Emerging Pharmacotherapies for COPD

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COPD has become a major global epidemic that is increasing throughout the world, particularly in developing countries, and is now one of the leading causes of death and disability, with a prevalence of > 10% in individuals > 40 years of age in most countries. Despite the enormous global impact of COPD, there are no drug therapies that have been shown to prevent disease progression or reduce mortality. However, there has been greatly increased interest in COPD over the past few years by researchers and the pharmaceutical industry, and this has been linked to a better understanding of its cellular and molecular mechanisms and to the identification of novel targets for the discovery of new treatments (Fig 1).

**The Need for Novel Therapies**

There have been disappointingly few therapeutic advances in drug therapy for the treatment of COPD, in contrast to the enormous advances made in asthma management, which reflect a much better understanding of disease mechanisms. The only significant advances in drug therapy have been in the development of longer acting bronchodilators, but there are currently no effective antiinflammatory treatments, with the exception of theophylline, which has been largely ignored. Rational therapy depends on elucidating the cellular and molecular mechanisms that are involved in inflammation in COPD patients, and the structural changes and aberrant repair...
mechanisms that characterize the pathophysiology of COPD. The inflammation seen in COPD patients is quite different from that seen in asthma patients, with different inflammatory cells and mediators, indicating that different treatments are likely to be needed.7

**The Challenge of Drug Development**

There are several reasons why the development of new drugs for COPD has proved to be very difficult for the pharmaceutical industry. Only recently has there been any research interest8,9 in the molecular and cell biology of COPD in order to identify novel therapeutic targets. Animal models8 of COPD for early drug testing have been poor and have focused on emphysema, rather than the small airway disease that appears to underlie the progressive loss of FEV1 and the increasing symptoms over time that is characteristic of COPD patients. Better animal models9 of predominantly small airway disease are urgently needed.

There are also uncertainties about how to test drugs that will be used for the treatment of COPD; these may require long-term studies (ie, ≥ 3 years) with relatively large numbers of patients at an enormous cost. For example, a recent study10 looking at the effects of drug intervention on mortality is believed to have cost several hundred million dollars. Many patients with COPD may have comorbidities, such as ischemic heart disease and diabetes, which may exclude them from participating in clinical trials of new therapies. There is little information about surrogate markers, for example, biomarkers in blood, sputum, or breath, to monitor the short-term efficacy and to predict the long-term potential of new treatments.11 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.9

**New Bronchodilators**

Long-acting inhaled bronchodilators are now the mainstay of current management,12 so the logical approach is to improve the existing bronchodilators.
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Seventy inhaled \( \beta_2 \)-agonists that are to be used once daily, such as indacaterol and carmoterol, are now in clinical development. Indacaterol is a very effective dilator of small human airways as measured by videomicroscopy in a precision-cut lung slice preparation. Indacaterol has a bronchodilator action of > 24 h in patients with COPD with a fast onset of action and no evidence of tolerance or significant side effects.

The once-daily inhaled anticholinergic agent 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. Combination inhalers using a long-acting \( \beta_2 \)-agonist with a long-acting inhaled muscarinic antagonist are also in development as there is an additive effect between these two bronchodilator classes. Single molecules that link a muscarinic antagonist to a \( \beta_2 \)-agonist are now also in development.

It has proved to be difficult to discover novel classes of bronchodilator drugs. Potassium channel openers, while effective in relaxing human airways in vitro, were not effective in treating asthma as they were more potent as vasodilators; 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.

**Lipid Antagonists**

Leukotriene B4 (LTB4) is increased in the sputum and BAL fluid of patients with COPD, and is chemotactic for neutrophils and lymphocytes. Several antagonists of the major receptor BLT1 (leukotriene B4 receptor 1) have been developed, but so far clinical studies in COPD patients have been negative (and therefore have not been published). 5'-Lipoxygenase inhibitors should also be beneficial by blocking the production of endogenous LTB4, but it has been difficult to develop potent safe 5-lipoxygenase inhibitors.

**Cytokine Inhibitors**

Tumor necrosis factor (TNF)-\( \alpha \) appears to be a key mediator in COPD, as its concentrations are increased in sputum, particularly during exacerbations; it amplifies inflammation; and it may account not only for neutrophilic inflammation in the lungs but also for some systemic features such as skeletal muscle wasting. However, the blockade of TNF-\( \alpha \) with an injected antibody (infliximab) had no beneficial clinical effects in patients with COPD, using the same doses that are effective in patients with rheumatoid arthritis and that have shown a beneficial effect in asthma. Of particular concern was the finding that cancers of the respiratory tract and severe lung infections developed in more COPD patients who were treated with anti-TNF. This may have worrisome implications for other treatments that inhibit TNF-\( \alpha \) production, which will be discussed in the following sections of this article. Other cytokines that are currently targeted for inhibition include interleukin (IL)-1\( \beta \), IL-6, and IL-17. Levels of IL-6 are increased in the sputum and systemic circulation of COPD patients, and may account for the increase in circulating levels of C-reactive protein. A potent inhibitor of IL-6 is the receptor antibody tocilizumab, which is effective in the treatment of rheumatoid arthritis but has not yet been tested in COPD patients.

**Chemokine Antagonists**

Several chemokines are implicated in COPD, and there has been a lot of interest in small molecule chemokine receptor antagonists (Fig 2). A blocking antibody to CXC ligand (CXCL) 8 (i.e., IL-8) had a small effect in reducing dyspnea in COPD patients, but other CXC chemokines, such as CXCL1 (GRO-\( \alpha \)) and CXCL5 (epithelial-derived neutrophil attractant-78) are also increased in COPD patients and play a role similar to that of CXCL8. The chemotactic effects of CXCL8, CXCL1, and CXCL5 on neutrophils and monocytes is mediated by a common receptor.
CXC receptor (CXCR) 2. A CXCR1/2 antagonist (ADZ8309) has recently been shown to inhibit neutrophil inflammation in the lung following inhaled endotoxin challenge in healthy volunteers. 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 patients, and there is an increase in CD4+ and CD8+ T cells expressing CXCR3. CXCR3 antagonists have not yet been tested in COPD patients but are currently in development. Levels of CCL5 (ie, regulated on activation, normal T cell expressed, and secreted [or RANTES]) is increased in COPD patients, and CCR5 antagonists, such as maraviroc, have now been developed for the treatment of HIV/AIDS and so may be available for testing in COPD patients.

**Transforming Growth Factor-β Inhibitors**

Transforming growth factor (TGF)-β may play a key role in the fibrosis of small airways, which is turning out to be a major mechanism for the progressive loss of FEV1 and reduced exercise performance in COPD patients, and may be activated by oxidative stress and cigarette smoke. TGF-β-related genes show increased expression in the small airways of COPD patients. 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. However, there may be long-term concerns about inhibiting TGF-β, which plays an important role in maintaining levels of 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**

There is compelling evidence for 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 the number of endogenous antiproteases may be beneficial and theoretically should prevent the progression of emphysema. The fact that there are so many proteinases implicated in COPD might mean that blocking a single enzyme may not have a major effect. Endogenous antiproteases (eg, α1-antitrypsin, secretory leukoprotease inhibitor, elafin, and tissue inhibitors of matrix metalloproteinase [MMP]) may be administered either in recombinant form or by viral vector gene delivery. 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, which is released from macrophages, neutrophils, and epithelial cells, appears to be the predominant enzyme. Nonselective MMP inhibitors, such as marimastat,
Table 1—Antiinflammatory Treatments for COPD

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTB4 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>
</tr>
<tr>
<td>PDE4 inhibitors</td>
<td>Phase III trials but side effects a major limitation</td>
</tr>
<tr>
<td>p38 MAPK inhibitors</td>
<td>Phase I studies but problems with side effects and toxicity</td>
</tr>
<tr>
<td>NF-κB inhibitors</td>
<td>Preclinical but concerns about side effects</td>
</tr>
<tr>
<td>PI3K-γ inhibitors</td>
<td>Preclinical development</td>
</tr>
<tr>
<td>PPAR-γ agonists</td>
<td>Already developed for diabetes, clinical studies in progress</td>
</tr>
</tbody>
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appear to have major side effects, 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 and small airway thickening in guinea pigs that were exposed to cigarette smoke over 6 months, but the clinical development of this inhibitor has been stopped for unknown reasons.

**Antiinflammatory Treatments**

The inflammation in COPD lungs is resistant to therapy with corticosteroids so that alternative approaches to antiinflammatory therapy are needed (Table 1). There are several broad-spectrum antiinflammatory treatments for COPD that are now in development, but there are concerns over the safety of these approaches, since all of the drugs inhibit innate immunity, which may already be impaired in COPD patients. This increases the potential risk of lung infections and cancer as COPD patients are already predisposed to these problems.

**Phosphodiesterase 4 Inhibitors**

Phosphodiesterase (PDE) 4 is the predominant PDE that is expressed in neutrophils, T cells, and macrophages, suggesting that PDE4 inhibitors would be effective in controlling inflammation in COPD patients. A selective PDE4 inhibitor, roflumilast, has inhibited lung inflammation and emphysema in a smoking model of COPD in mice. In COPD patients, oral roflumilast administered over 4 weeks significantly reduces the numbers of neutrophils (by 36%) and CXCL8 concentrations in sputum. In clinical trials, roflumilast administered over 6 or 12 months improved lung function in COPD patients to a small extent but had no significant effect in reducing the number of exacerbations or improving quality of life. These disappointing results are likely to reflect the fact that side effects, particularly nausea, diarrhea, and headaches, limit the dose that can be tolerated. This indicates that it may not be possible to reach an oral dose that is effective and acceptable to patients. This 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 antiinflammatory effects, so that PDE4B-selective inhibitors may be better tolerated. However, PDE4D inhibition may also have some antiinflammatory effects (eg, in T lymphocytes), so that PDE4B-selective inhibitors may not be as effective as pan-PDE4 inhibitors. PDE7A is also expressed in the same inflammatory cells as PDE4, so the inhibition of PDE7 may be beneficial. However, a selective PDE7 inhibitor had only a small antiinflammatory effect when administered alone, but potentiated the antiinflammatory effects of a PDE4 inhibitor, suggesting that a combined inhibitor may be useful as it should not increase the number of side effects.

**Nuclear Factor-κB Inhibitors**

Nuclear factor (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 the macrophages and epithelial cells of COPD patients, particularly during exacerbations. Although there are several possible approaches to the inhibition of NF-κB, small-molecule inhibitors of the inhibitor of NF-κB kinase (IKK) 2 are the most promising. An IKK2 inhibitor has been effective in some animal models of COPD (LPS exposure), but not in others (neutrophil elastase instillation), indicating that the effects may be complex. Although several IKK2 inhibitors are now in development, so far none have been tested in COPD patients. IKK2 inhibitors not only block the activation of NF-κB-activated genes, but also have some unexpected beneficial effects such as the inhibition of CXCR3 chemokines, indicating complex interactions between signal transduction pathways. The hope is that IKK2 inhibitors will be effective in suppressing the corticosteroid-resistance inflammation of COPD. One 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 (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 IL-8, TNF-α, and MMPs. p38 MAPK (measured by phosphorylated p38 MAPK) is activated in alveolar macrophages from the lungs of COPD patients. Several small-molecule inhibitors of p38 MAPK have now been developed. A potent inhibitor of a p38-α isoform, SD-282, is effective in inhibiting TNF-α release from human lung macrophages in vitro, and the same inhibitor is also effective in suppressing inflammation in a smoking model of COPD in mice in which therapy with corticosteroids was ineffective. Several p38 MAPK inhibitors have now 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. All of these p38 MAPK inhibitors target p38-α and/or p38-β isoforms of the enzyme. Little is known about the function of the p38-γ and p38-δ isoforms of the enzymes, and there are no selective inhibitors currently available. In human alveolar macrophages, there is a high level of expression of the p38-δ isoform, but its function is currently unknown. Recent studies have indicated that other MAPK pathways, particularly extracellular signal-regulated kinases 1 and 2, may also play an important role in regulating the expression of proinflammatory cytokines in alveolar macrophages, in contrast to their lack of effect in blood monocytes.

Phosphoinositide 3-Kinase Inhibitors

Phosphoinositide 3-kinases (PI3Ks) comprise 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. Knockout of the PI-3K-γ gene results in the inhibition of neutrophil migration and activation, as well as in impaired T-lymphocyte and macrophage function, so PI3K-γ inhibitors may be potential antiinflammatory therapy for COPD. 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. 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 PI3K-γ and PI3K-δ isoforms have a distribution that is more restricted to leukocytes and may therefore be better tolerated, especially if delivered by inhalation.

Peroxisome Proliferator-Activated Receptor Activators

Peroxisome proliferator-activated receptors (PPARs) are a family of ligand-activated nuclear hormone receptors belonging to the steroid receptor superfamily, and the three recognized subtypes PPAR-α, PPAR-γ, and PPAR-δ are widely expressed. There is evidence that the activation of PPAR-α and PPAR-δ may have antiinflammatory 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 antiinflammatory effects in COPD patients. There is a reduction in PPAR-α expression in the 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 patients with severe disease.

Reversal of Corticosteroid Resistance

Even high doses of corticosteroids have minimal effects on the progression of COPD and no effects on mortality. Even their effect in preventing exacerbations has been questioned on the basis of flawed study design. This may reflect the resistance of COPD inflammation to the antiinflammatory 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. This results in the increased acetylation of the glucocorticoid receptor, which prevents it from inhibiting NF-κB-driven inflammation. A novel therapeutic strategy is therefore the 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. This has also been demonstrated in mice exposed to cigarette smoke, which develop a steroid-resistant inflammation in the lungs with increased numbers of 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. Understanding the molecular mechanisms of action of theophylline, which appear to be independent of PDE inhibition, may lead to novel therapeutic approaches to the restoration of corticosteroid responsiveness that avoid the side effects and drug interaction problems of theophylline itself.

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, the 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 nicotinamide adenine dinucleotide phosphate hydrogen oxidase inhibitors.

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. Recently, it has been shown that a nonantibiotic macrolide (EM-703) reverses corticosteroid resistance due to oxidative stress by increasing HDAC2 activity. Several nonantibiotic macrolides are now in development as anti-inflammatory therapies.

Lung Regeneration

Since a major mechanism of airway obstruction in COPD patients results from the loss of elastic recoil due to proteolytic destruction of the 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 histologic and physiologic changes induced by elastase treatment. This has not been seen in several other species, and there are doubts about whether emphysema is reversible in humans as alveolar formation ceases about the age of 6 years. A clinical trial of all-trans-retinoic and 9-cis-retinoic acid in patients with emphysema failed to show any improvement in clinical parameters, health status, or CT scan density after 6 months of therapy.

Stem Cells

Another possible approach to repairing damaged lung in emphysema patients 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. 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. The lung is a complex organ, and it would probably be necessary to grow both endothelial and alveolar cells to repair damage due to emphysema.

Future Directions

New drugs for the treatment of COPD are greatly needed, and there has been an enormous effort 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. It is important to identify the genetic factors that determine why COPD develops in only a minority of heavy smokers, and identifying the genes that predispose smokers 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 the analysis of sputum parameters (eg, cells, mediators, enzymes) or exhaled condensates (eg, lipid mediators or reactive oxygen species). The use of imaging techniques, such as high-resolution CT scanning, to measure disease progression is another promising approach as scanning resolution increases. It may also be important to more accurately define the presence of emphysema vs 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.

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 the long-term safety of these drugs in increasing lung infection and cancer through the inhibition of TNF-α synthesis. CXCR2 antagonists show promise as an antineutrophilic and antimacrophage therapy, and should be well tolerated by oral administration.

It is likely that effective antiinflammatory 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 the reversal of corticosteroid resistance, which is the main barrier to effective antiinflammatory treatments in COPD patients. Drugs derived from theophylline may be effective through increasing HDAC2 activity and expression, and should be relatively well tolerated. More potent antioxidants and nonantibiotic macrolide agents also deserve further study.

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