New Therapies for Chronic Obstructive Pulmonary Disease

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Abstract
Chronic obstructive pulmonary disease (COPD) is a major global health problem which is increasing throughout the world and a major cause of death. However, current therapies fail to prevent disease progression or mortality. The mainstay of current drug therapy are long-acting bronchodilators; several longer-acting inhaled β2-agonists and muscarinic antagonists (and combinations) are now in development. No treatments have so far been shown to suppress chronic inflammation in COPD lungs. With better understanding of the inflammatory and destructive process in the pathophysiology of COPD, several new targets have been identified. Several mediator antagonists tested in COPD have so far been disappointing, but CXCR2 antagonists that block pulmonary neutrophil and monocyte recruitment may be more promising. Broad-spectrum anti-inflammatory drugs may be more effective, and include inhibitors of the enzymes phosphodiesterase-4, p38 mitogen-activated protein kinase, NF-κB kinase and phosphoinositide 3 kinase, and histone deacetylase-2 activity. This might be achieved by theophylline-like drugs, phosphoinositide 3 kinase-δ inhibitors, more effective antioxidants and non-antibiotic macrolides.

Why New Therapies Are Needed
There have been few advances in the drug therapy of COPD, in contrast to the enormous strides made in asth-
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management. Not only are there no drugs that prevent disease progression and death, but prevention and treatment of exacerbations are poor. The only significant advances in drug therapy have been in the development of longer-acting bronchodilators, but there are currently no effective anti-inflammatory treatments, with the exception of theophylline that has attracted no clinical interest [7]. Development of new therapies depends on better understanding of the cellular and molecular mechanisms that are involved in inflammation, structural changes and aberrant repair mechanisms that characterize the pathophysiology of COPD. The inflammation of COPD is very different from that seen in asthma, with different inflammatory cells and mediators, indicating that different treatments are likely to be needed [8].

Why Is It Difficult to Find New Treatments?
Development of new drugs for COPD has proved to be very difficult for the pharmaceutical industry. The underlying cellular and molecular mechanisms are less well understood than in asthma and more research is needed. Animal models of COPD for early drug testing are poor and
focus on emphysema, rather than the small airway disease that appears to underlie the progressive loss of FEV₁ and the increasing symptoms over time that are characteristic of COPD patients [9]. Better animal models that have predominantly small airway disease are needed [10].

There are also uncertainties about how to test drugs for COPD, which may require long-term studies (3 years or longer) in relatively large numbers of patients at an enormous cost. For example, a recent study looking at the effects of drug intervention on mortality is believed to have cost several hundred million dollars [11]. It is likely that there are several clinical phenotypes that comprise the diagnosis of COPD and it may be necessary to differentiate these in clinical trials [12]. Many patients with COPD may have co-morbidities, such as ischaemic heart disease and diabetes, which may exclude them from clinical trials of new therapies [6]. There is little information about surrogate markers, for example biomarkers in blood, sputum or breath, to monitor the short-term efficacy and predict the long-term potential of new treatments [12, 13]. Finally, it is difficult to accurately measure small airway function in patients with COPD, so there is a need to develop better tests of small airway function that are not affected by emphysema or abnormalities of large airway function [10].

**New Bronchodilators**

Long-acting inhaled bronchodilators (long-acting β₂-agonists and a long-acting muscarinic antagonist) are now the mainstay of current management of COPD [14], so there are several attempts to improve existing bronchodilators. Several once-daily inhaled β₂-agonists, such as indacaterol and carmoterol, are now in clinical development [15]. Indacaterol is a very effective dilator of small human airways measured by videomicroscopy in a precision-cut lung slice preparation [16] and has a bronchodilator action of over 24 h in patients with COPD with a fast onset of action and no evidence of tolerance or significant side effects [17].

The once-daily inhaled anticholinergic tiotropium bromide has been an important advance in therapy and several other long-acting inhaled muscarinic antagonists, such as aclidinium bromide and glycopyrrolate, are now in development [18, 19]. Combination inhalers with a long-acting β₂-agonist with a long-acting inhaled muscarinic antagonist are also in development as there is an additive effect between these two bronchodilator classes [20]. Single molecules that link a muscarinic antagonist to a β₂-agonist, such as GSK-961081, are now also in clinical development [21].

It has proved difficult to discover novel classes of bronchodilator drug. Potassium channel openers, while effective in relaxing human airways in vitro, were not effective in asthma as they were more potent as vasodilators and this limited the dose that could be administered. There has been interest in developing drugs that inhibit the contractile machinery in airway smooth muscle, including rho kinase inhibitors, inhibitors of myosin light chain kinase and direct smooth muscle myosin inhibitors. As these agents also cause vasodilatation it will be necessary to administer them by inhalation.

**Smoking Cessation Therapies**

Current smoking cessation strategies are not very effective, although partial nicotinic agonists, such as varenicline, appear to be more effective than previous therapies [22]. More effective treatments for nicotine addiction are needed and several non-nicotinic drugs are currently in development, including dopamine D₂ receptor antagonists and several nicotine vaccines [23].

**Blocking Inflammatory Mediators**

Many mediators have been implicated in the pathophysiology of COPD [24, 25], but as in asthma it seems unlikely that these will prove to be very effective therapies as there is considerable redundancy in the effects of these mediators.

**Lipid Antagonists**

Leukotriene B₄ (LTB₄) is increased in sputum and broncho-alveolar lavage fluid of patients with COPD and is chemotactic for neutrophils and lymphocytes. Several antagonists of the major receptor BLT1 have been developed [26], but so far clinical studies in COPD have been negative. 5’-Lipoxygenase inhibitors should also be beneficial by blocking the production of endogenous LTB₄, but it has been difficult to discover 5-lipoxygenase inhibitors without hepatic toxicity.

**Cytokine Inhibitors**

Tumour necrosis factor-α (TNF-α) concentrations are increased in sputum, particularly during exacerbations, and this cytokine amplifies inflammation and may account not only for neutrophilic inflammation in the lungs but also some systemic features such as skeletal muscle wasting. However, blockade of TNF-α with a blocking antibody (infliximab) has no beneficial clinical effects in patients with COPD, using the same doses which are effective in rheumatoid arthritis [27]. Of particular concern was the finding that more COPD patients...
treated with anti-TNF developed respiratory cancers and severe lung infections. Other cytokines that are currently targeted for inhibition include interleukin (IL)-1β, IL-6 and IL-17. IL-6 is increased in sputum and in the systemic circulation of COPD patients and may account for the increase in circulating C-reactive protein. A potent inhibitor of IL-6 is the receptor antibody tocilizumab, which is effective in rheumatoid arthritis but has not yet been tested in COPD patients [28].

Chemokine Antagonists

Several chemokines are implicated in COPD and there has been a lot of interest in small-molecule chemokine receptor antagonists [29]. A blocking antibody to CXCL8 (IL-8) had a small effect in reducing dyspnoea in COPD patients [30], but other CXC chemokines, such as CXCL1 (GRO-α) and CXCL5 (ENA-78) are also increased in COPD and play a similar role to CXCL8. The chemotactic effect of CXCL8, CXCL1 and CXCL5 on neutrophils and monocytes is mediated by a common receptor CXCR2. A CXCR1/2 antagonist (ADZ8309) has been shown in a pilot study to inhibit neutrophil inflammation in the lung following inhaled endotoxin challenge in normal volunteers [31]. This is an oral medication, so it may have a particular advantage in COPD patients. Another chemokine receptor target is CXCR3 as the CXCR3 ligands CXCL9 (Mig), CXCL10 (IP-10) and CXCL11 (I-TAC) are increased in COPD and there is an increase in CD4+ and CD8+ T cells expressing CXCR3 [32]. CXCR3 antagonists have not yet been tested in COPD patients but are currently in development. CCL5 (RANTES) is also increased in COPD and CCR5 antagonists, such as maraviroc, have now been developed for HIV/AIDS and so may be available for testing in COPD.

Transforming Growth Factor-β Inhibitors

Transforming growth factor-β (TGF-β) may play a key role in the fibrosis of small airways, which is turning out to be a major mechanism for progressive loss of FEV1 and reduced exercise performance in COPD and may be activated by oxidative stress and cigarette smoke [33]. TGF-β-related genes show increased expression in small airways of COPD patients [34]. Small-molecule inhibitors of TGF-β receptor tyrosine kinase (activin receptor-like kinase 5), such as SD-280, have been developed and shown to inhibit airway fibrosis in a model of asthma [35]. However, there may be long-term concerns about inhibiting TGF-β, which plays an important role in maintaining regulatory T lymphocytes. Many of the effects of TGF-β are mediated via connective tissue growth factor so that inhibiting this cytokine or its receptor may be a more attractive approach in the future.

Antiproteases

In COPD there is an imbalance between proteases that digest elastin (and other structural proteins) and antiproteases that protect against this. This suggests that either inhibiting these proteolytic enzymes or increasing endogenous antiproteases may be beneficial and should prevent the progression of emphysema. However, several proteases are implicated in COPD so that blocking a single enzyme may not have a major therapeutic effect. Endogenous antiproteases (α1-antitrypsin, secretory leukocyte protease inhibitor, elafin, tissue inhibitors of matrix metalloproteinase, MMP) may be given either in recombinant form or by viral vector gene delivery, but these approaches are unlikely to be cost-effective as large amounts of protein have to be delivered and gene therapy is unlikely to provide sufficient protein. A more promising approach is to develop small-molecule inhibitors of proteases, particularly those that have elastolytic activity. Neutrophil elastase inhibitors have been developed but have all failed in clinical trials. MMPs with elastolytic activity are also a target for drug development, and MMP-9 appears to be the predominant enzyme, which is released from macrophages, neutrophils and epithelial cells. Non-selective MMP inhibitors, such as marimastat, have major side effects [36], suggesting that isoenzyme-selective inhibitors or inhaled delivery may be needed. A dual MMP-9/MMP-12 inhibitor, AZ11557272, has been shown to prevent emphysema, small airway thickening and inflammation in guinea pigs exposed to cigarette smoke over 6 months [37].

New Anti-Inflammatory Treatments

Inflammation in COPD lungs is corticosteroid-resistant so that alternative anti-inflammatory approaches are needed (table 1) [38, 39]. There are several broad-spectrum anti-inflammatory treatments in development for COPD but there are concerns over the safety of these approaches, since these drugs hit targets that are widely distributed. This suggests that inhaled delivery may be necessary to increase the therapeutic ratio.

Phosphodiesterase-4 Inhibitors

Phosphodiesterase-4 (PDE4) is the predominant PDE expressed in neutrophils, T cells and macrophages, suggesting that PDE4 inhibitors would be effective in con-
trolling inflammation in COPD [40]. A selective PDE4 inhibitor, roflumilast, inhibits lung inflammation and emphysema in a smoking model of COPD in mice [41]. In COPD patients oral roflumilast given over 4 weeks significantly reduces the numbers of neutrophils (by 36%) and CXCL8 concentrations in sputum [42]. In clinical trials roflumilast (500 mg once daily) given over 12 months improved lung function in COPD patients to a small extent but had little effect in reducing exacerbations or improving quality of life [43]. More recently roflumilast has been shown to significantly improve FEV$_1$ (by approximately 50 ml) and reduce exacerbation (by about 15%) in patients with severe disease who have frequent exacerbations and mucus hypersecretion, although disappointingly there was no reduction in symptoms [44]. Roflumilast provides clinical benefit when added to salmeterol or tiotropium [45] and so may be used as an additional treatment in patients with severe disease. These results reflect the fact that side effects, particularly nausea, diarrhoea and headaches, limit the dose that can be tolerated. This problem could be overcome by inhaled delivery, but to date two inhaled PDE4 inhibitors have been found to be ineffective, although well tolerated. Another approach is to develop isoenzyme-selective inhibitors. PDE4D inhibition appears to account for nausea and vomiting, whereas PDE4B inhibition may account for the anti-inflammatory effects, so that PDE4B selective inhibitors may be better tolerated. PDE7A is also expressed in the same inflammatory cells as PDE4, so inhibition of PDE7 may be beneficial. However, a selective PDE7 inhibitor had only a small anti-inflammatory effect alone, but potentiated the anti-inflammatory effects of a PDE4 inhibitor, suggesting that a combined inhibitor may be useful as it should not increase side effects [46, 47]. PDE3 inhibitors may produce bronchodilatation so that dual PDE3/4 inhibitors may combine bronchodilatation with anti-inflammatory activity [48]. However, there are concerns about the potential cardiovascular toxicity of PDE3 inhibition, so these drugs may also have to be given by inhalation.

**Nuclear Factor-κB Inhibitors**

Nuclear factor-κB (NF-κB) regulates the expression of CXCL8 and other chemokines, TNF-α and other inflammatory cytokines, as well as MMP-9. NF-κB is activated in macrophages and epithelial cells of COPD patients, particularly during exacerbations. Inhibitors of NF-κB kinase 2 (IKK2) are effective in some animal models of COPD (LPS exposure) but not in others (neutrophil elastase instillation), indicating that the effects may be complex [49]. Although several IKK2 inhibitors are now in development, so far none have been tested in COPD patients. A major concern about long-term inhibition of NF-κB is that effective inhibitors may result in immune suppression and impair host defences, since mice which lack NF-κB genes succumb to septicemia.

**p38 Mitogen-Activated Protein Kinase Inhibitors**

Mitogen-activated protein kinases (MAPKs) play a key role in chronic inflammation and several complex enzyme cascades have now been defined. One of these, the p38 MAPK pathway, is activated by cellular stress and regulates the expression of inflammatory cytokines, including CXCL8, TNF-α and MMPs. p38 MAPK (measured by phosphorylated p38 MAPK) is activated in alveolar macrophages of COPD lungs [50]. Several small-molecule inhibitors of p38 MAPK have now been developed. A potent inhibitor of p38-α isofrom, SD-282, is effective in inhibiting TNF-α release from human lung macrophages in vitro [51] and in suppressing inflammation in a smoking model of COPD in mice in which corticosteroids are ineffective [52]. Several p38 MAPK inhibitors have entered clinical trials, but there have been major problems with side effects and toxicity, indicating that it is probably necessary to deliver these drugs by inhalation to reduce systemic exposure. Recent studies indicate that other MAPK pathways, particularly extracellular signal-regulated kinase 1/2, may also play an important role in regulating the expression of proinflammatory cytokines in alveolar macrophages, in contrast to its lack of effect in blood monocytes [53].

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**Table 1. Some new anti-inflammatory treatments in development for COPD**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Clinical development</th>
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<tr>
<td>LTB$_4$ antagonists</td>
<td>development stopped</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>development stopped</td>
</tr>
<tr>
<td>CXCR2 antagonists</td>
<td>in early clinical development</td>
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<tr>
<td>MMP-9 inhibitors</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>Neutrophil elastase inhibitor</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>PDE4 inhibitors</td>
<td>phase III trials but side effects</td>
</tr>
<tr>
<td>p38 MAPK inhibitors</td>
<td>a major limitation</td>
</tr>
<tr>
<td>NF-κB (IKK2) inhibitors</td>
<td>phase I studies but problems</td>
</tr>
<tr>
<td>P3K-γ/δ inhibitors</td>
<td>side effects and toxicity</td>
</tr>
<tr>
<td>PPAR-γ agonists</td>
<td>pre-clinical but concerns about</td>
</tr>
<tr>
<td></td>
<td>side effects</td>
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<td></td>
<td>early clinical development</td>
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<tr>
<td></td>
<td>already developed for diabetes, clinical</td>
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<td>studies in progress</td>
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Phosphoinositide 3 Kinase Inhibitors

Phosphoinositide 3 kinases (PI3Ks) are a family of enzymes that lead to the generation of lipid second messengers that regulate a number of cellular events, including innate and adaptive immune responses. A particular isoform, PI3K-γ, is involved in neutrophil recruitment and activation. Knock-out of the PI3K-γ gene results in inhibition of neutrophil migration and activation, as well as impaired T-lymphocyte and macrophage function, so PI3K-γ inhibitors may be a potential anti-inflammatory therapy for COPD [54]. PI3K-δ is also involved in expression of inflammatory genes and several PI3K-δ or mixed PI3K-γ/δ inhibitors are now in development [55]. Pan-isoform inhibitors of PI3K are likely to be associated with side effects as these enzymes appear to serve a number of key cell function, but the -γ and -δ isoforms have a distribution more restricted to leucocytes and may therefore be better tolerated, especially if delivered by inhalation. PI3K-δ inhibitors also have the potential to reverse corticosteroid resistance in COPD patients [56].

Peroxisome Proliferator-Activated Receptor Activators

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated nuclear hormone receptors belonging to the steroid receptor superfamily, and the three recognized subtypes PPAR-α, -γ and -δ are widely expressed. There is evidence that activation of PPAR-α and PPAR-δ may have anti-inflammatory and immunomodulatory effects. For example PPAR-γ agonists, such as troglitazone and rosiglitazone, inhibit the release of inflammatory cytokines from monocytes and induce apoptosis of T lymphocytes, suggesting that they may have anti-inflammatory effects in COPD [57]. PPAR-γ agonists also inhibit lung fibrosis and therefore have the potential to prevent progression of small airway fibrosis in COPD [58]. There is a reduction in PPAR-α expression in skeletal muscle of COPD patients that correlates with muscular weakness, indicating that PPAR-α agonists, such as clofibrate, may be useful in treating muscle weakness in severe disease [59].

Reversal of Corticosteroid Resistance

Even high doses of corticosteroids have minimal effects on the progression of COPD and no effects on mortality [60]. Even their effect in preventing exacerbations has been questioned on the basis of flawed study design [39, 61]. This may reflect the resistance of COPD inflammation to the anti-inflammatory effects of corticosteroids. There is increasing evidence that this may be due to a reduction in HDAC2 as a result of oxidative and nitrative stress [62]. This results in increased acetylation of the glucocorticoid receptor which prevents it from inhibiting NF-κB-driven inflammation [63]. A novel therapeutic strategy is therefore reversal of this corticosteroid resistance by increasing the expression and activity of HDAC2 and this may be achieved in several ways.

Theophylline-Like Drugs. Low doses of oral theophylline increase HDAC2 expression in alveolar macrophages from COPD patients and thereby restore steroid responsiveness [7, 64]. This has also been demonstrated in mice exposed to cigarette smoke, which develop a steroid-resistant inflammation in the lungs with increased neutrophils and macrophages. This inflammation is not reversed by high doses of corticosteroids or by theophylline alone but is reversed by low-dose oral or inhaled theophylline combined with a corticosteroid via an increase in HDAC2 activity [65]. Understanding the molecular mechanisms of action of theophylline, which appear to be independent of PDE inhibition, may lead to novel therapeutic approaches to restoration of corticosteroid responsiveness which avoid the side effects and drug interaction problems of theophylline itself. Theophylline appears to reverse steroid resistance by inhibiting PI3K-δ, so that PI3K-δ inhibitors may also be effective [56].

Antioxidants. Oxidative stress is increased in patients with COPD, particularly during exacerbations, and reactive oxygen species contribute to its pathophysiology. Oxidative stress reduces steroid responsiveness via a reduction in HDAC2 activity and expression. This suggests that antioxidants may reverse corticosteroid resistance and also reduce inflammation. Unfortunately currently available antioxidants based on glutathione are relatively weak and are inactivated by oxidative stress, so new more potent and stable antioxidants are needed, such as superoxide dismutase mimics and NADPH oxidase inhibitors [66]. The transcription factor Nrf2 (nuclear factor erythroid 2-related factor-2) plays a key role in the regulation of endogenous antioxidant genes and is defective in COPD patients. Several Nrf2 activators, such as sulforaphane (which occurs naturally in broccoli) and the synthetic triterpenoid 1-[2-cyano-3,12-dioxooleana-1,9-dien-28-oyl] imidazole-methyl ester, have now been identified [67]. The transcription factor Nrf2 (nuclear factor erythroid 2-related factor-2) plays a key role in the regulation of endogenous antioxidant genes and is defective in COPD patients. Several Nrf2 activators, such as sulforaphane (which occurs naturally in broccoli) and the synthetic triterpenoid 1-[2-cyano-3,12-dioxooleana-1,9-dien-28-oyl] imidazole-methyl ester, have now been identified [67].

Macrolides. It has long been recognized that macrolides have anti-inflammatory effects that may be independent of their antibiotic effects. Macrolides appear to inhibit inflammation by inhibiting NF-κB and other transcription factors. A non-antibiotic macrolide (EM-703) reverses corticosteroid resistance due to oxidative stress by increasing HDAC2 activity [68]. Several non-antibiotic macrolides are now in development as anti-inflammatory therapies.
Lung Regeneration

Since a major mechanism of airway obstruction in COPD is due to loss of elastic recoil due to proteolytic destruction of lung parenchyma, it seems unlikely that this could be reversible by drug therapy, although it might be possible to reduce the rate of progression by preventing the inflammatory and enzymatic disease process.

Retinoic Acid

Retinoic acid increases alveolar septation during lung development and in adult rats and mice reverses the histological and physiological changes induced by elastase treatment [69]. This has not been seen in several other species and there are doubts whether emphysema is reversible in humans as alveolar formation ceases about the age of 6 years. A clinical trial of all-trans-retinoic and 13-cis-retinoic acid in patients with emphysema failed to show any improvement in clinical parameters, health status or computed tomography (CT) density after 6 months of therapy [70].

Stem Cells

Another possible approach to repairing damaged lung in emphysema is the use of stem cells to seed the lung combined with drugs that stimulate their homing and proliferation in the lung. Human embryonic stem cells have been transformed into alveolar type II pneumocytes which have the capacity to repair alveolar damage [71]. Adult bone marrow-derived stem cells may also be suitable for populating the lung, particularly if enhanced by retinoic acid or granulocyte-macrophage colony-stimulating factor. However, there are several concerns about the use of stem cells for lung repair as there may be a problem engrafting these cells in the alveoli and there is always a risk of cancer or teratoma development [72]. The lung is a complex organ and it would probably be necessary to grow both endothelial and alveolar cells to repair emphysema.

Future Developments

New drugs for the treatment of COPD are greatly needed and there has been an enormous effort now invested by the pharmaceutical industry to find such treatments. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult in the majority of smokers. Furthermore, it is now recognized that not all COPD is due to cigarette smoking, particularly in developing countries [73]. It is important to identify the genetic factors that determine why only a minority of heavy smokers develop COPD, and identification of genes that predispose to the development of COPD may provide novel therapeutic targets in the future. However, it will be difficult to demonstrate the efficacy of novel treatments on the rate of decline in lung function, since this requires large studies over 3 years. Hence, there is a need to develop novel outcome measures and surrogate biomarkers, such as analysis of sputum parameters (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species) [13]. The use of imaging techniques, such as high-resolution CT, to measure disease progression is another promising approach as scanning resolution increases [74]. It may also be important to more accurately define the presence of emphysema versus small airway obstruction using CT scans, as some drugs may be more useful for preventing emphysema, whereas others may be more effective against the small airway inflammatory-fibrotic process. More research on the basic cellular and molecular mechanisms of COPD and on more useful animal models is urgently needed to aid the logical development of new therapies for this common and important disease, for which no effective preventative drugs currently exist.

Conclusion

Of the drugs currently in development, PDE4 inhibitors, p38 MAPK inhibitors and IKK2 inhibitors appear to be promising, but there are concerns about side effects so that inhaled administration is likely to be needed. There are also concerns about their long-term safety in increasing lung infection and cancer through inhibition of TNF-α. CXCR2 antagonists show promise as an anti-neutrophilic and anti-macrophage therapy and should be well tolerated by oral administration. It is likely that effective anti-inflammatory therapies would not only reduce exacerbations, but would also improve symptoms and health status. In the long term these drugs should slow the decline in lung function and prevent the considerable morbidity imposed by this common disease. Perhaps the most promising approach is reversal of corticosteroid resistance, which is the main barrier to effective anti-inflammatory treatments in COPD. Drugs derived from theophylline may be effective through increasing HDAC2 activity and expression and should be relatively well tolerated. More potent antioxidants and non-antibiotic macrolides also deserve further study.
References


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