Novel mechanisms and new therapies for chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is now one of the leading causes of death and disability, with a prevalence of over 10% in individuals over the age of 40 years in most countries. Despite the enormous and increasing global impact of COPD, there are no drug therapies that significantly prevent disease progression or reduce mortality. This is in marked contrast to asthma, for which there are highly effective drugs, particularly inhaled corticosteroids, which are effective controllers in most patients. There has recently been increased interest in COPD resulting from the recognition that more effective treatments are a major unmet need, and from a better understanding of its cellular and molecular mechanisms [1], leading to the identification of novel therapeutic targets [2] (Figure 1).

Need for new therapies
The only significant advances in drug therapy for COPD have been in the development of longer-acting bronchodilators, but there are currently no effective anti-inflammatory treatments, with the exception of theophylline, which has been ignored [3]. Finding 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 [1]. The inflammation of COPD is very different from that seen in asthma, involving different inflammatory cells and mediators, indicating that different treatments are likely to be required [4].

Challenge of drug development for COPD
Development of new drugs for COPD has proved to be surprisingly difficult, apart from the logical development of long-acting bronchodilators. Despite significant advances in understanding, the underlying cellular and molecular mechanisms are less well understood than in asthma, and more research is required. 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 forced expiratory volume in one second (FEV1).

There are also uncertainties about how new drugs for COPD should be tested, as definitive studies may need to be long term (≥3 years) with a relatively large number of patients and at enormous cost. 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 as there may be different responses to drugs, particularly as therapies become more specific [5]. Many patients with COPD may have co-morbidities, such as ischemic heart disease and diabetes, which may exclude them from clinical trials for 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 [5,7]. 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 [8].

**New bronchodilators**

Long-acting inhaled bronchodilators (long-acting β₂-agonists and a long-acting muscarinic antagonist) are now the mainstay of current management [9], so there are several approaches to improving existing bronchodilators. Long-acting bronchodilators stabilize the airways, and this may contribute to their clinical effect of reducing exacerbations. However, a reduction in mechanical forces may theoretically also reduce airway remodeling and inflammation. Several once-daily inhaled β₂-agonists, such as indacaterol and carmoterol, are now in clinical development [10]. Indacaterol is a very effective dilator of small human airways, measured by videomicroscopy in a precision-cut lung slice preparation [11], 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 [12].

The once-daily inhaled anticholinergic tiotropium bromide has been an important advance in therapy, and several other long-acting inhaled
muscarinic antagonists (LAMA), such as aclininium bromide and glycopyrrolate, are now in development [13,14]. Combination inhalers with a long-acting β₂-agonist (LABA) and a LAMA are also in development, as there is an additive effect between these two bronchodilator classes [15]. Single molecules that link a muscarinic antagonist to a β₂-agonist (MABA), such as GSK961081, are now also in clinical development [16].

It has proven difficult to discover novel classes of bronchodilator drugs. Potassium channel openers, while effective in relaxing human airways in vitro, proved not to be 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.

**Inflammation in COPD**

The inflammation in COPD airways is different from that found in asthma and, in sharp contrast to asthma, there are no treatments that are effective in suppressing inflammation in COPD, as corticosteroids are largely ineffective. This means that the mechanisms of inflammation in COPD need to be better understood. In bronchial biopsies, small airways and lung parenchyma from patients with COPD, there is an infiltration of lymphocytes and increased numbers of neutrophils and macrophages. Fibrosis around small airways is thought to be a major mechanism contributing to progressive irreversible airway narrowing [17]. There is evidence of activated innate immunity, with increased numbers and activation of macrophages and neutrophils at all stages of COPD. However, in more severe disease, adaptive immune mechanisms with increased numbers of T lymphocytes and B lymphocytes come into play [4,18]. Both types of immunity are mediated by cytokines, and it is likely that the link between these immune mechanisms is through dendritic cells, which are modified by cytokines [19]. There is also mucus hyperplasia and increased expression of mucin genes [20]. Destruction of alveolar walls (emphysema) occurs in COPD as a result of protease-mediated degradation of connective tissue elements, particularly elastin, and apoptosis of type I pneumocytes and endothelial cells [21]. A striking characteristic of the chronic inflammation in COPD lungs is its failure to resolve on smoking cessation, even after several years, suggesting that some endogenous mechanism, such as autoimmunity or persistent infection, may be driving the inflammatory process [22,23].

**Inflammatory mediator antagonists**

Many mediators have been implicated in the pathophysiology of COPD [24,25], but it seems no more likely than in asthma that these will prove to be very effective therapies, as there is considerable redundancy in the effects of these mediators.

- **Lipid antagonists**
  
  Leukotriene B₄ is increased in sputum and bronchoalveolar 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'-lipoxigenase inhibitors should also be beneficial by blocking the production of endogenous LTB₄, but it has been difficult to develop these inhibitors without hepatic toxicity.

- **Cytokine inhibitors**

  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 for some systemic features such as skeletal muscle wasting. Tobacco smoke-exposed animal models of COPD have strongly implicated a central role for TNF-α [27]. Disappointingly, blockade of TNF-α with a blocking antibody (infliximab) has no beneficial clinical effects in patients with COPD using the same doses that are effective in rheumatoid arthritis [28]. Of particular concern is the finding that more COPD patients treated with anti-TNF developed respiratory cancers and severe lung infections, raising questions about the long-term safety of drugs that suppress the TNF-α approach in COPD patients. Several other cytokines are currently targeted for inhibition, including IL-1β, IL-6 and IL-17 [25]. IL-6 is increased in sputum and in the systemic circulation of COPD patients, and may account for the increased in circulating C-reactive protein and be contributory to comorbidities and systemic manifestations of COPD. 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 [29].
Chemokine antagonists
Several chemokines are implicated in COPD, and there has been a lot of interest in small-molecule chemokine receptor antagonists \[30\]. A blocking antibody to CXCL8 (interleukin-8) had a small effect in reducing dyspnea in COPD patients \[31\], but other CXC chemokines, such as CXCL1 (GRO-\(\alpha\)) 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. In a pilot study, a CXCR1/2 antagonist (ADZ8309) has been shown to inhibit neutrophil inflammation in the lung following inhaled endotoxin challenge in normal volunteers \[32\]. This is an oral medication and so may have a particular advantage in COPD patients. Another chemokine receptor target is CXCR3. 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 and B cells expressing CXCR3 \[33,34\]. CXCR3 antagonists have not yet been tested in COPD patients but are in development. CCL5 (RANTES) is also increased in COPD, and CCR5 antagonists, such as maraviroc, have now been developed for HIV/AIDS, and therefore may be available for testing in COPD.

TGF-\(\beta\) inhibitors
TGF-\(\beta\) may play a key role in the fibrosis of small airways. This is turning out to be a major mechanism for progressive loss of FEV\(_1\), and reduced exercise performance in COPD, and may be activated by oxidative stress and cigarette smoke \[35\]. TGF-\(\beta\)-related genes demonstrate increased expression in small airways of COPD patients \[36\]. Small-molecule inhibitors of TGF-\(\beta\) receptor tyrosine kinase (activin receptor-like kinase 5), such as SD-280, have been developed and have been shown to inhibit airway fibrosis in a model of asthma \[37\]. However, there may be long-term concerns about inhibiting TGF-\(\beta\), which plays an important role in maintaining regulatory T lymphocytes. Many of the effects of TGF-\(\beta\) are mediated via connective tissue growth factor so that inhibiting this cytokine or its receptor may be a more attractive approach in the future.

Protease inhibitors
In COPD, there is an imbalance between proteases that digest elastin (and other structural proteins) and antiproteases that protect against this, suggesting that either inhibiting these proteolytic enzymes or administering 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 (\(\alpha\)-antitrypsin, secretory leukoprotease inhibitor, elafin, tissue inhibitors of matrix metalloproteinases (MMPs)) may be given either in recombinant form or by viral vector gene delivery. However, 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 the development of small-molecule inhibitors of proteases, particularly those that have elastolytic activity. Neutrophil elastase inhibitors have been developed, but have failed in clinical trials. MMPs with elastolytic activity are also a target for drug development, and MMP-9 appears to be the predominant elastolytic enzyme, that is released from macrophages, neutrophils and epithelial cells. Nonselective MMP inhibitors, such as marimastat, have major side effects \[38\], suggesting that isoenzyme-selective inhibitors or inhaled delivery may be required. A dual

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Table 1. Some new anti-inflammatory treatments in development for chronic obstructive pulmonary disease.
MMP9/MMP12 inhibitor (AZ11557272) has been shown to prevent emphysema, small airway thickening and inflammation in guinea pigs exposed to cigarette smoke over 6 months [39].

**New anti-inflammatory treatments**

As discussed above, there is now a better understanding of the inflammatory process in COPD. Inflammation in COPD lungs is essentially corticosteroid-resistant, so that alternative anti-inflammatory approaches are required (Table 1). 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 phosphodiesterase expressed in neutrophils, T cells and macrophages, suggesting that PDE4 inhibitors should be effective in controlling 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 given over 12 months improves lung function in COPD patients to a small extent and reduces exacerbations, but does not improve health status or symptoms [43]. These results are likely to reflect the fact that side effects, particularly nausea, diarrhea and headaches, limit the dose that can be tolerated. This could be overcome by inhaled delivery, but to date two or more 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 expressed in the same inflammatory cells as PDE4, so inhibition of PDE7 may be beneficial. A selective PDE7 inhibitor has only a small anti-inflammatory effect alone, but potentiates the anti-inflammatory effects of a PDE4 inhibitor, suggesting that a combined PDE4/7 inhibitor may be more useful [44,45]. PDE3 inhibitors may produce bronchodilatation so that dual PDE3/4 inhibitors may combine bronchodilatation with anti-inflammatory activity [46]. However, there are concerns about the potential cardiovascular toxicity of PDE3 inhibitors, so these drugs may also have to be given by inhalation.

- **NF-κB inhibitors**
  NF-κB regulates the expression of CXCL8 and other chemokines, TNF-α and other inflammatory cytokines, as well as MMP9. NF-κB is activated in macrophages and epithelial cells of COPD patients, particularly during exacerbations. Inhibitors of inhibitor of NF-κB kinase (IKK)2 are effective in some animal models of COPD (lipopolysaccharide exposure), but not in others (neutrophil elastase instillation), indicating that the effects may be complex [47]. Although several IKK2 inhibitors are now in development, so far none have been tested in COPD patients. A major concern about the long-term inhibition of NF-κB is that effective inhibitors may result in immune suppression and impair host defenses, since mice that lack NF-κB genes succumb to septicemia.

- **p38 MAP kinase inhibitors**
  Mitogen-activated protein kinases (MAPK) 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 [48]. Several small-molecule inhibitors of p38 MAPK have now been developed. A potent inhibitor of p38-α isofrom, SD-282, is effective at inhibiting TNF-α release from human lung macrophages in vitro [49] and in suppressing inflammation in a murine smoking model of COPD, in which corticosteroids are ineffective [50]. 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.

  Other MAPK pathways, particularly extracellular signal-regulated kinase (ERK1/2) 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 [51].

- **Phosphoinositide 3-kinase inhibitors**
  Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes that control 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. Knockout of the PI-3Kγ gene results in inhibition of neutrophil migration and activation, as well as impaired T-lymphocyte and macrophage function, so PI3K-γ inhibitors may be potential anti-inflammatory therapy for COPD [52]. PI3K-δ is also involved in the expression of inflammatory genes, and several PI3K-δ or mixed PI3K-γ/δ inhibitors are now in development [53]. Pan-isoform inhibitors of PI3K are likely to be associated with side effects, as these enzymes appear to serve a number of key cell functions, but the -γ and -δ isoforms have a distribution more restricted to leukocytes, 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 [54].

**PPAR 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 [55]. PPAR-γ agonists also inhibit lung fibrosis, and therefore have the potential to prevent progression of small-airway fibrosis in COPD [56]. 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 [57].

**Reversing corticosteroid resistance: a novel therapeutic strategy**
Even high doses of corticosteroids have minimal effects on the progression of COPD and no effects on mortality [58]. Even their effect in preventing exacerbations has been questioned on the basis of flawed study design [59,60]. 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 histone deacetylase 2 (HDAC2) as a result of oxidative and nitrative stress [63]. This results in increased acetylation of the glucocorticoid receptor, which prevents it inhibiting NF-κB-driven inflammation [62]. A novel therapeutic strategy is therefore reversal of this corticosteroid resistance by restoring the activity and expression 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 [3,63]. 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 [64]. 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 that 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 [54].

**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 required, such as superoxide dismutase mimics and NADPH oxidase inhibitors [65]. The transcription factor nuclear factor erythroid 2-related factor-2 (Nrf2) 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 [66].
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-kB and other transcription factors. A nonantibiotic macrolide (EM-703) reverses corticosteroid resistance due to oxidative stress by increasing HDAC2 activity [67]. 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 owing 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. Furthermore, COPD may be regarded as a failure of normal repair mechanisms in the lung.

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 [68]. This has not been seen in several other species, and there are doubts as to whether emphysema is reversible in humans, as alveolar formation ceases at around the age of 6 years. A clinical trial of all-trans-retinoic and 13-cis-retinoic acid in patients with emphysema failed to demonstrate any improvement in clinical parameters, health status or CT density after 6 months of therapy [69].

Stem cells
Another possible approach to repairing damaged lungs 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 [70]. 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 [71]. The lung is a complex organ and it would probably be necessary to grow both endothelial and alveolar cells to repair emphysema.

Focusing on exacerbations
Exacerbations are a much-feared consequence of COPD, accounting for a large proportion of the high costs of this disease [72]. Current therapies, including long-acting bronchodilators, inhaled corticosteroids and PDE4 inhibitors, may reduce exacerbation frequency by approximately 15–25%, so more effective preventers are required. Little attention has been paid to the treatment of COPD exacerbations, which recover very slowly leading to prolonged impairment of quality of life. Drugs that can be administered acutely at the time of exacerbation to speed recovery would therefore be of enormous advantage, and this may include some of the drugs discussed previously for chronic treatment [73]. More effective antiviral drugs would also be of particular value, as upper respiratory tract viruses, such as rhinovirus and respiratory syncytial virus, are increasingly recognized to be the triggers of exacerbations, including bacterial exacerbations [74].

Routes of drug delivery
Inhalation is currently used as the choice route of delivery for bronchodilators in order to avoid the side effects of LABA and LAMA. Inhalers that deliver drugs to the lung periphery are needed in the future, with smaller aerosol particles (ideally ~2–3 µM monomethyl adipate). For new anti-inflammatory therapies, oral administration is the preferred route, as this makes it easier to reach inflammation in peripheral airways and alveoli, as well as treating systemic manifestations of COPD. However, oral administration is associated with systemic side effects and this has, so far, been a problem with novel anti-inflammatory treatments, so that inhaled administration is likely to be necessary. However, designing drugs that are retained in the lung and do not cause systemic effects is currently proving to be a major challenge. For chemokine antagonists, oral administration is required to prevent the movement of inflammatory cells from the circulation into the lung.

Future perspective
New drugs for the treatment of COPD are greatly required, 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. It is important to identify the genetic factors that determine why only a minority of heavy smokers develop COPD, and the 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 and enzymes) or exhaled condensates (lipid mediators and reactive oxygen species). The use of imaging techniques, such as high-resolution computed tomography to measure disease progression over shorter periods of time is another promising approach as scanning resolution increases. It may also be important to more accurately define the presence of emphysema versus small airway obstruction using computed tomography 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 required to aid the logical development of new therapies for this common and important disease, for which no effective preventative drugs currently exist.

Of the drugs currently in development, PDE4 inhibitors, p38 MAPK inhibitors and 1KK-2 inhibitors appear to be promising, but there are concerns about side effects and so 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 demonstrate promise as an antineutrophilic and antimacrophage 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 nonantibiotic macrolides also deserve further study.

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Papers of special note have been highlighted as:
* of interest
** of considerable interest

* Discusses current thinking about cellular and molecular mechanisms in chronic obstructive pulmonary disease (COPD) pathogenesis.


** Comprehensive summary of outcome measures used in assessing the drug therapy of COPD, with their value and limitations and the way forward for assessing new treatments.


* Sets out current management strategies for COPD.


* Recent review of the immunological mechanisms involved in COPD.


* Discusses the potential for chemokine antagonists as new treatments for COPD.


