

REVIEW SERIES

Chronic obstructive pulmonary disease • 12:
New treatments for COPD

P J Barnes

Thorax 2003;58:803–808

Drugs currently available or under development for the treatment of chronic obstructive pulmonary disease (COPD) are reviewed. More research on the basic cellular and molecular mechanisms of COPD and emphysema is urgently needed to aid the logical development of new treatments for this common and important disease for which no effective preventative treatments currently exist.

drugs for COPD which may require long term studies (over 3 years) in relatively large numbers of patients. Furthermore, there is little information about surrogate markers to monitor the short term efficacy of new treatments. However, some progress is underway and several classes of drug are now in preclinical and clinical development.^{6–11}

SMOKING CESSATION

Cigarette smoking is the major cause of COPD worldwide, and smoking cessation is the only therapeutic intervention so far shown to reduce disease progression. Nicotine addiction is the major problem and treatment should be directed at dealing with this addictive state. The main approaches have involved behavioural approaches and nicotine replacement therapy, but the overall rates of quitting are small (5–15%).¹² One important advance has been the discovery that the antidepressant bupropion given as a short course (6–9 weeks) is the most effective treatment so far described, with sustained quit rates of 18% at 12 months, compared with 9% with nicotine skin patches and 6% with placebo.¹³ Results in patients with COPD are similar.¹⁴ This does not appear to be a general effect of antidepressants, although nortryptiline has some effect.¹⁵ Bupropion is well tolerated apart from sleeplessness, but epileptic fits occur in approximately 0.1% of patients, predominantly those with previous epilepsy.¹⁶ In the future more effective drugs may arise from a better understanding of the neurotransmitter pathways involved in nicotine addiction and advances are likely to come from research in neurosciences.

NEW BRONCHODILATORS

Since bronchodilators are the mainstay of current management, a logical approach is to improve existing bronchodilators. Once daily inhaled β_2 agonists are not in clinical development, but the long acting inhaled anticholinergic tiotropium has recently become available in some countries.

Tiotropium bromide

Tiotropium bromide is a long acting anticholinergic drug that has a unique kinetic selectivity with very slow dissociation from M_1 and M_3 muscarinic receptors.^{17,18} Clinical studies in COPD now indicate that inhaled tiotropium once daily is an effective bronchodilator in patients with COPD and is more effective than conventional ipratropium bromide four times daily.^{19–21} Long term studies with tiotropium bromide have demonstrated significant improvement in symptoms and improvement in the quality of life, as well as

There is a major need to develop new treatments for chronic obstructive pulmonary disease (COPD), as no currently available drug therapy reduces the relentless progression of the disease. In particular, there is a need to develop drugs that control the underlying inflammatory and destructive processes. There have been few therapeutic advances in the drug treatment of COPD, in contrast to the enormous advances made in asthma management which reflect a much better understanding of the underlying disease.^{1–3} Although COPD is commonly treated with drugs developed for asthma, this is often inappropriate as the inflammatory processes in the two conditions differ markedly.^{4,5} Recognition of the global importance and rising prevalence of COPD and the absence of effective treatments has now led to a concerted effort to develop new drugs for this disease.^{6,7}

Rational treatment depends on understanding the underlying disease process and there have been recent advances in understanding the cellular and molecular mechanisms that may be involved. COPD involves a chronic inflammation in the small airways and lung parenchyma with the involvement of neutrophils, macrophages, and cytotoxic (CD8+) T lymphocytes. This inflammation results in fibrosis with narrowing of the small airways (chronic obstructive bronchitis) and lung parenchymal destruction due to the action of various proteases such as neutrophil elastase and matrix metalloproteinases (emphysema). This inflammation is quite different from that seen in asthma, indicating that different treatments are likely to be needed.⁴

DISCOVERING NEW DRUGS FOR COPD

There are several reasons why drug development in COPD may be difficult. Only recently has there been any research interest in the molecular and cell biology of COPD in order to identify new therapeutic targets.⁸ There are no satisfactory animal models of COPD for early drug testing,^{9,10} and there are uncertainties about how to test

Correspondence to:
P J Barnes, National Heart
and Lung Institute, Imperial
College School of
Medicine, London
SW3 6LY, UK
p.j.barnes@ic.ac.uk

Box 1 Mediator antagonists for COPD

- Leukotriene B4 (LTB4) antagonists: LY29311, SC-53228, CP-105696, SB 201146, BIIL284
- 5'-lipoxygenase inhibitors: zileuton, Bay x1005
- Chemokine inhibitors
 - Interleukin-8 antagonists: CXCR2 antagonists, e.g. SB225002
 - Monocyte chemotactic protein (MCP) antagonists (CCR2 antagonists)
- Tumour necrosis factor (TNF) inhibitors: monoclonal antibodies, soluble receptors, TNF- α converting enzyme inhibitors
- Antioxidants: e.g. stable glutathione analogues
- Inducible nitric oxide synthase (iNOS) inhibitors: e.g. L-N⁶-(1-imminoethyl)lysine (L-NIL)

an unexpected reduction in exacerbations.^{22, 23} Tiotropium is likely to become the bronchodilator of choice in COPD and may have additive effects with long acting β_2 agonists.

MEDIATOR ANTAGONISTS

Several inflammatory mediators are likely to be involved in COPD as many inflammatory cells and structural cells are activated and there is an ongoing inflammatory process, even in patients who have given up smoking.²⁴ The profile of mediators in COPD is different from that in asthma, so different drugs are likely to be effective. Since COPD is characterised by a neutrophilic inflammation, attention has largely focused on mediators involved in recruitment and activation of neutrophils or on reactive oxygen species in view of the increased oxidative stress in COPD (box 1).

Leukotriene B4 inhibitors

LTB4 is a potent chemoattractant of neutrophils and is increased in the sputum of patients with COPD.²⁵ It is probably derived from alveolar macrophages as well as neutrophils and may be synergistic with interleukin (IL)-8. Two subtypes of receptor for LTB4 have been described; BLT₁ receptors are mainly expressed on granulocytes and monocytes, whereas BLT₂ receptors are expressed on T lymphocytes.²⁶ BLT₁ antagonists such as LY29311 have now been developed for the treatment of neutrophilic inflammation.²⁷ LY29311 inhibits the neutrophil chemotactic activity of sputum from COPD patients, indicating the potential clinical value of such drugs.²⁸ Selective LTB4 receptor antagonists are now in development, including SC-53228, CP-105696, SB201146, and BIIL284. LTB4 is synthesised by 5'-lipoxygenase (5-LO), of which there are several inhibitors, although there have been problems in the clinical development of drugs in this class because of side effects.

Chemokine inhibitors

Several chemokines are involved in neutrophil chemotaxis and mainly belong to the CXC family, of which the most prominent member is IL-8. IL-8 levels are markedly increased in the sputum of patients with COPD and are correlated with disease severity.²⁹ Blocking antibodies to IL-8 and related chemokines inhibit certain types of neutrophilic inflammation in experimental animals and reduce the chemotactic response of neutrophils to sputum from COPD patients.²⁵ A human monoclonal antibody to IL-8 blocks the chemotactic response of neutrophils to IL-8 and is effective in animal models of neutrophilic inflammation.³⁰ This antibody is now in clinical trials, but it may be less effective than drugs that block the common receptor for other members of the CXC chemokine family. IL-8 activates neutrophils via a specific low affinity G-protein coupled receptor (CXCR1) coupled to activation and degranulation and a high affinity receptor

(CXCR2), shared by other members of the CXC family, which is important in chemotaxis.³¹ Other CXC chemokines such as growth related oncoprotein- α (GRO- α) are also increased in patients with COPD,³² so a CXCR2 antagonist is likely to be more useful than a CXCR1 antagonist, particularly as CXCR2 are also expressed on monocytes. Small molecule inhibitors of CXCR2 such as SB225002 have now been developed and are entering clinical trials.^{33, 34}

CC chemokines are also involved in COPD. There is increased expression of monocyte chemotactic protein 1 (MCP-1) and its receptor CCR2 in macrophages and epithelial cells from patients with COPD, and this may play a role in recruitment of blood monocytes to the lungs of these patients.³⁵ This suggests that CCR2 antagonists may be of use and small molecule inhibitors are now in development.

Tumour necrosis factor (TNF)- α inhibitors

TNF- α levels are also raised in the sputum of COPD patients and TNF- α induces IL-8 in airway cells via activation of the transcription factor nuclear factor- κ B (NF- κ B).²⁹ The severe wasting in some patients with advanced COPD might be caused by skeletal muscle apoptosis resulting from increased levels of circulating TNF- α . Patients with COPD with cachexia have increased release of TNF- α from circulating leucocytes.³⁶ Humanised monoclonal TNF antibody (infliximab) and soluble TNF receptors (etanercept) effective in other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease should also be effective in COPD.^{37, 38} There may be problems with long term administration because of the development of blocking antibodies and repeated injections are inconvenient. TNF- α converting enzyme (TACE), which is required for the release of soluble TNF- α , may be a more attractive target as it is possible to discover small molecule TACE inhibitors, some of which are also MMP inhibitors.^{39, 40} General anti-inflammatory drugs such as phosphodiesterase inhibitors and p38 MAP kinase inhibitors also potentially inhibit TNF- α expression.

Antioxidants

Oxidative stress is increased in patients with COPD,^{41, 42} particularly during exacerbations, and reactive oxygen species contribute to its pathophysiology.⁴³ This suggests that antioxidants may be of use in the treatment of COPD. *N*-acetyl cysteine (NAC) provides cysteine for enhanced production of glutathione (GSH) and has antioxidant effects in vitro and in vivo. Recent systematic reviews of studies with oral NAC in COPD suggest small but significant reductions in exacerbations.^{44, 45} More effective antioxidants, including stable glutathione compounds, analogues of superoxide dismutase and selenium based drugs, are now in development for clinical use.^{43, 46}

iNOS inhibitors

Oxidative stress and increased nitric oxide release from expression of inducible nitric oxide synthase (iNOS) may result in the formation of peroxynitrite which is a potent radical and may nitrate proteins, resulting in altered function. 3-Nitrotyrosine may indicate peroxynitrite formation and is markedly increased in sputum macrophages of patients with COPD.⁴⁷ Selective inhibitors of iNOS are now in development,⁴⁸ one of which—L-N⁶-(1-imminoethyl)lysine (L-NIL)—causes a profound and long lasting reduction in exhaled nitric oxide.⁴⁹

NEW ANTI-INFLAMMATORY TREATMENTS

COPD is characterised by chronic inflammation of the respiratory tract, even in ex-smokers, with increased numbers of macrophages, neutrophils and cytotoxic (CD8+) T lymphocytes in airways and lung parenchyma.^{1, 5} This suggests

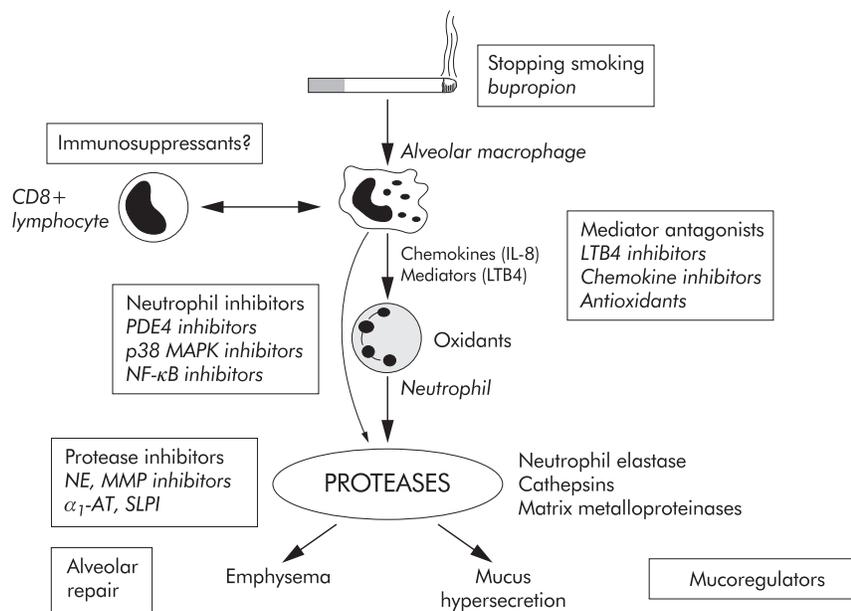


Figure 1 Targets for COPD treatment based on current understanding of the inflammatory mechanisms. Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release neutrophil chemotactic factors including interleukin 8 (IL-8) and leukotriene B4 (LTB4). These cells then release proteases that break down connective tissue in the lung parenchyma, resulting in emphysema, and also stimulate mucus hypersecretion. These enzymes are normally counteracted by protease inhibitors including α_1 -antitrypsin, secretory leukoprotease inhibitor (SLPI), and tissue inhibitor of matrix metalloproteinases (TIMP). Cytotoxic T cells (CD8+) may also be involved in the inflammatory cascade.

that anti-inflammatory treatments may be of value and there are several possible approaches (fig 1).

Resistance to corticosteroids

Because there is chronic inflammation in COPD airways, it was argued that inhaled corticosteroids might prevent the progression of the disease. However, four large 3 year controlled trials of inhaled corticosteroids have shown no reduction in disease progression.⁵⁰⁻⁵³ This might be predicted by the demonstration that neither inhaled nor oral corticosteroids have any significant effect on neutrophil counts, granule proteins, inflammatory or proteases in induced sputum.⁵⁴⁻⁵⁶ Inhaled corticosteroids do not inhibit neutrophilic inflammation induced by ozone in humans,⁵⁷ and this may reflect the finding that corticosteroids prolong neutrophil survival.⁵⁸ There may also be an active resistance to corticosteroids due to an inhibitory effect of cigarette smoke on histone deacetylation which is required for corticosteroids to switch off inflammatory genes.⁵⁹ The disappointing action of corticosteroids in COPD suggests that new types of non-steroidal anti-inflammatory treatment may be needed. Alternatively, therapeutic strategies that unlock the molecular mechanism of resistance might be possible. For example, drugs that increase histone deacetylase activity may resensitise cells to the effects of corticosteroids. There are several new approaches to anti-inflammatory treatment in COPD (box 2).

Phosphodiesterase-4 (PDE4) inhibitors

PDE4 is the predominant PDE expressed in neutrophils, CD8+ cells, and macrophages,⁶⁰ suggesting that PDE4 inhibitors might be effective in controlling inflammation in COPD. Selective PDE4 inhibitors such as cilomilast and roflumilast are active in animal models of neutrophil inflammation.^{61, 62} Cilomilast has some beneficial clinical effect in patients with COPD,⁶³ and larger studies are currently underway.⁶⁴ Roflumilast appears to be well tolerated at doses that significantly inhibit TNF- α release from peripheral blood monocytes.⁶⁵ PDE4 inhibitors are limited by side effects, particularly nausea and other gastrointestinal effects, but it might be possible to develop isoenzyme subtype selective inhibitors in the future which are less likely to be dose limited by adverse effects.

NF- κ B inhibitors

NF- κ B regulates the expression of IL-8 and other chemokines, TNF- α , and some matrix metalloproteinases. There are several possible approaches to inhibition of NF- κ B, including gene transfer of the inhibitor of NF- κ B (I κ B), a search for inhibitors of I κ B kinases (IKK), NF- κ B inducing kinase (NIK) and I κ B ubiquitin ligase which regulate the activity of NF- κ B, and the development of drugs that inhibit the degradation of I κ B.⁶⁶ The most promising approach may be the inhibition of IKK β by small molecule inhibitors which are now in development. An apparently selective IKK inhibitor, hypoestoxide, is a component of African folk remedy for inflammatory diseases. One concern about long term inhibition of NF- κ B is that effective inhibitors may result in immune suppression and impair host defences, since mice which lack NF- κ B genes succumb to septicemia. However, there are alternative pathways of NF- κ B activation that might be more important in inflammatory disease.⁶⁷

Adhesion molecule inhibitors

Recruitment of neutrophils, monocytes, and cytotoxic T cells into the lungs and respiratory tract is dependent on adhesion molecules expressed on these cells and on endothelial cells in the pulmonary and bronchial circulations. Several adhesion

Box 2 New anti-inflammatory drugs for COPD

- Phosphodiesterase-4 inhibitors: SB 207499, CP 80633, CDP-840
- Nuclear factor-kappa B (NF- κ B) inhibitors: proteasome inhibitors, inhibitor of NF- κ B (I κ B) kinase inhibitors, I κ B- α gene transfer
- Adhesion molecule inhibitors: anti-CD11/CD18, anti-ICAM-1, E-selectin inhibitors
- Interleukin-10 and analogues
- p38 mitogen activated protein (MAP) kinase inhibitors: SB203580, SB 220025, RWJ 67657
- Phosphoinositide (PI)-3 kinase- γ inhibitors
- Immunomodulators: CD8+ lymphocyte inhibitors

molecules can now be inhibited pharmacologically. For example, E-selectin on endothelial cells interacts with sialyl-Lewis^x on neutrophils. A mimic of sialyl-Lewis^x, TBC1269, blocks selectins and inhibits granulocyte adhesion, with preferential effects on neutrophils.⁶⁸ However, there are concerns about this therapeutic approach for a chronic disease, as an impaired neutrophilic response may increase the susceptibility to infection. The expression of Mac-1 (CD11b/CD18) is increased on neutrophils of patients with COPD, suggesting that targeting this adhesion molecule, which is also expressed on monocytes and macrophages, might be beneficial.⁶⁹

Interleukin-10

IL-10 is a cytokine with a wide spectrum of anti-inflammatory actions. It inhibits the secretion of TNF- α and IL-8 from macrophages, but tips the balance in favour of antiproteases by decreasing the expression of matrix metalloproteinases while increasing the expression of endogenous tissue inhibitors of matrix metalloproteinases (TIMP). IL-10 concentrations are reduced in induced sputum from patients with COPD, so this may be a mechanism for increasing lung inflammation.⁷⁰ IL-10 is currently in clinical trials for other chronic inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis and psoriasis), including patients with steroid resistance, but it may cause haematological side effects.⁷¹ Treatment with daily injections of IL-10 over several weeks has been well tolerated. IL-10 may have therapeutic potential in COPD, especially if a selective activator of IL-10 receptors or unique signal transduction pathways can be developed in the future.

p38 mitogen activated protein (MAP) kinase inhibitors

Mitogen activated protein (MAP) kinases play a key role in chronic inflammation and several complex enzyme cascades have now been defined. One of these, the p38 MAP kinase pathway, is involved in the expression of inflammatory cytokines including IL-8, TNF- α , and matrix metalloproteinases (MMPs).⁷²⁻⁷³ Non-peptide inhibitors of p38 MAP kinase, such as SB 203580, SB 239063 and RWJ 67657, have now been developed and these drugs have a broad range of anti-inflammatory effects.⁷⁴ SB 239063 reduces neutrophil infiltration after inhaled endotoxin and the concentrations of IL-6 and MMP-9 in bronchoalveolar lavage fluid of rats, indicating its potential as an anti-inflammatory agent in COPD.⁷⁵ It is likely that such a broad spectrum anti-inflammatory drug will have some toxicity, but inhalation may be a feasible therapeutic approach.

Phosphoinositide-3 kinase (PI-3K) inhibitors

PI-3Ks are a family of enzymes which promote the generation of lipid second messengers that regulate a number of cellular events. A particular isoform, PI-3K γ , is involved in neutrophil recruitment and activation. Knock out of the PI-3K γ gene results in inhibition of neutrophil migration and activation, as well as impaired T lymphocyte and macrophage function.⁷⁶ This suggests that selective PI-3K γ inhibitors may have relevant anti-inflammatory activity in COPD.

PROTEASE INHIBITORS

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 endogenous antiproteases may be beneficial and theoretically should prevent the progression of airflow obstruction in COPD. Considerable progress has been made in identifying the enzymes involved in elastolytic activity in emphysema and in characterising the endogenous antiproteases that counteract this activity.⁷⁷⁻⁷⁸

Endogenous antiproteases

One approach is to give endogenous antiproteases (α_1 -antitrypsin, secretory leukoprotease inhibitor, elafin, tissue inhibitors of MMP), 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.

Protease inhibitors

A more promising approach is to develop small molecule inhibitors of proteinases, particularly those that have elastolytic activity. Small molecule inhibitors such as ONO-5046 and FR901277 have been developed which have high potency.⁷⁹⁻⁸⁰ These drugs inhibit neutrophil elastase-induced lung injury in experimental animals, whether given by inhalation or systemically, and also inhibit the other serine proteases released from the neutrophils cathepsin G and proteinase-3. Small molecule inhibitors of neutrophil elastase are now entering clinical trials, but there is concern that neutrophil elastase may not play a critical role in emphysema and that other proteases are more important in elastolysis. Inhibitors of elastolytic cysteine proteases such as cathepsins K, S and L that are released from macrophages⁸¹ are also in development.⁸² Matrix metalloproteinases with elastolytic activity (such as MMP-9) may also be a target for drug development, although non-selective MMP inhibitors such as marimastat appear to have considerable side effects. It is possible that side effects could be reduced by increasing selectivity for specific MMPs or by targeting delivery to the lung parenchyma. MMP-9 is markedly overexpressed by alveolar macrophages from patients with COPD,⁸³ so a selective inhibitor might be useful in the treatment of emphysema.

REMODELLING AGENTS

Since a major mechanism of airway obstruction in COPD is the loss of elastic recoil resulting from proteolytic destruction of lung parenchyma, it seems unlikely that this could be reversible by drug treatment although it might be possible to reduce the rate of progression by preventing the inflammatory and enzymatic disease process. Retinoic acid increases the number of alveoli in developing rats and, remarkably, reverses the histological and physiological changes induced by elastase treatment of adult rats.⁸⁴⁻⁸⁵ Retinoic acid activates retinoic acid receptors which act as transcription factors to regulate the expression of many genes involved in growth and differentiation. The molecular mechanisms involved have not been identified, and it is not yet known whether this can be extrapolated to humans. Several retinoic acid receptor subtype agonists have been developed that may have a greater selectivity for this effect and therefore a lower risk of side effects. A short term trial of all-*trans*-retinoic acid in patients with emphysema who did not show any improvement in clinical parameters is currently underway.⁸⁶

DRUG DELIVERY

Bronchodilators are currently given as metered dose inhalers or dry powder inhalers that have been optimised to deliver drugs to the respiratory tract in asthma. However, in emphysema the inflammatory and destructive process takes place in the lung parenchyma and in chronic obstructive bronchitis the predominant irreversible changes are in the small airways. This implies that, if a drug is to be delivered by inhalation, it should have a lower mass median diameter so that there is preferential deposition in the lung periphery. It may be more appropriate to give drug treatment parenterally as it will reach the lung parenchyma via the pulmonary circulation, but parenteral administration may increase the risk of systemic side effects. One way of limiting toxicity is the targeted delivery of drugs to particular cell types. For example, alveolar macrophages may be targeted by molecules that are

packaged to be phagocytosed by these cells. Another important concept is the idea of disease activation of drugs—for example, in COPD active drugs that are released from inactive prodrugs by elastases might be considered. This would concentrate the active drug at the site of disease activity and reduce systemic exposure.

FUTURE DIRECTIONS

New drugs for the treatment of COPD are needed. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult in most patients and, even with bupropion, only about 15% of patients are sustained quitters.¹³ In addition, it is likely that the inflammatory process initiated by cigarette smoking may continue even when smoking has ceased.²⁴ Furthermore, COPD may be caused by other environmental factors—such as cooking fumes, pollutants, passive smoking, or other inhaled toxins—or by developmental changes in the lungs.⁸⁷

Identification of novel therapeutic targets

It is important to identify the genetic factors that determine why only 10–20% of smokers develop COPD.^{88–89} Identification of genes that predispose to the development of COPD in smokers may identify novel therapeutic targets. Powerful techniques such as high density DNA arrays (gene chips) are able to identify multiple polymorphisms; differential display may identify the expression of novel genes and the proteomics of novel proteins expressed.

Surrogate markers

It will be difficult to demonstrate the efficacy of novel treatments as determination of the effect of any drug on the rate of decline in lung function will require large studies over at least 2 years. There is a need to develop surrogate markers—such as analysis of sputum parameters (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species, cytokines)⁹⁰—that may predict the clinical usefulness of such drugs. More research on the basic cellular and molecular mechanisms of COPD and emphysema is urgently needed to aid the logical development of new treatments for this common and important disease for which no effective preventative treatments currently exist. It may also be important to define more accurately the presence of emphysema versus small airway obstruction using improved imaging techniques, as some drugs may be more useful for preventing emphysema while others may be more effective against the small airway inflammatory fibrosis process.

REFERENCES

- Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:269–80.
- Hogg JC. Chronic obstructive pulmonary disease: an overview of pathology and pathogenesis. *Novartis Found Symp* 2001;**234**:4–19.
- Barnes PJ. New concepts in COPD. *Ann Rev Med* 2003;**54**:113–29.
- Barnes PJ. Mechanisms in COPD: differences from asthma. *Chest* 2000;**117**:10–45.
- Saetta M, Turato G, Maestrelli P, et al. Cellular and structural bases of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:1304–9.
- Barnes PJ. New treatments for chronic obstructive pulmonary disease. *Curr Opin Pharmacol* 2001;**1**:217–22.
- Barnes PJ. New treatments for COPD. *Nature Rev Drug Disc* 2002;**1**:437–45.
- Barnes PJ. Novel approaches and targets for treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:S72–9.
- Shapiro SD. Animal models for COPD. *Chest* 2000;**117**:223–75.
- Dawkins PA, Stockley RA. Animal models of chronic obstructive pulmonary disease. *Thorax* 2001;**56**:972–7.
- Hansel TT, Barnes PJ. *New drugs for asthma and COPD*. Basel: Karger, 2001.
- Lancaster T, Stead L, Silagy C, et al. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000;**321**:355–8.
- Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;**340**:685–91.
- Tashkin DP, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo controlled, randomised trial. *Lancet* 2001;**357**:1571–5.
- Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation (Cochrane Review). *Cochrane Database Syst Rev* 2000;**4**:CD000031.
- Holm KJ, Spencer CM. Bupropion: a review of its use in the management of smoking cessation. *Drugs* 2000;**59**:1007–24.
- Disse B, Speck CA, Rominger KL, et al. Tiotropium (Spiriva): mechanical considerations and clinical profile in obstructive lung disease. *Life Sci* 1999;**64**:457–64.
- Barnes PJ. The pharmacological properties of tiotropium. *Chest* 2000;**117**:63–65.
- Littner MR, Ilowite JS, Tashkin DP, et al. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:1136–42.
- Casaburi R, Briggs DDJ, Donohue JF, et al. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. *Chest* 2000;**118**:1294–302.
- van Noord JA, Bantje TA, Eland ME, et al. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax* 2000;**55**:289–94.
- Casaburi R, Mahler DA, Jones PW, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;**19**:217–24.
- Vincken W, van Noord JA, Greefhorst AP, et al. Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J* 2002;**19**:209–16.
- Rutgers SR, Postma DS, ten Hacken NH, et al. Ongoing airway inflammation in patients with COPD who do not currently smoke. *Thorax* 2000;**55**:12–8.
- Hill AT, Bayley D, Stockley RA. The interrelationship of sputum inflammatory markers in patients with chronic bronchitis. *Am J Respir Crit Care Med* 1999;**160**:893–8.
- Yokomizo T, Kato K, Terawaki K, et al. A second leukotriene B₄ receptor, BLT₂. A new therapeutic target in inflammation and immunological disorders. *J Exp Med* 2000;**192**:421–32.
- Silbaugh SA, Stengel PW, Cockerham SL, et al. Pharmacologic actions of the second generation leukotriene B₄ receptor antagonist LY293111: in vivo pulmonary studies. *Naunyn Schmiedeberg Arch Pharmacol* 2000;**361**:397–404.
- Crooks SW, Bayley DL, Hill SL, et al. Bronchial inflammation in acute bacterial exacerbations of chronic bronchitis: the role of leukotriene B₄. *Eur Respir J* 2000;**15**:274–80.
- Keatings VM, Collins PD, Scott DM, et al. Differences in interleukin-8 and tumor necrosis factor- α in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am J Respir Crit Care Med* 1996;**153**:530–4.
- Yang XD, Corvalan JR, Wang P, et al. Fully human anti-interleukin-8 monoclonal antibodies: potential therapeutics for the treatment of inflammatory disease states. *J Leuk Biol* 1999;**66**:401–10.
- Rossi D, Zlotnik A. The biology of chemokines and their receptors. *Annu Rev Immunol* 2000;**18**:217–42.
- Traves SL, Culpitt S, Russell REK, et al. Increased levels of the chemokines GRO- α and MCP-1 in sputum samples from patients with COPD. *Thorax* 2002;**57**:590–5.
- White JR, Lee JM, Young PR, et al. Identification of a potent, selective non-peptide CXCR2 antagonist that inhibits interleukin-8-induced neutrophil migration. *J Biol Chem* 1998;**273**:10095–8.
- Hay DWP, Sarau HM. Interleukin-8 receptor antagonists in pulmonary diseases. *Curr Opin Pharmacol* 2001;**1**:242–7.
- de Boer WI, Sont JK, van Schadewijk A, et al. Monocyte chemoattractant protein 1, interleukin 8, and chronic airways inflammation in COPD. *J Pathol* 2000;**190**:619–26.
- de Godoy I, Donahoe M, Calhoun WJ, et al. Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. *Am J Respir Crit Care Med* 1996;**153**:633–7.
- Markham A, Lamb HM. Infliximab: a review of its use in the management of rheumatoid arthritis. *Drugs* 2000;**59**:1341–59.
- Jarvis B, Faulds D. Etanercept: a review of its use in rheumatoid arthritis. *Drugs* 1999;**57**:945–66.
- Barlaam B, Bird TG, Lambert-Van DB, et al. New α -substituted succinate-based hydroxamic acids as TNF α convertase inhibitors. *J Med Chem* 1999;**42**:4890–908.
- Rabinowitz MH, Andrews RC, Becherer JD, et al. Design of selective and soluble inhibitors of tumor necrosis factor- α converting enzyme (TACE). *J Med Chem* 2001;**44**:4252–67.
- Montuschi P, Collins JV, Ciabattini G, et al. Exhaled 8-isoprostane as an in vivo biomarker of lung oxidative stress in patients with COPD and healthy smokers. *Am J Respir Crit Care Med* 2000;**162**:1175–7.
- Paredi P, Kharitonov SA, Leck D, et al. Exhaled ethane, a marker of lipid peroxidation, is elevated in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**162**:369–73.
- Macnee W. Oxidants/antioxidants and COPD. *Chest* 2000;**117**:303–175.
- Grandjean EM, Berthet P, Ruffmann R, et al. Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials. *Clin Ther* 2000;**22**:209–21.
- Poole PJ, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *BMJ* 2001;**322**:1271–4.
- Cuzzocrea S, Riley DP, Caputi AP, et al. Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia/reperfusion injury. *Pharmacol Rev* 2001;**53**:135–59.

- 47 **Ichinose M**, Sugiura H, Yamagata S, *et al*. Increase in reactive nitrogen species production in chronic obstructive pulmonary disease airways. *Am J Respir Crit Care Med* 2000;**160**:701–6.
- 48 **Hobbs AJ**, Higgs A, Moncada S. Inhibition of nitric oxide synthase as a potential therapeutic target. *Annu Rev Pharmacol Toxicol* 1999;**39**:191–220.
- 49 **Erin EM**, Hansel TT, Kharitonov SA, *et al*. A selective inhibitor of inducible nitric oxide synthase inhibits exhaled breath nitric oxide. *Am J Respir Crit Care Med* 2002;**165**:A187.
- 50 **Vestbo J**, Sorensen T, Lange P, *et al*. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 1999;**353**:1819–23.
- 51 **Pauwels RA**, Lofdahl CG, Laitinen LA, *et al*. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. *N Engl J Med* 1999;**340**:1948–53.
- 52 **Burge PS**, Calverley PMA, Jones PW, *et al*. Randomised, double-blind, placebo-controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease; the ISOLDE trial. *BMJ* 2000;**320**:1297–303.
- 53 **Lung Health Study Research Group**. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *N Engl J Med* 2000;**343**:1902–9.
- 54 **Barnes PJ**. Inhaled corticosteroids are not helpful in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;**161**:342–4.
- 55 **Keatings VM**, Jatakanon A, Worsdell YM, *et al*. Effects of inhaled and oral glucocorticoids on inflammatory indices in asthma and COPD. *Am J Respir Crit Care Med* 1997;**155**:542–8.
- 56 **Culpitt SV**, Nightingale JA, Barnes PJ. Effect of high dose inhaled steroid on cells, cytokines and proteases in induced sputum in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:1635–9.
- 57 **Nightingale JA**, Rogers DF, Chung KF, *et al*. No effect of inhaled budesonide on the response to inhaled ozone in normal subjects. *Am J Respir Crit Care Med* 2000;**161**:479–86.
- 58 **Meagher LC**, Cousin JM, Seckl JR, *et al*. Opposing effects of glucocorticoids on the rate of apoptosis in neutrophilic and eosinophilic granulocytes. *J Immunol* 1996;**156**:4422–8.
- 59 **Ito K**, Lim S, Caramori G, *et al*. Cigarette smoking reduces histone deacetylase 2 expression, enhances cytokine expression and inhibits glucocorticoid actions in alveolar macrophages. *FASEB J* 2001;**15**:1100–2.
- 60 **Souness JE**, Aldous D, Sargent C. Immunosuppressive and anti-inflammatory effects of cyclic AMP phosphodiesterase (PDE) type 4 inhibitors. *Immunopharmacology* 2000;**47**:127–62.
- 61 **Spond J**, Chapman R, Fine J, *et al*. Comparison of PDE 4 inhibitors, rolipram and SB 207499 (ariflo), in a rat model of pulmonary neutrophilia. *Pulm Pharmacol Ther* 2001;**14**:157–64.
- 62 **Bundschuh DS**, Eltze M, Barsig J, *et al*. In vivo efficacy in airway disease models of roflumilast, a novel orally active PDE4 inhibitor. *J Pharmacol Exp Ther* 2001;**297**:280–90.
- 63 **Compton CH**, Gubb J, Nieman R, *et al*. Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: a randomised, dose-ranging study. *Lancet* 2001;**358**:265–70.
- 64 **Edelson J**, Compton CH, Nieman R, *et al*. Cilomilast (Ariflo) a potent, selective phosphodiesterase 4 inhibitor, reduces exacerbations in COPD patients: results of a 6-month trial. *Am J Respir Crit Care Med* 2001;**163**:A771.
- 65 **Timmer W**, Leclerc V, Birraux G, *et al*. The new phosphodiesterase 4 inhibitor roflumilast is efficacious in exercise-induced asthma and leads to suppression of LPS-stimulated TNF- α ex vivo. *J Clin Pharmacol* 2002;**42**:297–303.
- 66 **Delhase M**, Li N, Karin M. Kinase regulation in inflammatory response. *Nature* 2000;**406**:367–8.
- 67 **Nasuhara Y**, Adcock IM, Catley M, *et al*. Differential IKK activation and I κ B α degradation by interleukin-1 β and tumor necrosis factor- α in human U937 monocytic cells: evidence for additional regulatory steps in κ B-dependent transcription. *J Biol Chem* 1999;**274**:19965–72.
- 68 **Davenpeck KL**, Berens KL, Dixon RA, *et al*. Inhibition of adhesion of human neutrophils and eosinophils to P-selectin by the sialyl Lewis x antagonist TBC1269: preferential activity against neutrophil adhesion in vitro. *J Allergy Clin Immunol* 2000;**105**:769–75.
- 69 **Noguera A**, Batle S, Miralles C, *et al*. Enhanced neutrophil response in chronic obstructive pulmonary disease. *Thorax* 2001;**56**:432–7.
- 70 **Takanashi S**, Hasegawa Y, Kanehira Y, *et al*. Interleukin-10 level in sputum is reduced in bronchial asthma, COPD and in smokers. *Eur Respir J* 1999;**14**:309–14.
- 71 **Fedorak RN**, Gangl A, Elson CO, *et al*. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. *Gastroenterology* 2000;**119**:1473–82.
- 72 **Carter AB**, Monick MM, Hunninghake GW. Both erk and p38 kinases are necessary for cytokine gene transcription. *Am J Respir Cell Mol Biol* 1999;**20**:751–8.
- 73 **Meja KK**, Seldon PM, Nasuhara Y, *et al*. p38 MAP kinase and MKK-1 cooperate in the generation of GM-CSF from LPS-stimulated human monocytes by an NF- κ B-independent mechanism. *Br J Pharmacol* 2000;**131**:1143–53.
- 74 **Lee JC**, Kumar S, Griswold DE, *et al*. Inhibition of p38 MAP kinase as a therapeutic strategy. *Immunopharmacology* 2000;**47**:185–201.
- 75 **Underwood DC**, Osborn RR, Bochnowicz S, *et al*. SB 239063, a p38 MAPK inhibitor, reduces neutrophilia, inflammatory cytokines, MMP-9, and fibrosis in lung. *Am J Physiol Lung Cell Mol Physiol* 2000;**279**:L895–902.
- 76 **Sasaki T**, Irie-Sasaki J, Jones RG, *et al*. Function of PI3Kgamma in thymocyte development, T cell activation, and neutrophil migration. *Science* 2000;**287**:1040–6.
- 77 **Stockley RA**. Neutrophils and protease/antiprotease imbalance. *Am J Respir Crit Care Med* 1999;**160**:S49–52.
- 78 **Shapiro SD**, Senior RM. Matrix metalloproteinases. Matrix degradation and more. *Am J Respir Cell Mol Biol* 1999;**20**:1100–2.
- 79 **Kawabata K**, Suzuki M, Sugitani M, *et al*. ONO-5046, a novel inhibitor of human neutrophil elastase. *Biochem Biophys Res Commun* 1991;**177**:814–20.
- 80 **Fujie K**, Shinguh Y, Yamazaki A, *et al*. Inhibition of elastase-induced acute inflammation and pulmonary emphysema in hamsters by a novel neutrophil elastase inhibitor FR901277. *Inflamm Res* 1999;**48**:160–7.
- 81 **Punturieri A**, Filippov S, Allen E, *et al*. Regulation of elastolytic cysteine proteinase activity in normal and cathepsin K-deficient human macrophages. *J Exp Med* 2000;**192**:789–800.
- 82 **Leung-Toung R**, Li W, Tam TF, *et al*. Thiol-dependent enzymes and their inhibitors: a review. *Curr Med Chem* 2002;**9**:979–1002.
- 83 **Russell RE**, Culpitt SV, DeMatos C, *et al*. Release and activity of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by alveolar macrophages from patients with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2002;**26**:602–9.
- 84 **Massaro G**, Massaro D. Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats. *Nature Med* 1997;**3**:675–7.
- 85 **Belloni PN**, Garvin L, Mao CP, *et al*. Effects of all-trans-retinoic acid in promoting alveolar repair. *Chest* 2000;**117**:235–41S.
- 86 **Mao JT**, Goldin JG, Dermand J, *et al*. A pilot study of all-trans-retinoic acid for the treatment of human emphysema. *Am J Respir Crit Care Med* 2002;**165**:718–23.
- 87 **Smith KR**. Inaugural article: national burden of disease in India from indoor air pollution. *Proc Natl Acad Sci USA* 2000;**97**:13286–93.
- 88 **Barnes PJ**. Molecular genetics of chronic obstructive pulmonary disease. *Thorax* 1999;**54**:245–52.
- 89 **Lomas DA**, Silverman EK. The genetics of chronic obstructive pulmonary disease. *Respir Res* 2001;**2**:20–6.
- 90 **Kharitonov SA**, Barnes PJ. Exhaled markers of pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**:1693–772.