Novel mechanisms and new therapies for chronic obstructive pulmonary disease

There is a pressing requirement to develop new therapies for chronic obstructive pulmonary disease (COPD), as current therapies fail to prevent disease progression or mortality and do not deal with the underlying inflammatory process. The mainstay of current drug therapy is long-acting bronchodilators, but no treatments suppress chronic inflammation in COPD, which is corticosteroid-resistant. With better understanding of the inflammatory and destructive process in the pathophysiology of COPD, several novel therapeutic targets have been identified, leading to the development of various mediator antagonists, novel broad-spectrum anti-inflammatory treatments and drugs that may reverse the molecular mechanisms of corticosteroid resistance.

Peter J Barnes

National Heart and Lung Institute, Imperial College School of Medicine, Dovehouse St, London SW3 6LY, UK
Tel.: +44 207 351 8174;
Fax: +44 207 351 5675
p.j.barnes@imperial.ac.uk

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 (FEV_1).

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
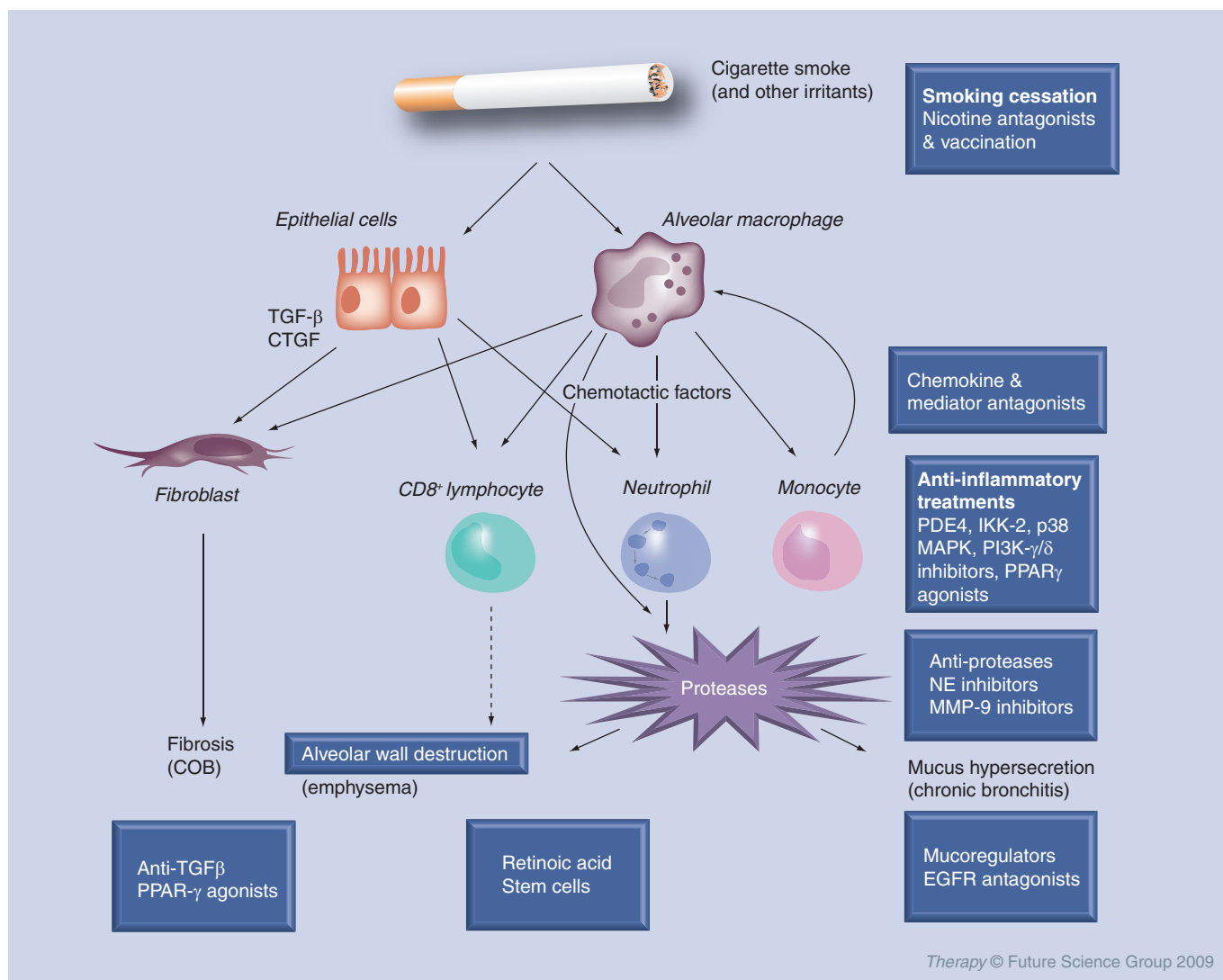
Figure 1. Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release multiple chemotactic factors attracting neutrophils, monocytes and T lymphocytes (particularly CD8+ cells). Several cells also release proteases, such as neutrophil elastase and matrix metalloproteinase-9, which break down connective tissue in the lung parenchyma (emphysema) and also stimulate mucus hypersecretion (chronic bronchitis). CD8+ may also be involved in alveolar wall destruction. TGF-β and CTGF released from inflammatory cells may mediate small airway fibrosis. The inflammatory process may be inhibited at several stages (shown in the boxes).
COB: Chronic obstructive bronchitis; CTGF: Connective tissue growth factor; EGFR: EGF receptor; IKK: Inhibitor of nuclear factor-κB kinase; MAPK: Mitogen-activated protein kinase; NE: Neutrophil elastase; PDE: Phosphodiesterase; PI3K: Phosphoinositide-3-kinase; PPAR: Peroxisome proliferator activated receptor.

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 aclidinium bromide and glycopyrrolate, are now in development [13,14]. Combination inhalers with a long-acting β_2-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 β_2-agonist (MABA), such as GSK-961081, 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 B_4 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 BLT_1 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 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 increase 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-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. 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-β inhibitors

TGF-β 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-β-related genes demonstrate increased expression in small airways of COPD patients [36]. Small-molecule inhibitors of TGF-β 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-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.

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 (α_1-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

Table 1. Some new anti-inflammatory treatments in development for chronic obstructive pulmonary disease.

Drug class	Clinical development
LTB$_4$ antagonists	Development stopped
Anti-TNF	Development stopped
Anti-IL-1β	Phase II study in progress
CXCR2 antagonists	In early clinical development
CXCR3 antagonists	In preclinical development
Phosphodiesterase-4 inhibitors	Phase III trials (roflumilast), but side effects limit dose
p38 MAP kinase inhibitors	Phase I studies but problems with side effects and toxicity
NF-κB (IKK2) inhibitors	Preclinical, but concerns about side effects
PI3 kinase-γ/δ inhibitors	Early clinical development
PPAR-γ agonists	Already developed for diabetes, clinical studies in progress

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 isoform, 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 [61]. 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-κB and other transcription factors. A nonantibiotic macrolide (EM-703) reverses corticosteroid resistance due to oxidative stress by increasing HDAC2 activity [67]. Several nonantibiotic 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 [75]. 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) [7]. The use of imaging techniques, such as high-resolution computerized tomography to measure disease progression over shorter periods of time is another promising approach as scanning resolution increases [76]. It may also be important to more accurately define the presence of emphysema versus small airway obstruction using computerized 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 IKK-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.

Executive summary

Need for new therapies
- Current treatments for chronic obstructive pulmonary disease (COPD) are poorly effective and do not reduce disease progression or mortality.
- Long-acting bronchodilators are the mainstay of current therapy, but do not affect the underlying disease process.
- Corticosteroids, even in high doses, do not have anti-inflammatory effects because of an active corticosteroid resistance.
- Animal models of COPD are poor and do not reflect many aspects of the disease.
- Clinical studies are difficult as large studies over long periods are required.
- Biomarkers that predict long-term efficacy are urgently required.
- Drugs that affect the systemic manifestations and co-morbidities of COPD are also needed.

What drugs are in development?
- New bronchodilators with a long-duration of action or combinations of bronchodilators are in development.
- Mediator antagonists and inhibitors have, so far, been disappointing, as they may be too specific in view of the large numbers of mediators.
- Chemokine receptor antagonists, especially CXCR2 CXCR3 antagonists, are more promising.
- Broad-spectrum anti-inflammatory treatments, including PDE4, p38 MAPK and PI3K inhibitors, are likely to be effective, but have a high risk of side effects so inhaled administration may be required.
- Drugs that reverse the molecular mechanisms of corticosteroid-resistance in COPD, such as PI3K-δ inhibitors, Nrf2 activators and nonantibiotic macrolides, may be more promising.

Bibliography

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

1   Barnes PJ, Shapiro SD, Pauwels RA: Chronic obstructive pulmonary disease: molecular and cellular mechanisms. *Eur. Respir. J.* 22, 672–688 (2003).

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

2   Barnes PJ: Emerging pharmacotherapies for COPD. *Chest* 134, 1278–1286 (2008).

3   Barnes PJ: Theophylline for COPD. *Thorax* 61, 742–743 (2006).

4   Barnes PJ: Immunology of asthma and chronic obstructive pulmonary disease. *Nat. Immunol. Rev.* 8, 183–192 (2008).

5   Cazzola M, Macnee W, Martinez FJ *et al.*: Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur. Respir. J.* 31, 416–469 (2008).

▪▪   **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.**

6   Barnes PJ, Celli BR: Systemic manifestations and comorbidities of COPD. *Eur. Respir. J.* 33, 1165–1185 (2009).

7   Barnes PJ, Chowdhury B, Kharitonov SA *et al.*: Pulmonary biomarkers in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 174, 6–14 (2006).

8   Sturton G, Persson C, Barnes PJ: Small airways: an important but neglected target in the treatment of obstructive airway diseases. *Trends Phamacol. Sci.* 29, 340–345 (2008).

9   Rabe KF, Hurd S, Anzueto A *et al.*: Global strategy for the diagnosis, management, and prevention of COPD – 2006 Update. *Am. J. Respir. Crit. Care Med.* 176, 532–555 (2007).

▪   **Sets out current management strategies for COPD.**

10   Cazzola M, Matera MG: Novel long-acting bronchodilators for COPD and asthma. *Br. J. Pharmacol.* 155, 291–299 (2008).

11   Sturton RG, Nicholson AG, Trifilieff A, Barnes PJ: Pharmacological characterisation of indacaterol, a novel once-daily inhaled β2-adrenoceptor agonist, on small airways in human and rat precision-cut lung slices. *J. Pharmacol. Exp. Ther.* 324, 270–275 (2008).

12   Rennard S, Bantje T, Centanni S *et al.*: A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. *Respir. Med.* 102, 1033–1044 (2008).

13   Hansel TT, Neighbour H, Erin EM *et al.*: Glycopyrrolate causes prolonged bronchoprotection and bronchodilatation in patients with asthma. *Chest* 128, 1974–1979 (2005).

14   Cazzola M: Aclidinium bromide, a novel long-acting muscarinic M3 antagonist for the treatment of COPD. *Curr. Opin. Investig. Drugs* 10, 482–490 (2009).

15   van Noord JA, Aumann JL, Janssens E *et al.*: Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest* 129, 509–517 (2006).

16   Ray NC, Alcaraz L: Muscarinic antagonist-β-adrenergic agonist dual pharmacology molecules as bronchodilators: a patent review. *Expert. Opin. Ther. Pat.* 19, 1–12 (2009).

17   Hogg JC, Chu F, Utokaparch S *et al.*: The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N. Engl. J. Med.* 350, 2645–2653 (2004).

18   Curtis JL, Freeman CM, Hogg JC: The immunopathogenesis of chronic obstructive pulmonary disease: insights from recent research. *Proc. Am. Thorac. Soc.* 4, 512–521 (2007).

19   Tsoumakidou M, Demedts IK, Brusselle GG, Jeffery PK: Dendritic cells in chronic obstructive pulmonary disease: new players in an old game. *Am. J. Respir. Crit. Care Med.* 177, 1180–1186 (2008).

20   Caramori G, Di Gregorio C, Carlstedt I *et al.*: Mucin expression in peripheral airways of patients with chronic obstructive pulmonary disease. *Histopathology* 45, 477–484 (2004).

21   Majo J, Ghezzo H, Cosio MG: Lymphocyte population and apoptosis in the lungs of smokers and their relation to emphysema. *Eur. Respir. J.* 17, 946–953 (2001).

22   Taraseviciene-Stewart L, Douglas IS, Nana-Sinkam PS *et al.*: Is alveolar destruction and emphysema in chronic obstructive pulmonary disease an immune disease? *Proc. Am. Thorac. Soc.* 3, 687–690 (2006).

23   Cosio MG, Saetta M, Agusti A: Immunologic aspects of chronic obstructive pulmonary disease. *N. Engl. J. Med.* 360, 2445–2454 (2009).

▪   **Recent review of the immunological mechanisms involved in COPD.**

24   Barnes PJ: Mediators of chronic obstructive pulmonary disease. *Pharm. Rev.* 56, 515–548 (2004).

25   Barnes PJ: Cytokine networks in asthma and chronic obstructive pulmonary disease. *J. Clin. Invest.* 118, 3546–3556 (2008).

26   Hicks A, Monkarsh SP, Hoffman AF, Goodnow R, Jr: Leukotriene B4 receptor antagonists as therapeutics for inflammatory disease: preclinical and clinical developments. *Expert. Opin. Investig. Drugs* 16, 1909–1920 (2007).

27   Churg A, Wang RD, Tai H *et al.*: Tumor necrosis factor-α drives 70% of cigarette smoke-induced emphysema in the mouse. *Am. J. Respir. Crit. Care Med.* 170, 492–498 (2004).

28   Rennard SI, Fogarty C, Kelsen S *et al.*: The safety and efficacy of infliximab in moderate-to-severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 175, 926–934 (2007).

29   Paul-Pletzer K: Tocilizumab: blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. *Drugs Today* 42, 559–576 (2006).

30   Donnelly LE, Barnes PJ: Chemokine receptors as therapeutic targets in chronic obstructive pulmonary disease. *Trends Pharmacol. Sci.* 27, 546–553 (2006).

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

31   Mahler DA, Huang S, Tabrizi M, Bell GM: Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in COPD: a pilot study. *Chest* 126, 926–934 (2004).

32   O'Connor BJ, Leaker BR, Barnes PJ *et al.*: Inhibition of LPS-induced neutrophilic inflammation in healthy volunteers. *Eur. Resp. J.* 30 (Suppl. 51), 1294 (2007).

33   Costa C, Rufino R, Traves SL *et al.*: CXCR3 and CCR5 chemokines in the induced sputum from patients with COPD. *Chest* 133, 26–33 (2008).

34   Kelsen SG, Aksoy MO, Georgy M *et al.*: Lymphoid follicle cells in chronic obstructive pulmonary disease overexpress the chemokine receptor CXCR3. *Am. J. Respir. Crit. Care Med.* 179, 799–805 (2009).

35   Koli K, Myllarniemi M, Keski-Oja J, Kinnula VL: Transforming growth factor-β activation in the lung: focus on fibrosis and reactive oxygen species. *Antioxid. Redox. Signal.* 10, 333–342 (2008).

36   Wang IM, Stepaniants S, Boie Y *et al.*: Gene expression profiling in patients with chronic obstructive pulmonary disease and lung cancer. *Am. J. Respir. Crit. Care Med.* 177, 402–411 (2008).

37   Leung SY, Niimi A, Noble A *et al.*: Effect of transforming growth factor-β receptor I kinase inhibitor 2,4-disubstituted pteridine (SD-208) in chronic allergic airway inflammation and remodeling. *J. Pharmacol. Exp. Ther.* 319, 586–594 (2006).

38   Hu J, Van Den Steen PE, Sang QX, Opdenakker G: Matrix metalloproteinase inhibitors as therapy for inflammatory and vascular diseases. *Nat. Rev. Drug Discov.* 6, 480–498 (2007).

39   Churg A, Wang R, Wang X *et al.*: Effect of an MMP-9/MMP-12 inhibitor on smoke-induced emphysema and airway remodelling in guinea pigs. *Thorax* 62, 706–713 (2007).

40   Giembycz MA: Can the anti-inflammatory potential of PDE4 inhibitors be realized: guarded optimism or wishful thinking? *Br. J. Pharmacol.* 155, 288–290 (2008).

41   Martorana PA, Beume R, Lucattelli M, Wollin L, Lungarella G: Roflumilast fully prevents emphysema in mice chronically exposed to cigarette smoke. *Am. J. Respir. Crit. Care Med.* 172, 848–853 (2005).

42   Grootendorst DC, Gauw SA, Verhoosel RM *et al.*: Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor roflumilast in patients with COPD. *Thorax* 62, 1081–1087 (2007).

43   Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ: Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 374, 685–694 (2009).

44   Smith SJ, Cieslinski LB, Newton R *et al.*: Discovery of BRL 50481, a selective inhibitor of phosphodiesterase 7: *in vitro* studies in human monocytes, lung macrophages and CD8⁺ T-lymphocytes. *Mol. Pharmacol.* 66, 1679–1689 (2004).

45   Giembycz MA: Phosphodiesterase-4: selective and dual-specificity inhibitors for the therapy of chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 2, 326–333 (2005).

46   Banner KH, Press NJ: Dual PDE3/4 inhibitors as therapeutic agents for chronic obstructive pulmonary disease. *Br. J. Pharmacol.* 157, 892–906 (2009).

47   Edwards MR, Bartlett NW, Clarke D *et al.*: Targeting the NF-κB pathway in asthma and chronic obstructive pulmonary disease. *Pharmacol. Ther.* 121, 1–13 (2009).

48   Renda T, Baraldo S, Pelaia G *et al.*: Increased activation of p38 MAPK in COPD. *Eur. Respir. J.* 31, 62–69 (2008).

49   Smith SJ, Fenwick PS, Nicholson AG *et al.*: Inhibitory effect of p38 mitogen-activated protein kinase inhibitors on cytokine release from human macrophages. *Br. J. Pharmacol.* 149, 393–404 (2006).

50   Medicherla S, Fitzgerald M, Spicer D *et al.*: p38a selective MAP kinase inhibitor, SD-282, reduces inflammation in a sub-chronic model of tobacco smoke-induced airway inflammation. *J. Pharmacol. Exp. Ther.* 324, 921–929 (2007).

51   Tudhope SJ, Finney-Hayward TK, Nicholson AG *et al.*: Different mitogen-activated protein kinase-dependent cytokine responses in cells of the monocyte lineage. *J. Pharmacol. Exp. Ther.* 324, 306–312 (2008).

52   Medina-Tato DA, Ward SG, Watson ML: Phosphoinositide 3-kinase signalling in lung disease: leucocytes and beyond. *Immunology* 121, 448–461 (2007).

53   Ward S, Sotsios Y, Dowden J, Bruce I, Finan P: Therapeutic potential of phosphoinositide 3-kinase inhibitors. *Chem. Biol.* 10, 207–213 (2003).

54   Marwick JA, Caramori G, Stevenson CC *et al.*: Inhibition of PI3Kδ restores glucocorticoid function in smoking-induced airway inflammation in mice. *Am. J. Respir. Crit. Care Med.* 179, 542–548 (2009).

55   Belvisi MG, Hele DJ, Birrell MA: Peroxisome proliferator-activated receptor γ agonists as therapy for chronic airway inflammation. *Eur. J. Pharmacol.* 533, 101–109 (2006).

56   Milam JE, Keshamouni VG, Phan SH *et al.*: PPAR-γ agonists inhibit profibrotic phenotypes in human lung fibroblasts and bleomycin-induced pulmonary fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol.* 294, L891–L901 (2008).

57   Remels AH, Schrauwen P, Broekhuizen R *et al.*: Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. *Eur. Respir. J.* 30, 245–252 (2007).

58   Yang IA, Fong KM, Sim EH, Black PN, Lasserson TJ: Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane. Database. Syst. Rev.* CD002991 (2007).

59   Suissa S, Ernst P, Vandemheen KL, Aaron SD: Methodological issues in therapeutic trials of COPD. *Eur. Respir. J.* 31, 927–933 (2008).

▪   **Highlights the defects in trial design in studies of inhaled corticosteroids in COPD.**

60   Suissa S, Barnes PJ: Inhaled corticosteroids in COPD: the case against. *Eur. Respir. J.* 34, 13–16 (2009).

61   Barnes PJ: Role of HDAC2 in the pathophysiology of COPD. *Ann. Rev. Physiol.* 71, 451–464 (2009).

62   Ito K, Yamamura S, Essilfie-Quaye S *et al.*: Histone deacetylase 2-mediated deacetylation of the glucocorticoid receptor enables NF-κB suppression. *J. Exp. Med.* 203, 7–13 (2006).

63   Cosio BG, Tsaprouni L, Ito K *et al.*: Theophylline restores histone deacetylase activity and steroid responses in COPD macrophages. *J. Exp. Med.* 200, 689–695 (2004).

64   Fox JC, Spicer D, Ito K, Barnes PJ, Fitzgerald MF: Oral or inhaled corticosteroid combination therapy with low dose theophylline reverses corticosteroid insensitivity in a smoking mouse model. *Proc. Am. Thorac. Soc.* 2, A637 (2007).

65   Kirkham P, Rahman I: Oxidative stress in asthma and COPD: antioxidants as a therapeutic strategy. *Pharmacol. Ther.* 111, 476–494 (2006).

66   Sussan TE, Rangasamy T, Blake DJ *et al.*: Targeting Nrf2 with the triterpenoid CDDO-imidazolide attenuates cigarette smoke-induced emphysema and cardiac dysfunction in mice. *Proc. Natl Acad. Sci. USA* 106, 250–255 (2009).

67   Charron C, Sumakuza T, Oomura S, Ito K: EM-703, a non-antibacterial erythromycin derivative, restores HDAC2 activation diminished by hypoxia and oxidative stress. *Proc. Am. Thorac. Soc.* 175, A640 (2007).

68   Stinchcombe SV, Maden M: Retinoic acid-induced alveolar regeneration: critical differences in strain sensitivity. *Am. J. Respir. Cell Mol. Biol.* 38, 185–191 (2008).

69   Roth MD, Connett JE, D'Armiento JM *et al.*: Feasibility of retinoids for the treatment of emphysema study. *Chest* 130, 1334–1345 (2006).

70   Varanou A, Page CP, Minger SL: Human embryonic stem cells and lung regeneration. *Br. J. Pharmacol.* 155, 316–325 (2008).

71   Loebinger MR, Janes SM: Stem cells for lung disease. *Chest* 132, 279–285 (2007).

72   Celli BR, Barnes PJ: Exacerbations of chronic obstructive pulmonary disease. *Eur. Respir. J.* 29, 1224–1238 (2007).

73   Hansel TT, Barnes PJ: New drugs for COPD exacerbations based on modulation of innate immune responses. *Lancet* (2009) (In press).

74   Sykes A, Mallia P, Johnston SL: Diagnosis of pathogens in exacerbations of chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* 4, 642–646 (2007).

75   Salvi SS, Barnes PJ: Chronic obstructive pulmonary disease: beyond tobacco. *Lancet* (2009) (In press).

76   Stolk J, Versteegh MI, Montenij LJ *et al.*: Densitometry for assessment of effect of lung volume reduction surgery for emphysema. *Eur. Respir. J.* 29, 1138–1143 (2007).