A retrospective epidemiological study of veterans with both diabetes and COPD indicated that the 7,887 veterans treated with a PPARγ agonist for their diabetes (97.1% rosiglitazone) significantly reduced the risk of COPD exacerbations in comparison to those receiving other diabetes medications (n=42,347; incidence rate ratio [IRR]=0.85; CI: 0.80–0.91) (Table 4).72 Taken together, these data support further studies of PPARγ agonists in COPD patients with early signs of emphysema.

COPD also involves progressive increase in pulmonary arterial pressure, and 20%–91% (depending on definition, COPD severity, and method of measurement) of COPD patients have progressed to pulmonary hypertension.73 Endothelin signaling plays a major role in vascular remodeling and hence in development of pulmonary hypertension.74,75 An 18-month treatment with the

Table 3 (Continued)

<table>
<thead>
<tr>
<th>Mediator</th>
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<th>Clinical development</th>
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</tr>
</thead>
<tbody>
<tr>
<td>5-LO (5-lipoxygenase)</td>
<td>Involved in synthesis of leukotrienes.</td>
<td>5-Lipoxygenase inhibitor (zileuton) used clinically for asthma</td>
<td>Zileuton (14-day treatment) reduced urinary LTE, levels in hospitalized COPD patients with acute exacerbations in DBPCRT (NCT00493974) but did not significantly shorten stay or reduce treatment failure.</td>
<td>113</td>
</tr>
<tr>
<td>Prostaglandin D₃ receptor or chemoattractant</td>
<td>Highly expressed on eosinophils, basophils, Th2 (not Th1) lymphocytes, and subset of monocytes. Blocking this receptor inhibits chemotaxis of these cells. CRTh2 is expressed on mucosal epithelia and mononuclear infiltrates from COPD lungs.</td>
<td>AZD1981</td>
<td>AZD1981 (4-week treatment) did not induce significant differences in lung function, quality of life variables, nor use of reliever medication in COPD patients in DBPCRT (NCT00690482).</td>
<td>114</td>
</tr>
<tr>
<td>Selectins</td>
<td>Involved in migration of leukocytes from blood to surrounding tissues. Overexpressed in lung tissue of COPD patients.</td>
<td>Adenosine A₁a receptor</td>
<td>Inhalation of bimosiamose (28-day treatment) attenuated inflammation by significantly reducing numbers of macrophages and concentrations of CXCL8 in sputum of COPD patients in DBPCRT (NCT01108913). Adverse events were similar between the groups.</td>
<td>68</td>
</tr>
<tr>
<td>Vasoactive intestinal peptide (VIP)</td>
<td>Bronchodilatory and immunomodulatory effects in the lungs. Anti-inflammatory activity requires activation of both VPAC1 and VPAC2 receptors. With VPAC1 being particularly elevated in AMs of COPD patients.</td>
<td>VIP; available derivatives have not been tested in human COPD</td>
<td>VIP (3-month inhaled treatment) was tested in DBPCRT in severe COPD patients (NCT00464932). Study was completed in 2006 but no results are available.</td>
<td>116–119</td>
</tr>
</tbody>
</table>

Abbreviations: AM, alveolar macrophage; TNF-α, tumor necrosis factor α; DBPCRT, double-blind, placebo-controlled, randomized trial; FEV₁, forced expiratory volume in 1 second; NF-κB, nuclear factor-κB; Th, T helper.
endothelin antagonist bosentan improved measures of pulmonary hypertension compared to those at baseline, especially in GOLD grade III and IV COPD patients, while pulmonary hypertension worsened in placebo-treated patients (Table 4). However, bosentan can actually worsen hypoxemia in COPD patients without pulmonary hypertension. Although statins are known to have anti-inflammatory properties, simvastatin treatment (40 mg/day) of COPD

### Table 4 Developmental status of miscellaneous inflammatory modulators for COPD

<table>
<thead>
<tr>
<th>Mediator</th>
<th>Role in COPD</th>
<th>Drug</th>
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<tbody>
<tr>
<td>PPARγ (peroxisome proliferator-activated receptor γ)</td>
<td>Cigarette smoke downregulates PPARγ; Reduced PPARγ expression and activity seen in COPD.</td>
<td>Thiazolidinediones: rosiglitazone and pioglitazone</td>
<td>Retrospective cohort study of patients with diabetes and COPD showed that patients who filled ≥2 thiazolidinedione prescriptions (97.1% rosiglitazone) had a significantly lower number of COPD exacerbations than those receiving other diabetic medications.</td>
<td>69, 72</td>
</tr>
<tr>
<td>IgE activity</td>
<td>The high affinity IgE receptor is overexpressed on myeloid and plasmacytoid dendritic cells (DCs) of current smokers. Expression on plasmacytoid DCs correlates with COPD stage.</td>
<td>Omalizumab</td>
<td>The clinical trial of omalizumab (NCT00851370) was withdrawn due to lack of patients meeting inclusion criteria (elevated IgE and positive skin prick test to environmental allergens).</td>
<td>120</td>
</tr>
<tr>
<td>RARγ (retinoic acid receptor γ)</td>
<td>Regulates function of multiple cells of the immune system.</td>
<td>Palovarotene</td>
<td>RARγ agonist (2 year treatment) was tested for ability to improve lung function in patients with emphysema in DBPCRT (NCT00413205); in patients with lower lobe emphysema, palovarotene significantly reduced the decline in lung function (from conference report). In another study, over 1 year, palovarotene failed to show a significant benefit on lung density in moderate-to-severe emphysema secondary to severe alpha-1 antitrypsin deficiency.</td>
<td>121, 142, 143</td>
</tr>
<tr>
<td>Angiotensin receptor</td>
<td>Angiotensin II receptor blockers reduce in-hospital mortality during first COPD exacerbation.</td>
<td>Losartan</td>
<td>Open-label clinical trial of losartan (4-week treatment) (NCT02416102) to assess effects on mucociliary dysfunction (nasal potential difference, IL-8 and TGF-β in nasal discharge) in COPD patients is recruiting; a 4-year study of losartan for prevention of emphysema progression (NCT02696564) is not yet recruiting.</td>
<td>122</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Vasoconstrictor, contributes to pulmonary hypertension in COPD.</td>
<td>Bosentan</td>
<td>Bosentan (18-month treatment) halted progression of PH and led to improvements in most patients, especially those in GOLD grades III and IV. A study of bosentan effects on acute exacerbations and lung function in patients with GOLD III or IV COPD and pulmonary hypertension was initiated but status is unknown (NCT02093195).</td>
<td>73–75</td>
</tr>
<tr>
<td>Statins</td>
<td>Statins exert anti-inflammatory effects by several mechanisms independent of cholesterol lowering.</td>
<td>Simvastatin, rosvuastatin</td>
<td>Although retrospective studies suggested that statins may reduce frequency of exacerbations, hospitalization, and mortality in COPD patients, a recent prospective large randomized trial of simvastatin in COPD patients (NCT01061671) did not detect significant differences.</td>
<td>77, 78, 123, 124</td>
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patients at high risk for exacerbation did not increase the time to first exacerbation nor reduce the number of exacerbations. However, rosuvastatin (12-week treatment) improved endothelium-dependent vascular function in a prespecified subgroup (patients with supramedian circulating high-sensitivity C-reactive protein [hsCRP]) but not in the total COPD population in a double-blind, placebo-controlled trial. This study found no statistically significant effect on pulmonary function parameters, however.

**PDE inhibitors**

The 11-membered phosphodiesterase enzyme family (PDE1-11) differentially hydrolyzes cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which regulate many cellular processes including release of inflammatory mediators and relaxation of smooth muscles. PDE3 appears to be involved in bronchoconstriction since its inhibitors induce bronchodilation in humans. PDE4 is expressed in most inflammatory cell types and is a main target for emerging COPD therapies (Table 5), with the PDE4 inhibitor roflumilast having been approved by the FDA as a COPD treatment. In vitro studies of low-dose combinations of PDE4 and PI3Kδ inhibitors significantly reduced cigarette smoke extract-induced apoptosis of lung epithelial cells, neutrophil elastase production, and macrophage secretion of TNF-α, phosphorylated protein kinase B, and matrix metalloproteinase 9 (MMP-9).

Gastrointestinal adverse effects can be a significant problem with roflumilast, but PDE4 inhibitors with inhaled or nebulized (eg, RPL554, GSK-256066) formulations appear to have more tolerable side effect profiles than orally administered roflumilast.

The severity of emphysema and small airways disease is associated with higher expression of multiple MMPs. However, despite promising results in an animal model, an inhibitor of MMP-9 and -12 has not shown significant benefit for COPD patients in a clinical trial (Table 6).

**Oxidative stress and antioxidants**

Oxidants, both from inhaled pollutants and produced as part of the inflammatory response, are major contributors to COPD pathophysiology. Furthermore, inflammation-associated production of ROS and reactive nitrogen species (RNS) is accompanied by downregulation of the antioxidant transcription factor Nrf2. ROS activates the proinflammatory transcription factors activator protein 1 (AP-1) and NF-κB, with consequent production of inflammatory proteins and mediators. Excess ROS in COPD patients also directly contributes to airspace epithelial injury and inactivates proteases that help prevent emphysema. Therapeutic agents that activate Nrf2 and thus neutralize the excess oxidants may prove beneficial to COPD treatment.

The antioxidant transcription factor Nrf2, the primary mechanism for limiting oxidative stress, is reduced in COPD patients. Kelch-like ECH-associated protein 1 (Keap1) sequesters Nrf2 in the cytoplasm and under healthy conditions targets Nrf2 to Cullin-3 for ubiquitination and degradation. Keap1 monitors oxidative stress through its multiple cysteines with distinct stressors binding one or more

<table>
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<tbody>
<tr>
<td>T cells</td>
<td>T cells infiltrate airways, and are key mediators in the immune response; numbers of senescent cells, which produce increased amounts of proinflammatory and cytotoxic mediators and are relatively resistant to GC treatment, are elevated in blood and lungs of COPD patients.</td>
<td>Cyclosporine, an immunosuppressant affecting T-cell responses</td>
<td>A phase I dose-escalation study of inhaled cyclosporine (28-day treatment) in severe COPD patients (NCT00783107) also evaluated inflammatory biomarkers; no results of 2009 study are available. An ongoing phase II DBPCRT (16-week treatment) (NCT00974142) is evaluating oral cyclosporine in severe COPD.</td>
<td>125, 126</td>
</tr>
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</table>

**Abbreviations:** Ig, immunoglobulin; IL, interleukin; TGF-β, transforming growth factor β; GOLD, Global Initiative for Chronic Obstructive Lung Disease; DBPCRT, double-blind, placebo-controlled, randomized trial; hsCRP, high-sensitivity C-reactive protein. |
specific cysteines. Following binding of these stress-related compounds, release of Nrf2 from Keap1 occurs, which transfers to the nucleus and activates multiple antioxidant enzymes and phase II proteins that counteract oxidative stress. This makes the Nrf2/Keap1 system an attractive therapeutic target in COPD and other inflammatory diseases. The natural product sulforaphane activated Nrf2 in AMs isolated from COPD patients, denitrosylated HDAC2, and restored sensitivity to the glucocorticoid dexamethasone in a glutathione-dependent manner.

A study of the effect of two doses of sulforaphane on Nrf2 expression in 89 COPD patients was recently completed, and sulforaphane administered for four weeks to patients with COPD did not induce the expression of Nrf2 target genes or have an effect on oxidative stress, airway inflammation, or lung function (NCT01335971). Erdosteine and N-acetylcysteine directly scavenge ROS via their thiol groups (of the metabolite in the case of erdosteine) and also have mucolytic activity. High-dose (900 mg/day) erdosteine increased the ability of salbutamol to improve %FEV₁ reversibility, and long-term treatment reduces exacerbations and improves quality of life. Another study (NCT01862536) did not improve exercise capability or quality of life. Mucus hypersecretion

Mucus hypersecretion can be modulated by blocking its overproduction and/or by inhibiting its secretion (Table 7). Erdosteine and N-acetylcysteine directly scavenge ROS via their thiol groups (of the metabolite in the case of erdosteine) and also have mucolytic activity. High-dose (900 mg/day) erdosteine increased the ability of salbutamol to improve %FEV₁ reversibility, and long-term treatment reduces exacerbations and improves quality of life. High-dose (600 mg bid) N-acetylcysteine reduces the number of exacerbations patients experience; reported effects with a lower dose (600 mg/day) have been inconsistent.

Mucus hypersecretion can be modulated by blocking its overproduction and/or by inhibiting its secretion (Table 7). Hypothetically, a rebound effect after cessation of an inhibitor of mucin secretion may involve a rapid release of produced but unsecreted mucin. In contrast, the rebound effect after cessation of an inhibitor of mucin production may involve a lag phase for mucin production and a more gradual increase of mucin secretion. Multiple mucins comprise the gel-forming layer of normal airway mucus. Numerous signals can promote

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<td>PDE4 (phosphodiesterase subtype 4)</td>
<td>Hydrolyzes cAMP, an inhibitor of inflammatory pathways; expressed in a wide variety of cells.</td>
<td>Roflumilast, a selective PDE4 inhibitor; GSK-256066; CHF6001; MK0359; MK-0873; tofimilast; UK-500,001; tetomilast (OPC-6535, PDE4 inhibitor with modest PDE3 inhibitory activity); oglemilast; QAK423A; TPI 1100.</td>
<td>Roflumilast is only US FDA approved PDE4 inhibitor; it reduced exacerbation frequency and also produced clinically significant improvements in dyspnea. GSK-256066 (4-week inhaled treatment) in DBPCRT (NCT00549679) improved residual volume and showed a nonsignificant trend toward augmenting postbronchodilator FEV₁. Preclinical testing of CHF6001 (inhaled) shows efficacy and low toxicity in several rat models of pulmonary inflammation. It is in clinical testing (28-day treatment) (NCT01730404) but no results have been reported. Numerous other PDE inhibitors are in clinical testing, including MK-0359 (NCT00482235); MK-0873 (NCT00132730); tofimilast (NCT00219622); UK-500,001 (NCT00263874); tetomilast (OPC-6535) (NCT00874497); terminated, NCT00917150; oglemilast (NCT00671073); QAK423A (NCT01197287); and TPI 1100 (NCT00914433).</td>
<td>10, 42, 80, 99, 127–129</td>
</tr>
<tr>
<td>PDE3/PDE4</td>
<td>PDE3 degrades both cAMP and cGMP. It is expressed on airway smooth muscle cells and acts as a bronchoconstrictor. Combined PDE3/PDE4 inhibition is often additive or synergistic.</td>
<td>RPL554</td>
<td>RPL554 (up to 94-day treatment) is being investigated as an adjunct to salbutamol and ipratropium in COPD patients in DBPCRT (NCT02542254).</td>
<td>10</td>
</tr>
<tr>
<td>PDE5</td>
<td>PDE5 promotes pulmonary arterial vasoconstriction and vessel wall hypertrophy.</td>
<td>Tadalafil (inhibits PDE5)</td>
<td>Tadalafil, which is approved for pulmonary arterial hypertension, in DBPCRT (12-week treatment) (NCT01197469) did not improve exercise capability or quality of life. Another study (NCT01862536) is in progress.</td>
<td>130</td>
</tr>
</tbody>
</table>

Abbreviations: FEV₁, forced expiratory volume in 1 second; DBPCRT, double-blind, placebo-controlled, randomized trial; FDA, Food and Drug Administration.
The heterogeneity of COPD presentation augments the challenges in identifying and developing therapeutic compounds for the treatment of COPD patients. It also emphasizes the importance of tailoring therapy to individual patients and their disease status, which may involve considerations beyond the standard GOLD categories. Several distinct emerging therapies have shown efficacy in at least some COPD patients. The length of treatment (>3 months) and the inhaled route of administration can be associated with a higher probability of observing a positive effect on COPD variables and a reduced side effect profile, respectively. Although some of the emerging compounds showed significant activity in the total COPD population tested,\textsuperscript{55,68,74,88,99} sometimes only in connection with assessed biomarkers rather than clinically significant outcomes, subgroup analysis showed that most compounds were significantly affected in one or more of the following subgroups: smokers or ex-smokers,\textsuperscript{44,99} patients with chronic bronchitis or emphysema,\textsuperscript{80,99} use of standard COPD therapies,\textsuperscript{99} patients with alteration of relevant biomarkers,\textsuperscript{78} or at different COPD grades.\textsuperscript{74} These data suggest that subgroup analyses and the possibility of individualized therapy can benefit developers of emerging therapies by identification of the patients most likely to benefit from a new therapy.

### Acknowledgments
This work was supported by a Merit Review award from the US Department of Veterans Affairs and the National Institutes of Health grants HL093196 and AI125338 (RCR). We gratefully acknowledge the scientific and writing expertise of KL Molnar-Kimber, PhD. The contents in this article do not represent the views of the US Department of Veterans Affairs or the United States Government.

### Disclosure
The authors report no conflicts of interest in this work.
Table 7 Developmental status of modulators of mucus-mediated airway obstruction for COPD

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<td>Epidermal growth factor receptor (EGFR)</td>
<td>EGFR regulates mucin stores in airway epithelium, which are significantly increased in COPD.</td>
<td>BIBW 2948 (inhibits EGFR autophosphorylation)</td>
<td>Inhalation of BIBW 2948 (4-week treatment) in DBPCRT (NCT00423137) reduced internalization of EGFR but did not reduce mucin stores; BIBW 2948 treatment was associated with higher discontinuation rate (24%) than placebo (4.3%). FEV\textsubscript{1} in the higher dose group significantly declined by visit 5 but returned to baseline by visit 7.</td>
<td>134</td>
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<tr>
<td>Myristoylated alanine-rich C kinase substrate (MARCKS)</td>
<td>Mediates movement of mucin granules to the apical membrane as part of mucin exocytosis.</td>
<td>BIO-11006</td>
<td>A 21-day phase II DBPCRT of BIO-11006 (inhaled) in COPD (NCT00648245) has been completed; a 2011 abstract reported improved lung function and reduced mucus hypersecretion.</td>
<td>98, 135, 136</td>
</tr>
<tr>
<td>Epithelial sodium channel</td>
<td>Role in homeostasis of mucus hydration, ciliary beating, and clearance of mucus.</td>
<td>GS-5737; compound A</td>
<td>Study of effects of GS-5737 on ciliary action in healthy controls (NCT01793649) was terminated. Preclinical study of compound A shows improved ciliary movement, mucus clearance, and airway hydration.</td>
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Multiple mechanisms

- Anti-inflammatory and mucolytic
  - Inflammation, oxidative stress and mucus hypersecretion are well-established in COPD.
  - N-acetylcysteine (NAC)

- Mucolytic, anti-inflammatory, antioxidant, promotes activity of antibiotics
  - Inflammation, oxidative stress, and mucus hypersecretion are well-established in COPD.
  - Erdosteine

- Cystic fibrosis transmembrane conductance regulator (CFTR)
  - One study found that CFTR is downregulated in smokers with and without COPD; another found that expression of CFTR inversely correlated with emphysema severity.
  - Ivacaftor potentiates chloride transport

Table 7 continues...

References


42. Rennard SI, Calverley PM, Goehring UM, Breedenbroker D, Martinez FJ. Reduction of exacerbations by the PDE4 inhibitor roflumilast – the importance of defining different subsets of patients with COPD. Respir Rev. 2011;12:18.


