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Therapy for Chronic Obstructive Pulmonary Disease in the 21st Century

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Abstract

Chronic obstructive pulmonary disease (COPD) is a common, smoking-related, severe respiratory condition characterised by progressive, irreversible airflow limitation. Current treatment of COPD is symptomatic, with no drugs capable of halting the relentless progression of airflow obstruction. Better understanding of the airway inflammation, oxidative stress and alveolar destruction that characterise COPD has delineated new disease targets, with consequent identification of novel compounds with therapeutic potential.

These new drugs include aids to smoking cessation (e.g. bupropion) and improvements to existing therapies, for example long-acting rather than short-acting bronchodilators, as well as combination therapy. New antiproteases include acyl-enzyme and transition state inhibitors of neutrophil elastase (e.g. sivelestat and ONO-6818), matrix metalloprotease inhibitors (e.g. batimastat), cathepsin inhibitors and peptide protease inhibitors (e.g. DX-890 [EPI-HNE-4] and trappin-2). New antioxidants include superoxide dismutase mimetics (e.g. AEOL-10113) and spin trap compounds (e.g. *N*-tert-butyl-α-phenylnitrone). New anti-inflammatory interventions include phosphodiesterase-4 inhibitors (e.g. cilomilast), inhibitors of tumour necrosis factor-α (e.g. humanised monoclonal antibodies), adenosine A_{2a} receptor agonists (e.g. CGS-21680), adhesion molecule inhibitors (e.g. bimosiamose [TBC1269]), inhibitors of nuclear factor-κB (e.g. the naturally occurring compounds hypoestoxide and (–)-epigallocatechin-3-gallate) and activators of histone deacetylase (e.g. theophylline). There are also selective inhibitors of specific extracellular mediators such as chemokines (e.g. CXCR2 and CCR2 antagonists) and leukotriene B_4 (e.g. SB201146), and of intracellular signal transduction molecules such as p38 mitogen activated protein kinase (e.g. RWJ67657) and phosphoinositide 3-kinase. Retinoids may be one of the few potential treatments capable of reversing alveolar destruction in COPD, and a number of compounds are in clinical trial (e.g. all-trans-retinoic acid). Talniflumate (MSI-1995), an inhibitor of human calcium-activated chloride channels, has been developed to treat mucous hypersecretion. In addition, the purinoceptor $P2Y_2$ receptor agonist diquafosol (INS365) is undergoing clinical trials to increase mucus clearance.

The challenge to transferral of these new compounds from preclinical research to disease management is the design of effective clinical trials. The current scarcity of well characterised surrogate markers predicts that long-term studies in

large numbers of patients will be needed to monitor changes in disease progression.

Chronic obstructive pulmonary disease (COPD) is a severe respiratory condition that is increasing in prevalence worldwide.[1] It is currently the fourth leading cause of death in the UK and US, and is predicted to rank third in the global impact of disease by the year 2020. COPD does not have a precise definition but has been given a 'working' physiological definition of a disease state characterised by airflow limitation that is not fully reversible.[2] The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Three conditions comprise COPD, namely mucus hypersecretion, emphysema (alveolar destruction) and bronchiolitis (small airways disease).[3] The contribution of each component to airflow obstruction, pathophysiology and clinical symptoms varies between individual patients. The economic burden of COPD is considerable. Annual treatment costs in the mid 1990s for COPD-related illness were estimated at $US14.7 billion in the US and £846 million in the UK.[4]

Cigarette smoking is the major risk factor for the development of COPD and accounts for >85% of cases.[2] However, only 10–20% of smokers develop COPD, which suggests an underlying genetic susceptibility.[5] Other risk factors include air pollution (especially sulphur dioxide and particulates), chest infections in infancy, latent virus infections and low dietary intake of antioxidants.[6]

Current pharmacotherapy of stable COPD is merely symptomatic, with bronchodilators as the mainstay of management.[2] Exacerbations are treated with oral glucocorticosteroids, supplemental oxygen and broad spectrum antibacterials, albeit that many exacerbations may be viral rather than bacterial in origin.[7] No drugs halt the relentless progression of airflow obstruction. Consequently, there is a need for new and improved therapeutic interventions in COPD. This article discusses new therapeutic options for COPD, concentrating on advances reported in the literature over the last 3 years (year 2000 onwards). Consideration of new antibacterials and antivirals is beyond the scope of this article and the interested reader is referred to two recent reviews.[8,9] This review starts with an overview of the pathophysiology, current therapy and difficulties in development of new therapies for COPD.

1. Pathophysiology of Chronic Obstructive Pulmonary Disease (COPD)

Chronic airway inflammation is a feature of COPD that is characterised by an increased number of inflammatory cells in the airways.[10] These cells include cytotoxic T lymphocytes (CD8+ cells), neutrophils and macrophages.[11] The macrophage is a long-lived cell derived from peripheral blood monocytes and may be responsible for the persistence of inflammation and, via production of proteolytic enzymes, the degradation of extra-cellular matrix leading to loss of elastic recoil in the lung.[12] In contrast, neutrophils are short-lived, transient cells that are recruited directly from peripheral blood, which also contribute to parenchymal destruction via the production of elastolytic enzymes.[13] The contribution of CD8+ lymphocytes to pathophysiology is unclear. They may orchestrate an 'antigenic' response to cigarette smoke[14] and could be central to the response to viral infections.[15] The majority of the pathophysiological changes are found in the peripheral airways and include inflammation of the bronchioli, goblet cell hyperplasia with increased luminal mucus, increased wall muscle, fibrosis and airway stenoses, also referred to as chronic obstructive bronchiolitis.[3,11] The latter pathophysiological changes may pre-dispose to centriacinar (also known as centrilobular) emphysema where destruction is limited to respiratory bronchioli. In panacinar emphysema there is destruction of the alveolar ducts and sacs, leading to permanent enlargement of airspaces distal to the terminal bronchioles accompanied by destruction of alveolar walls (figure 1). This

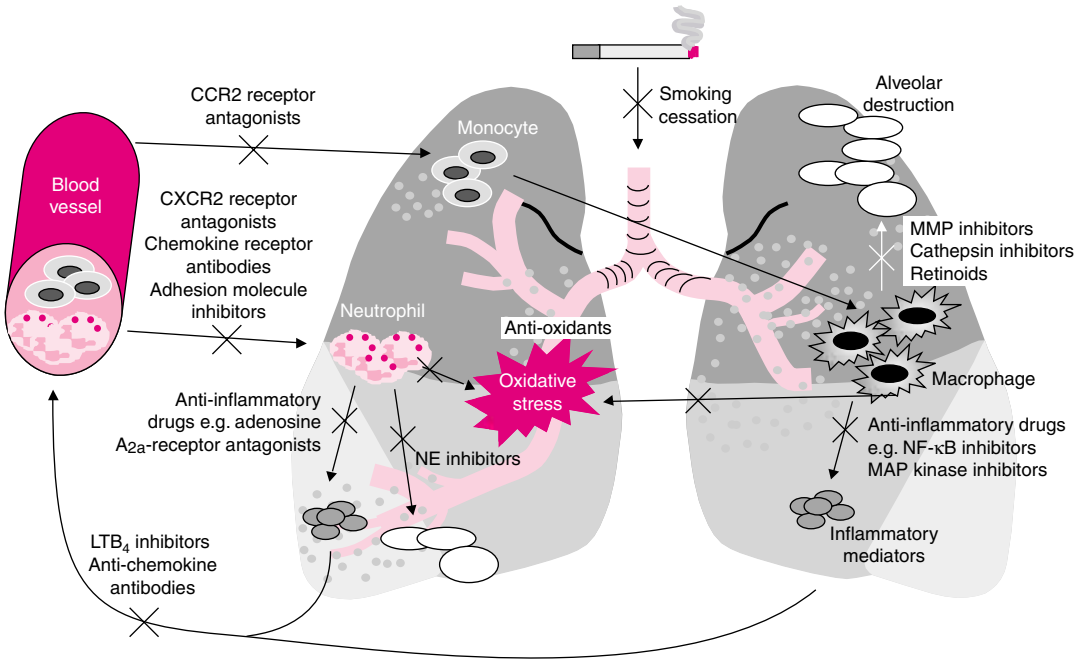


Fig. 1. Simplified schematic of the pathophysiology of chronic obstructive pulmonary disease and therapeutic targets. Recruitment of neutrophils and monocytes from the blood into the lung is regulated by specific chemokines (CXC, C-C). Monocytes differentiate into pulmonary macrophages, which are activated to release proteases, including matrix metalloproteases (MMP) and cathepsins, inflammatory mediators (e.g. interleukin-8) and reactive oxygen species, leading to oxidative stress. Activated neutrophils release neutrophil elastase (NE), inflammatory mediators and reactive oxygen species. There are a number of options for inhibition of these pathophysiological pathways (X). Leukocyte recruitment can be inhibited by chemokine receptor antagonists and antibodies, leukotriene (LT)-B_4 inhibitors and adhesion molecule inhibitors. Alveolar destruction can be inhibited by inhibitors of NE, MMPs and cathepsins. Inflammation and oxidative stress can be inhibited by a variety of anti-inflammatory drugs and antioxidants. **MAP** = mitogen activated protein; **NF-κB** = nuclear factor kappa B.

is the characteristic lesion of α-1 antitrypsin deficiency.

The critical point about the pulmonary inflammation in COPD is that it is different to that in asthma[3,16,17] (figure 2). Consequently, therapeutic interventions that are successful in asthma will not necessarily be effective in COPD. This means that current therapy of COPD, which is based primarily upon that of asthma, is unlikely to be optimal and future therapy will require increased understanding of the specifics of COPD pathophysiology if it is to be of benefit to patients.

2. Current Therapy and Difficulties in Development of New Therapies

The primary strategy in management of COPD is smoking cessation.[2] Pharmacotherapy of COPD is merely symptomatic, using essentially bronchodilators (anti-cholinergics, β_2-adrenoceptor agonists and theophylline), with no drugs currently available that will halt the relentless progression of airflow obstruction.[18] Routine use of corticosteroids in stable COPD is controversial.[19,20] Regular treatment is recommended only for patients with symptomatic COPD with a documented spirometric response to inhaled corticosteroids, or for those with a forced expiratory volume in 1 second (FEV_1) of <50% predicted or who are prone to exacerbations.[2]

The limitations of current therapy identify a need for new pharmacotherapeutic drugs to treat COPD. However, there are difficulties associated with the development and evaluation of new compounds for this condition. Firstly, interest in treatment of COPD is a relatively recent phenomenon.[21] As a conse-

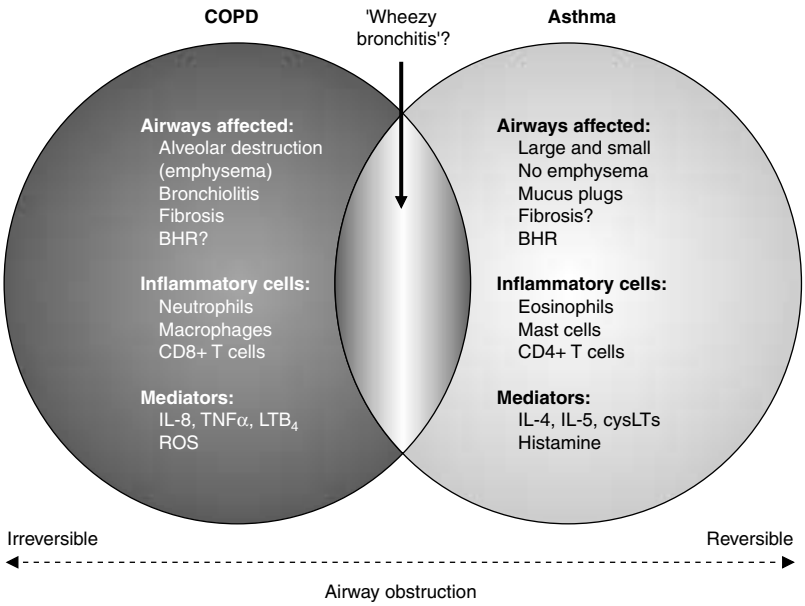


Fig. 2. Principal differences in pathophysiology between chronic obstructive pulmonary disease (COPD) and asthma. **BHR** = bronchial hyperresponsiveness; **cysLT** = cysteinyl leukotrienes (e.g. LTC_4 and LTD_4); **IL** = interleukin; **LT** = leukotriene; **ROS** = reactive oxygen species; **TNF**α = tumour necrosis factor-α.

quence, identification of molecular and cellular mechanisms underlying the pathophysiology of COPD lags behind that of other respiratory diseases, most notably asthma. Secondly, patients invariably present late in the course of the disease, which limits investigation of early pathophysiological events. The delay in understanding disease mechanisms has hindered the development of suitable animal models of COPD for preclinical drug testing.[22]

There are two challenges to clinical trial of potential therapies for COPD. Firstly, to assess their effects on disease progression, drugs will need to be in long-term trial (at least 3 years) in large numbers of patients.[23] This lengthens the drug development process and is expensive. Secondly, short-term trials are hindered by a lack of well-characterised surrogate markers to monitor potential drug efficacy[24,25] (table I). However, despite these problems a wide variety of potential new compounds are in development for treatment of COPD, with some being in clinical trial.

3. New Therapies

Current and emerging therapies can be broadly divided into those that relieve symptoms and improve quality of life, and those that impair tissue damage and disease progression. However, these divisions are not clear cut and many treatments have dual activity. For example, long-acting β_2-adrenoceptor agonists cause bronchodilation with consequent reduction in symptoms but may also have anti-inflammatory properties with possible beneficial effects on disease progression.[27] In the following sections, we have attempted to highlight the principal activity of the therapy discussed.

3.1 Smoking Cessation

Cigarette smoking is the primary risk factor for development of COPD and smoking cessation is the only current option for reduction of disease progression.[2] However, smoking is a highly addictive habit that is hard to quit. Consequently, interventions that aid smoking cessation should be of therapeutic benefit in patients with COPD. Nicotine addiction is thought to be the principal drive to continue to

smoke and nicotine replacement therapy is an important component of smoking cessation strategies. Nicotine replacement with gum, transdermal patches, nasal sprays, inhalers, tablets or lozenges increase quit rates by 1.5–2-fold during a minimum 6-month trial period.[28] Interestingly, the effectiveness of nicotine replacement is largely independent of the intensity of additional cessation support.

Although successful, at least in the short-term, nicotine replacement does not tackle directly the addictive nature of nicotine. One aspect of the addiction is that nicotine has antidepressant effects and this may make quitting more difficult in some smokers. Therefore, depression may be a symptom of nicotine withdrawal and smoking cessation itself may precipitate depression. Similarly, smoking may decrease anxiety and quitting may cause anxiety. Consequently, antidepressants and anxiolytics might aid smoking cessation.[29] Antidepressants (primarily modulators of noradrenergic/dopaminergic neurotransmission), in particular nortriptyline and bupropion, can aid smoking cessation.[30] In contrast to antidepressants, anxiolytics (primarily serotonin reuptake inhibitors), including buspirone and ondansetron, have variable effects and there is no consistent evidence that they aid smoking cessation.[31]

3.1.1 Bupropion

Sustained-release bupropion (bupropion SR) is significantly more effective than nicotine patches as an aid to smoking cessation in healthy smokers,[32] and is strongly advocated for smoking cessation regimes in both Europe[33] and the US.[34] Importantly, bupropion is an effective smoking cessation aid in patients with COPD.[35] One consideration is that, although bupropion is generally well tolerated, there is a risk of seizure (~0.1% of patients), especially in

Table I. Surrogate markers in stable chronic obstructive pulmonary disease (COPD)[24-26]

Marker	Indication	Change in levels	Usefulness
Exhaled NO	Airway/pulmonary inflammation	Elevated in mild disease; markedly elevated in severe disease	Less useful than in asthma for stable disease
Exhaled CO	Oxidative stress	Elevated	Limited by cigarette smoking
Exhaled hydrocarbons	Oxidative stress	Elevated	Potentially useful; differentiates smokers from non-smokers
Exhaled temperature	Alveolar destruction?	Lower than asthma	Potentially useful
Exhaled breath condensate			
NO metabolites	Inflammation, oxidative stress	Elevated	Potentially useful
H_2O_2	Oxidative stress	Elevated	Potentially useful
Lipid peroxides	Oxidative stress	Elevated	Doubtful
Eicosanoids	Inflammation	Usually elevated	PGE_2 and $PGF_{2\alpha}$ may differentiate COPD from asthma
Ammonia	Protection capacity (e.g. antibacterial)	Not tested in COPD	Potentially useful in detecting infection
Vasoactive amines	Inflammation	Not tested in COPD	Unknown
Hydrogen ions (pH)	Inflammation	Lower pH	Potentially useful
Electrolytes	Osmolality	Not tested in COPD	Detection of impaired mucociliary clearance?
Cytokines	Inflammation	Not tested in COPD	Potentially useful; technically difficult
Peripheral blood			
Markers of oxidative stress	Oxidative stress	Activated neutrophils; reduced plasma TEAC	Potentially useful
Inflammatory mediators	Inflammation	Elevated	Potentially useful
Adhesion molecules	Inflammation	Elevated	Potentially useful

CO = carbon monoxide; **H_2O_2** = hydrogen peroxide; **NO** = nitric oxide; **PG** = prostaglandin; **TEAC** = Trolox equivalent antioxidant capacity.

patients with a lowered seizure threshold (e.g. history of head trauma, history of seizures).[33] The sustained-release formulation of bupropion reduces this risk.

3.1.2 Other Aids to Smoking Cessation

A variety of other therapies aimed at aiding smoking cessation are available. Many of these are either not proven to be effective or have undesirable side effects, while others, for example nicotine vaccination and glucose tablets, show some promise.

Lobeline is a partial agonist at nicotine receptors but is not effective as a nicotine withdrawal aid.[30] In contrast, although clonidine, a centrally-acting α_2-adrenoceptor agonist, is effective in aiding smoking cessation, it has marked adverse effects (e.g. sedation) which limit its usefulness.[36] Another approach to smoking cessation is nicotine vaccination, whereby anti-nicotine antibodies intercept the nicotine molecule before it reaches its receptor and, thereby, diminishes nicotine influx to the brain. In rodents, nicotine vaccination reduces brain nicotine concentrations and effects.[37,38] This approach is not dissimilar to abrupt smoking cessation and may have poor patient acceptability. Smoking aversion therapies, including silver acetate to produce an unpleasant taste while smoking, do not appear to be effective,[30,39] and neither do acupuncture[40] nor hypnotherapy.[41] Interestingly, chewing glucose tablets appears to be an effective aid to smoking cessation because it may substitute for the hunger cravings in some smokers.[42] Definitive clinical trials are required. Given their low cost, glucose tablets may be helpful to some smokers wishing to quit the habit.

3.1.3 Summary

Smoking cessation strategies are current first line treatment for COPD, and there are a variety of pharmacotherapeutic and other aids to smoking cessation available. Of these, bupropion is receiving the greatest attention. However, more simple approaches, such as glucose tablets, merit investigation. These interventions, together with support and counselling, are the greatest hope currently for control of and to slow disease progression in COPD.

3.2 New Bronchodilators

Bronchodilators are currently recommended as mainstay therapy for COPD[2] and improving these drugs is a reasonable approach to improving treatment. The principal activity of these drugs is to relieve symptoms and hence improve quality of life. However, it may be that long-acting bronchodilators have anti-inflammatory activity[27,43] and hence may influence disease progression.

3.2.1 Long-Acting Inhaled β_2-Adrenoceptor Agonists

The long-acting β_2-agonists salmeterol and formoterol have been reported to produce only relatively small improvements in FEV_1 or exercise capacity in patients with COPD, although they may reduce breathlessness and improve quality of life.[44,45] However, at optimal dosage, salmeterol has been found to be as effective as the short-acting anticholinergic drug ipratropium bromide.[46] It should also be noted that salmeterol has activity additional to that of bronchodilation, including protection against bacterial damage to the airway mucosa.[27] The clinical significance of the latter effect, in particular in regard to reduction of infective exacerbations, is not established.

3.2.2 Long-Acting Anticholinergics

Tiotropium bromide is a once-daily anticholinergic that is now available in some countries. Tiotropium bromide has kinetic selectivity for M_1 and M_3 muscarinic receptors, which mediate bronchoconstriction and mucus secretion, over the autoinhibitory M_2 receptors that reduce cholinergic neurotransmission.[47] Steady state improvements in FEV_1 are reached within 48 hours (i.e. after two inhalations), with improvements in forced vital capacity (FVC) increasing steadily over, and beyond, 1 week.[48] In short-term studies (4–13 weeks), once-daily tiotropium bromide was a superior bronchodilator than placebo or four-times daily ipratropium bromide.[49,50] In two 1-year studies of patients with moderate-to-severe COPD, tiotropium bromide improved lung function, symptoms, health status and, possibly rather surprisingly, reduced exacerbations.[51,52] Long-term tiotropium bromide was well

tolerated with the main undesirable side effect being dry mouth. Consequently, it is suggested[49] that if the cost is not prohibitive, bronchodilation in COPD could move towards once-daily tiotropium bromide.

3.2.3 Combination Bronchodilators

A combination of bronchodilators may be superior to a single drug. For example, many patients respond but remain symptomatic on single drugs. Potential reductions in dosage for drugs in combination may reduce any toxicity of the individual drugs. The combination may have a collaborative or synergistic effect. The latter may be linked to differential distribution of β_2 receptors and muscarinic receptors in the airways, which suggests different sites of action, or to crosstalk in their signal transduction pathways leading to a potentiation of effects. Recent short-term and long-term studies demonstrate that combinations of ipratropium bromide with either salmeterol or formoterol, or of oxitropium bromide with formoterol, are significantly better than the single drugs and are well tolerated.[53,54] The combination of ipratropium bromide and the long-acting β_2-agonist formoterol is superior to ipratropium bromide and short-acting salbutamol.[55] Studies assessing tiotropium bromide in combination are not reported but are awaited with interest.

An alternative bronchodilator combination therapy is with theophylline. A 12-week study of combined salmeterol and theophylline in 943 patients with COPD demonstrated significant improvements in lung function, symptoms and reduced exacerbations compared with either drug alone.[56] In contrast, a similar study of the same combination in 80 patients failed to show any additive effect.[57] There was no increase in adverse events for the combination treatments in either study. More studies are required to determine the effectiveness, or otherwise, of this bronchodilator combination.

3.2.4 Summary

COPD is defined by a lack of, or minimal, reversibility to inhaled bronchodilators.[2] Nevertheless, long-acting bronchodilators appear to reduce symptoms in COPD and may lessen frequency of exacerbations. Whether or not the beneficial activity is due only to bronchodilation or to additional anti-inflammatory effects is unclear. Combination bronchodilators appear to have therapeutic advantage over single drugs.

3.3 Combination Long-Acting β_2-Agonist and Corticosteroid

The combination of inhaled long-acting β_2-agonist and corticosteroid is effective therapy in asthma.[58] There is now interest in this combination therapy for COPD. Three months treatment with salmeterol and fluticasone improved the bronchodilator response to salbutamol above that of salmeterol alone in patients with COPD.[57] A number of other trials are currently underway.[59] The combination of fluticasone and salmeterol administered twice daily for 24 weeks to patients with COPD significantly improved lung function and the severity of dyspnoea when compared with the individual components and placebo.[60] A 12-month study in patients with COPD examined the use of a combination of budesonide and formoterol reporting FEV_1 improvement of 15% compared with placebo and an improvement in all symptom scores.[61] These reports suggest that combination therapies may have therapeutic benefit in COPD.

3.4 Sibenadet

Sibenadet (ARC-68397AA) is a dual agonist at dopamine D_2 receptors and β_2-adrenoceptors that combines neural inhibition and bronchodilator properties in the same molecule.[62] Therefore, it might be expected to be primarily beneficial for relief of symptoms, although anti-inflammatory activity was also claimed. Sibenadet was in phase III clinical development for COPD. Despite preliminary studies showing it was well tolerated and improved subjective indices of well being, current information suggests that sibenadet has been dropped from clinical development. Nevertheless, it remains of interest to determine whether similar dual agonists, or selective dopamine agonists (for example at $D_{1/5}$ or $D_{2/3/4}$ receptor types), would have benefit in COPD.

3.5 Tachykinin Receptor Antagonists

Sensory nerve activation with release of the neurotransmitters substance P and neurokinin A (NKA) [collectively termed tachykinins] may potentially contribute to the pathophysiology of COPD.[63,64] The expected principal activity of these drugs is uncertain, but might be relief of symptoms and, hence, improvements in quality of life. However, tachykinin antagonists may have additional anti-inflammatory activity if neurogenic inflammation contributes to pathophysiology in COPD. To date, clinical studies using tachykinin antagonists have been solely in patients with asthma and the results have, for the most part, been inconclusive. Nevertheless, there are theoretical reasons to believe that activation of sensory nerves and release of tachykinins may be more involved in pathophysiology of COPD than in asthma, particularly in mucus secretion and cough.[63] There are numerous tachykinin antagonists in development,[63] including selective compounds and compounds with dual activity, and it would be of interest to determine the effect of these on the 'bronchitic' component of COPD.

3.6 Neuroregulation

Anticholinergics are effective in management of COPD and tachykinin antagonists may also be effective, at least in part, in treatment of some aspects of COPD (see section 3.5 above). Consequently, 'complete' treatment of the neural component of COPD by blocking neurotransmitter receptors would entail use of multiple antagonist drugs. An alternative to this would be to inhibit neurotransmission, for example by inhibiting neurotransmitter release.[65,66] Morphine and other μ- or δ-opioid receptor agonists effectively inhibit both cholinergic and tachykininergic airway neurotransmission in a variety of experimental preparations. There have been many studies on the effect of opioids, including nebulised, oral and subcutaneous morphine, on breathlessness in patients with COPD, with equivocal results (reviewed by Janssens et al.[67]). However, there are some patients who do benefit markedly from opioid treatment, and the latter review recommends that oral or subcutaneous morphine or dihydrocodeine be tried in patients with severe dyspnoea and advanced disease, with the caveat that doctors and patients are aware of the possibility of respiratory depression, sedation and drowsiness. Other potential neuroregulatory compounds are agonists at cannabinoid CB_2 receptors and at γ-aminobutyric acid B ($GABA_B$) receptors, and activators of large conductance calcium-activated potassium (BK_{Ca}) channels, such as NS1619.[65] To our knowledge, none of these classes of compound are currently in development for treatment of COPD.

3.7 Protease Inhibitors

Proteolytic damage in the lung leading to emphysema is one of the pathophysiological features of COPD (see section 1). Balances between degenerative and regenerative processes, for example between proteases and antiproteases, contribute to regulation of the magnitude of damage. Inhibition of proteases and enhancement of antiproteases are emerging therapeutic strategies in COPD. The principal activity of these drugs would be expected to be a reduction in tissue damage with concomitant impairment of disease progression.

3.7.1 Neutrophil Elastase Inhibitors

Neutrophil elastase inhibitors (figure 3) have been suggested as therapeutic agents to prevent further damage in the lungs of patients with COPD.[68] α-1 Anti-trypsin is a serum inhibitor of elastase that protects the lung against proteolytic destruction and smokers with α-1 anti-trypsin deficiency will develop emphysema.[69] Consequently, these patients have undergone several trials involving augmentation of α-1 anti-trypsin. Although a 4-week trial reduced elastase activity and leukotriene B_4 (LTB_4) levels in sputum,[70] data from longer-term studies are required to determine the efficacy of this treatment on lung destruction and disease progression.

Non-peptide inhibitors of neutrophil elastase, for example sivelestat (ONO-5046), reduce inflammation in animal models of lung injury[71,72] and show promise in treatment of acute lung injury in humans.[73] Different classes of elastase inhibitor are being evaluated in preclinical and clinical trial, in-

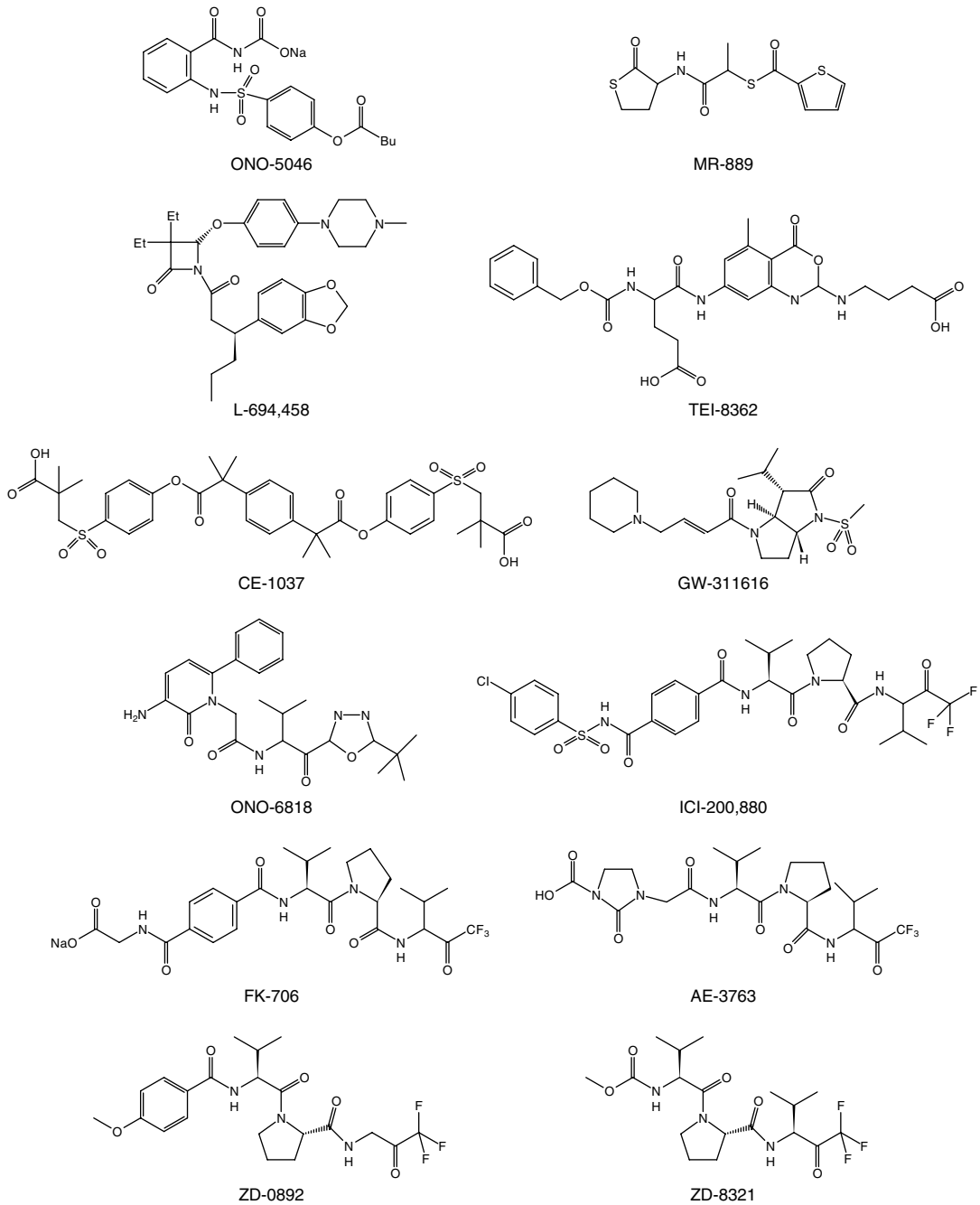


Fig. 3. Chemical structures of a selection of neutrophil elastase inhibitors.

cluding the acyl-enzyme inhibitors sivelestat, L-694,458, CE-1037, GW-311616, TEI-8362 and midesteine (MR-889), and the transition-state inhibitors ONO-6818, AE-3763, FK-706, ICI-200,880,

ZD-0892 and ZD-8321.[71] Since lung destruction in COPD is a slow, progressive process, long-term trials are needed to evaluate the effectiveness of elastase inhibitors in COPD.

3.7.2 Secretory Leukocyte Protease Inhibitor and Elafin

Secretory leukocyte protease inhibitor (SLPI) and elafin are endogenous inhibitors of neutrophil elastase.[74] Recombinant half-length SLPI stimulates anti-inflammatory cytokine expression in lipopolysaccharide (LPS)-stimulated macrophages[75] and, hence, may prove useful in inflammatory lung diseases. Pre-elafin, also known as trappin-2, inhibits neutrophil elastase-induced lung injury in hamsters, whereas elafin itself was ineffective.[76] Elastase peptide inhibitor, DX-890 (EPI-HNE-4) inhibits elastase-induced lung damage in rats[77] and may, therefore, be of therapeutic benefit in COPD. Interestingly, low molecular mass neutrophil elastase inhibitors also exhibit antimicrobial activity,[78] which may increase their therapeutic potential in COPD.

3.7.3 Matrix Metalloprotease Inhibitors

In emphysema, there is increased expression of the matrix metalloprotease inhibitors (MMPs) MMP-1, MMP-2 and MMP-9 in the lung.[12,79] Alveolar macrophages from patients with COPD release increased levels of MMP-9 compared with cells from healthy non-smoking individuals.[80] Therefore, inhibition of these proteases is being evaluated as a therapeutic target in COPD. In normal lung, the activity of MMPs is regulated by endogenous inhibitors termed tissue inhibitors of matrix metalloproteinases (TIMP).

The therapeutic potential of increasing levels of TIMP in the airways of patients with COPD has not been evaluated. Several MMP inhibitors including prinomastat, marimastat, rebimastat (BMS 275291), ONO-4817, MMI-166 and AE-941-neovastat (neovastat) are undergoing clinical trial in cancer and degenerative diseases such as arthritis[81-83] (figure 4). Little is known regarding the efficacy of MMP inhibitors in COPD. However bleomycin-induced pulmonary fibrosis in mice is inhibited by the MMP inhibitor batimastat (BB-94)[84] and ventilator-in-

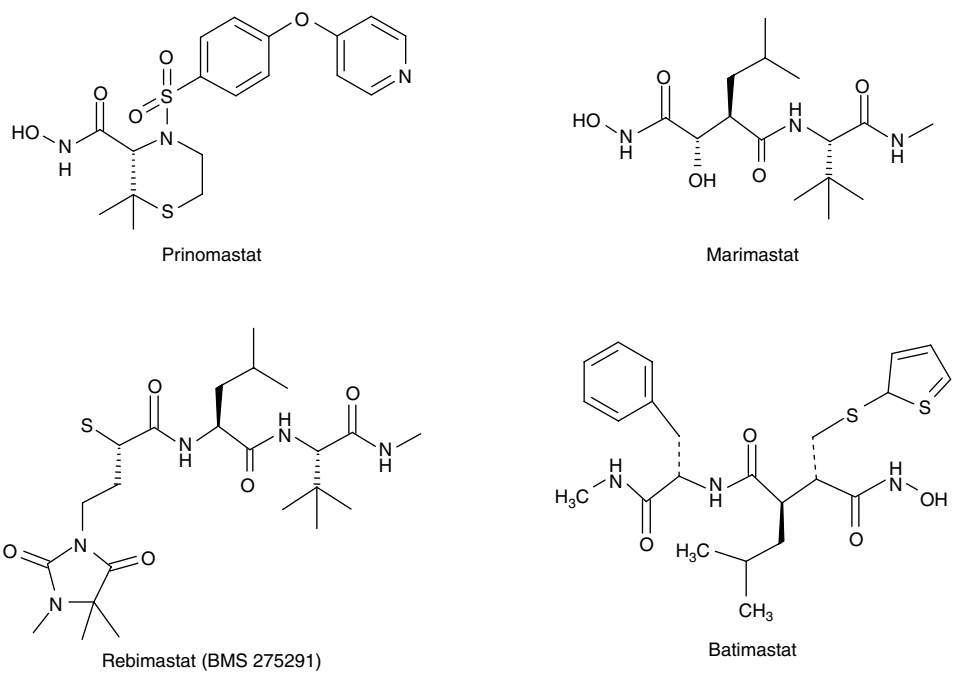


Fig. 4. Chemical structures of a selection of matrix metalloprotease inhibitors.

duced lung injury in rat lung is inhibited by prinomastat.[85] Furthermore, the broad-spectrum MMP inhibitor RS113456 inhibited a number of inflammatory indices in quartz-induced lung inflammation in mice,[86] while BAY 15-7496 abolished cigarette smoke-induced emphysema in mice.[87] Taken together, these data support the use of MMP inhibitors to reduce lung destruction in patients with emphysema. Interestingly, a number of small molecule inhibitors of tumour necrosis factor (TNF)-α converting enzyme (TACE) [see section 3.8.4] exhibit dual activity as MMP inhibitors.[88]

3.7.4 Cathepsin Inhibitors

Cathepsins L and S are members of the cysteine proteinase family, whereas cathepsin G is a serine protease.[74] Levels of cathepsins are elevated in the airways of patients with COPD and may contribute to parenchymal destruction and development of emphysema.[89] Cathepsins also cleave and inactivate SLPI, thereby increasing the proteolytic burden.[90] COPD is associated with an interleukin (IL)-13 promoter polymorphism,[91] which suggests a role for this cytokine in pathophysiology of COPD. Interestingly, inducible targeting of IL-13 in murine lungs causes emphysema that is inhibited by the cysteine proteinase inhibitors E-64 (figure 5) and leupeptin.[92] Alveolar macrophages from patients with COPD also release elevated levels of cysteine and serine proteases, and this can be inhibited by E-64 and BAY 39-6437, respectively.[93] Consequently, targeting cathepsins may be a therapeutic option in COPD.

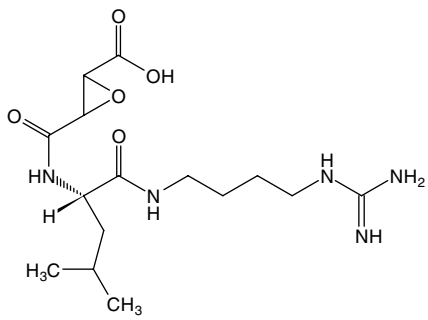


Fig. 5. Chemical structure of E-64, an inhibitor of cysteine proteases.

3.7.5 Summary

The relative contribution of the different proteases to pathophysiology of COPD is at present unclear. Similarly, the precise roles of the endogenous protease inhibitors in the development of COPD are also unknown. Consequently, the therapeutic impact of targeting any specific protease, or supplementing a specific antiprotease, remains to be elucidated. As a consequence, a broad-spectrum inhibitor, for example a non-selective MMP inhibitor, may have therapeutic advantage over more selective compounds.

3.8 New Anti-inflammatory Therapies

There are a number of possibilities for reducing pulmonary inflammation in COPD, either with new anti-inflammatory compounds such as phosphodiesterase (PDE) inhibitors or with selective drugs such as LTB_4 inhibitors. A range of these interventions is considered in the following subsections.

3.8.1 Alternatives to Corticosteroids

In marked contrast to asthma, the efficacy of corticosteroids in COPD is not established for routine management of stable disease.[2] There are a number of reasons for this lack of beneficial effect. In general terms, COPD is characterised by macrophage orchestration of neutrophilic pulmonary inflammation.[16] Corticosteroids do not inhibit the inflammation of COPD.[20] For example, dexamethasone does not inhibit IL-8 release by alveolar macrophages from patients with COPD[94] and, via upregulation of LTB_4 receptors (BLT1), can promote neutrophil activation and survival.[95] Consequently, alternative compounds with anti-inflammatory activity against neutrophils would have advantage in COPD. Another important effect of corticosteroids is on histone deactylation, which is a prerequisite for suppression of transcription of inflammatory genes.[96] Cigarette smoking inhibits the deacetylation and, thereby, both increases inflammation and decreases the anti-inflammatory potential of corticosteroids.[97] Consequently, drugs that reactivate histone deacetylase (HDAC) activity might be useful in combination with corticosteroids in suppressing inflammatory gene expression. In-

triguingly, low-dose theophylline activates HDAC.[98] In addition, we found recently that therapeutic doses of theophylline reduced sputum inflammatory cell count and neutrophil chemotaxis in patients with COPD.[99] This suggests that combination therapy with low-dose theophylline and a corticosteroid may be an effective anti-inflammatory strategy in COPD.

3.8.2 Phosphodiesterase (PDE)$_4$ Inhibitors

Phosphodiesterase enzymes degrade intracellular cyclic nucleotide signalling molecules, namely cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), with resultant limitation of cAMP- or cGMP-mediated responses, for example regulated inhibition of mediator release from inflammatory cells.[100] There are currently 11 families of PDE, of which PDE$_4$ is predominant in neutrophils, macrophages and CD8+ lymphocytes, indicating that selective inhibition of PDE$_4$ would inhibit the pulmonary inflammation of COPD.[101] Preclinical studies show that PDE$_4$ inhibitors suppress a wide variety of inflammatory effects both *in vitro* and *in vivo*, and clinical trials in COPD are underway.[102]

Two compounds in particular are currently in advanced development, namely roflumilast, for which there are as yet no full reports of the clinical data, and cilomilast. In a 6-week randomised, placebo-controlled trial involving 424 patients with moderate COPD, cilomilast significantly improved lung function with no more adverse effects than with placebo.[103] Larger clinical studies are currently underway. Despite being well tolerated in the latter study, there is concern that the effectiveness of PDE$_4$ inhibitors may be limited by adverse effects, most notably nausea and gastrointestinal upset.

Isoenzyme subtype selective inhibitors with an increased benefit-to-side-effect ratio are in development.[104] Another option is to explore the effects of inhibitors of other PDE isoenzymes for lung-selective anti-inflammatory activity, for example PDE$_7$.[105]

3.8.3 Adenosine A2a-Receptor Agonists

In experimental systems, activation of adenosine A2a-receptors mediates marked anti-inflammatory activity, both *in vitro* and *in vivo*.[106] Highly potent A2a-receptor agonists are in development, and can be 'tailored' to target neutrophils.[107] In a rat model of asthma, a new A2a-receptor agonist, CGS 21680, exhibited broad-spectrum anti-inflammatory activity.[108] Reports on the effect of these compounds in models of COPD are awaited with interest.

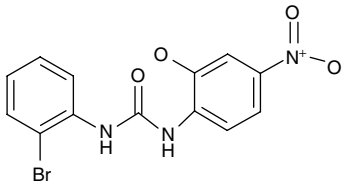
3.8.4 Tumour Necrosis Factor-α Inhibitors

TNFα may mediate a number of the pulmonary and systemic manifestations of COPD.[109,110] Consequently, inhibition of the effects of TNFα could have considerable benefit in COPD. Humanised monoclonal antibodies to TNFα (e.g. infliximab) and soluble TNFα receptors (e.g. etanercept) are effective in treatment of inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease, and their use could be extended to COPD.[111,112] The long-term usefulness of these interventions in patients may be limited by the development of antibodies and the inconvenience of repeated injections. An alternative target is TACE, which releases soluble TNFα and for which small molecule inhibitors are in development.[113]

3.8.5 Chemokine Inhibitors

Increased inflammatory cell migration and activation in the lung are key features of COPD. These processes are regulated by chemokines. Consequently, one strategy in the treatment of COPD would be to inhibit the effect of chemokines to recruit and activate leucocytes.[109] IL-8 is a potent neutrophil chemoattractant that is elevated in the airways of patients with COPD and correlates with disease severity.[10] IL-8 is a CXC chemokine that binds to CXCR1 and CXCR2 receptors, both of which are expressed on neutrophils and monocytes/macrophages.[114] Another CXC chemokine, growth regulated oncogene (GRO)-α, which also binds to the CXCR2 receptor, is also elevated in COPD[115] suggesting that these chemokines are important in the accumulation of neutrophils and monocytes/macrophages in the lungs of patients with COPD.

There are several non-peptide CXCR2 receptor antagonists in development (figure 6). For example, SB225002 is a selective CXCR2 antagonist that inhibits human neutrophil chemotaxis and IL-8-in-



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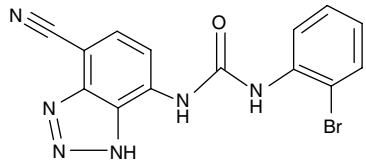

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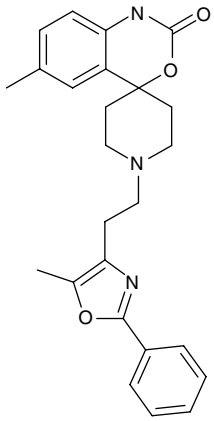
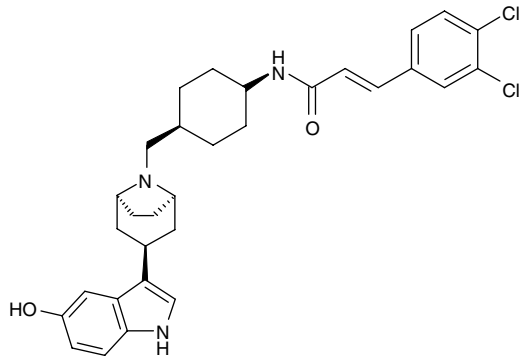


RS 504393



Conformationally restricted analogue 8

Fig. 6. Chemical structures of chemokine CXCR2 (upper panels) and CCR2 (lower panels) receptor antagonists. For details of analogue 8, see Witherington et al.[122]

duced neutropenia in rabbits.[116] Oral administration of an improved CXCR2 antagonist, SB 265610, also inhibits neutrophil migration in both a rabbit LPS-induced lung inflammation model[116] and a rat hypoxia model of lung injury.[117] Nicotinamide *N*-oxides and nicotinanilides are also CXCR2 antagonists that inhibit neutrophil chemotaxis.[118,119] Other non-peptide CXCR2 antagonists also inhibit neutrophil chemotaxis,[120,121] although there are no clinical trial data at present.

Monocyte chemoattractant protein (MCP)-1 is a C-C chemokine that is elevated in the airways of patients with COPD[115,123] and is a ligand for the CCR2 receptor. Small molecule antagonists for CCR2 receptors, including RS504393, are in development and have proved active in cell assays[122,124] (figure 6). In addition, selective anti-CCR2 antibodies inhibit macrophage recruitment into murine lungs following infection.[125]

Other strategies to block the effects of chemokines include use of monoclonal antibodies (mAb) to block specific chemokines. Monoclonal Ab, such as ABX-IL-8 that binds IL-8, are currently under development.[126]

The mechanism of recruitment of CD8+ lymphocytes into the lungs of patients with COPD is unclear. Expression of CXCR3 receptor and its ligand interferon-inducible protein 10 (IP-10) is elevated in peripheral airways of smokers and patients with COPD.[127] CXCR3 receptors are expressed on T cells,[114] and mediate CD8+ lymphocyte migration and activation.[128,129] Therefore, the CXCR3 receptor is a potential target for small molecule antagonists or antibodies.

One potential problem with targeting chemokines in COPD is the redundancy in the chemokine network such that inhibition of a single receptor or chemokine may not be sufficient to

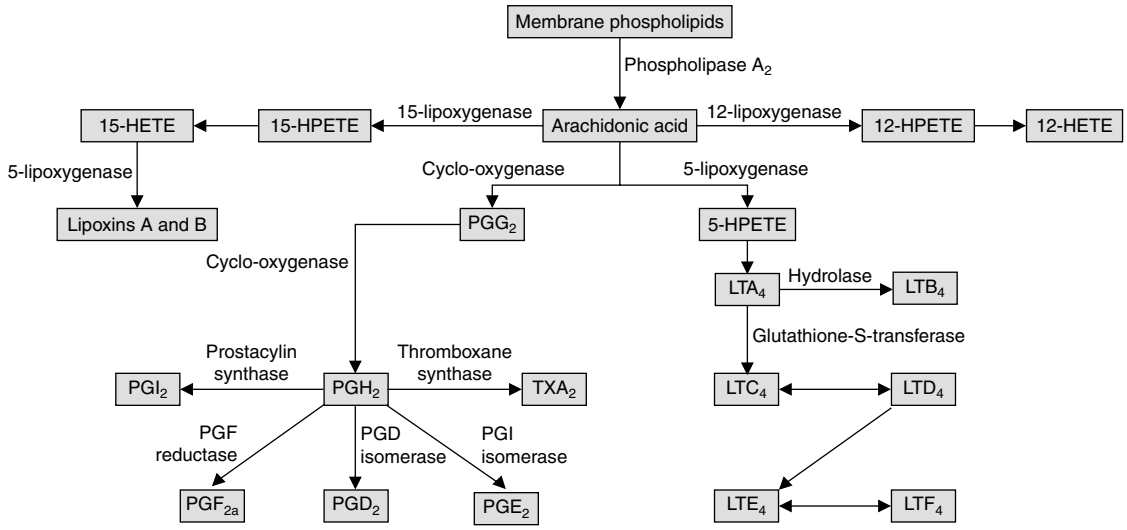


Fig. 7. Pathways of arachidonic acid metabolism leading to formation of eicosanoids. **HETE** = hydroxyeicosatetraenoic acid; **HPETE** = hydroperoxyeicosatetraenoic acid; **LT** = leukotriene; **PG** = prostaglandin; **TX** = thromboxane.

block the inflammatory response. Nonetheless, knock-out mouse models and animal studies with small molecule antagonists strongly suggest that there is a rationale for inhibiting the chemokine network,[130] thus leading to development of new drugs for treatment of COPD.

3.8.6 Interleukin 10

IL-10 is an endogenous anti-inflammatory cytokine.[131] It inhibits secretion of a number of proinflammatory cytokines by inflammatory cells, for example IL-8 and TNFα from macrophages. IL-10 also increases the antiprotease-protease ratio by downregulating MMPs and increasing TIMP levels.[132] There may be reduced IL-10 activity in COPD, with consequent reduction in endogenous anti-inflammatory 'shield' because patients have reduced IL-10 levels in their sputum.[133] Subcutaneous IL-10 is in clinical development for inflammatory diseases, including rheumatoid arthritis and inflammatory bowel disease.[134] Although the treatment is well tolerated by patients, there may be problems with haematological adverse effects. Development of synthetic agonists at IL-10 receptors may be a therapeutic option.

3.8.7 Leukotriene B_4 Inhibitors

LTB_4 is a potent neutrophil chemoattractant and its concentrations are elevated in the airways of patients with COPD.[13] LTB_4 is also extends neutrophil survival.[95] LTB_4 is synthesised by 5-lipoxgenase (5-LO) [figure 7], and 5-LO inhibitors might be useful in attenuating pulmonary neutrophilia in COPD. 5-LO inhibitors have been in development for many years,[135] but the incidence of adverse effects is limiting development of these compounds. LTB_4 exerts its effects via interaction with BLT1 and BLT2 receptors.[136] BLT1 receptors are localised predominantly to monocytes and granulocytes (including neutrophils), with BLT2 receptors localised to T cells. BLT1 receptor antagonists are in development, including SC53228, CP105696, amelubant (BIIL284), LY29311 and SB201146.[137] Both the latter compounds inhibit neutrophil chemotactic activity of sputum from patients with COPD.[138,139] Thus, LTB_4 antagonists may inhibit pulmonary neutrophilia and consequent lung damage in COPD.

3.8.8 Eicosanoid Inhibitors

Eicosanoids is a collective term for the arachidonic acid-derived inflammatory mediators prostaglandins, thromboxanes, leukotrienes and iso-

prostanes (figure 7).[140] These mediators generate a variety of responses in the airways, including bronchoconstriction, mucus secretion, plasma exudation, neural stimulation and inflammatory cell activation, most of which have a particular involvement in asthma.[141] In contrast, the role of eicosanoids in the pathophysiology of COPD is currently unclear. However, prostaglandin H synthase 2 (also known as cyclooxygenase 2 or COX-2) is upregulated in the airways of patients with COPD.[142] Consequently, exploration of the effects of selective COX-2 inhibitors, for example celecoxib, rofecoxib, valdecoxib and etoricoxib,[143] as well as inhibitors of other eicosanoids, in COPD would be of interest.

3.8.9 Adhesion Molecule Inhibitors

The sequential interaction between specific adhesion molecules on inflammatory cells and the pulmonary endothelium mediates the recruitment of monocytes, CD8+ lymphocytes and neutrophils into the lung of patients with COPD. Consequently, inhibition of these molecules is an option for reducing inflammatory cell influx into the lung, with consequent reduction in pulmonary inflammation in COPD.[144] Bimosiamose (TBC1269), a mimetic of sialyl-Lewis^x, an adhesion molecule on neutrophils, inhibits neutrophil adhesion by interfering with adhesion to E-selectin on endothelial cells.[145] Another adhesion molecule, Mac-1, is a potential target because its expression is increased on neutrophils from patients with COPD.[146] One potential problem with inhibition of neutrophil-related adhesion molecules is that suppressing pulmonary neutrophilia may increase susceptibility to infection in patients with COPD, who are often already at risk.

3.8.10 Nuclear Factor-κB Inhibitors

Nuclear factor κB (NF-κB) regulates inflammation by regulating the expression of inflammatory cytokines such as TNFα, chemokines such as IL-8, and MMPs.[147] NF-κB may be involved in the pathophysiology of COPD by synergistic actions between the effects of cigarette smoke and latent adenoviral infection.[148,149] Consequently, inhibition of NF-κB activity may be a therapeutic option in COPD.

There are a number of possibilities for inhibition of NF-κB.[150] These include gene transfer of the endogenous NF-κB inhibitor, IκB, and development of drugs that either inhibit degradation of IκB or that inhibit intracellular regulators of NF-κB activity, including IκB kinases (IKKs), NF-κB-inducing kinases (NIK) or IκB ubiquitin ligase. A number of these drugs are in development. For example, hypoestoxide, a naturally-occurring diterpene from *Hypoestes rosea*,[151] and (–)-epigallocatechin-3-gallate, a green tea polyphenol,[152] are IKK inhibitors that could act as prototypic molecules for development of potent and selective synthetic compounds. Further developments include NF-κB 'decoy' oligonucleotides that inhibit nuclear translocation of NF-κB.[153] However, it should be noted that an adverse effect of long-term inhibition of NF-κB could be immunosuppression.

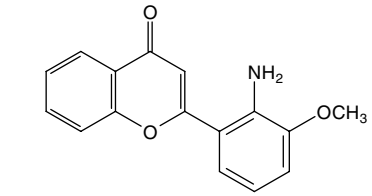
3.8.11 Inducible Nitric Oxide Synthase Inhibitors

Exhaled nitric oxide (NO) is elevated in patients with COPD,[154] together with an increase in reactive nitrogen species in the airways[155] and exhaled breath condensate.[156] The increased NO is considered to be derived from increased expression of inducible nitric oxide synthase (iNOS), which can react with superoxide to form peroxynitrite. Peroxynitrite can nitrate proteins and alter their function. Therefore, specific iNOS inhibitors might be of benefit in COPD.

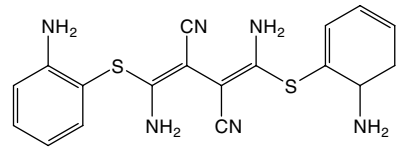
Several selective small molecule iNOS inhibitors are effective in animal models of inflammation, including GW273629,[157] thienopyridines[158] and L-*N*(6)-(1-iminoethyl)lysine (L-NIL) or L-NIL-5-tetrazole-amide.[159] A single dose of L-NIL reduces exhaled NO from both asthmatic and healthy volunteers,[160] which suggests that iNOS inhibitors would be of therapeutic benefit in airway inflammatory diseases, including COPD.

3.8.12 Mitogen Activated Protein Kinase Inhibitors

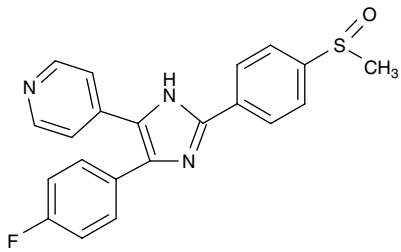
Mitogen activated protein (MAP) kinase (MAPK) signal transduction pathways are activated in response to mitogenic stimuli and environmental stresses. They influence cell functions as diverse as proliferation, cell cycle arrest, differentiation and apoptosis, and may play a key role in chronic in-



PD 98059



U 0126



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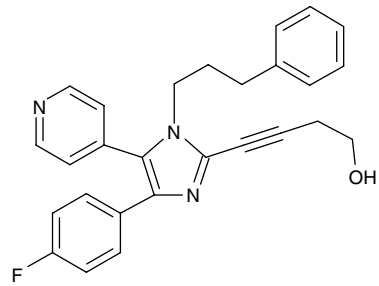
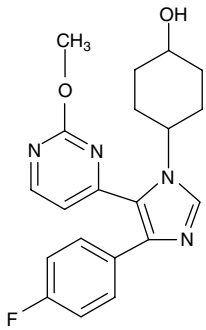


RWJ 67657



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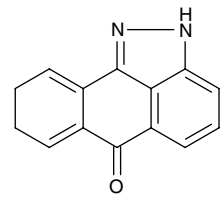


SP 600125

Fig. 8. Chemical structures of inhibitors of the mitogen activated protein kinase pathways. MEK inhibitors (upper two structures), p38 inhibitors (SB 203580, SB 239063, RWJ 67657) and a JNK inhibitor (SP 600125). **JNK** = c-Jun amino-terminal kinase; **MEK** = mitogen activated protein kinase kinase.

flammation.[161] Three distinct MAPKs have been identified in mammalian cells, namely extracellular signal-regulated kinase (ERK), c-Jun amino-terminal kinase/stress-activated protein kinase (JNK/SAPK), and p38 MAP kinase. All three MAP kinase pathways are targets for small molecule inhibitors (figure 8). Activation of the ERK pathway leads to activation of the transcription factors activator protein (AP)-1 and NF-κB and, hence, many inflammatory genes including IL-8.[162] With regard to COPD, neutrophil elastase stimulates the ERK pathway in bronchial epithelial cells and lung fibroblasts.[163] Specific inhibitors of the upstream MAP kinase kinase (MEK), PD 98059 and U 0126, inhibit these inflammatory effects.

JNK also plays an important role in the activation of AP-1. Unfortunately, detailed study of the role of JNK in inflammation has been hampered by lack of specific inhibitors and has largely depended on knockout mouse models.[164,165] However, SP600125, an anthrapyrazonolone JNK inhibitor, has recently been developed.[166] SP600125 inhibits

c-fos phosphorylation and the expression of pro-inflammatory genes in human CD4+ lymphocytes and monocytes, and LPS-induced TNFα expression in mice. Furthermore, SP600125 inhibits MMP expression in adjuvant-induced arthritis in rats.[167] These combined observations reinforce the suggestion that inhibition of JNK could have therapeutic potential.

Activation of the p38 MAP kinase pathway is implicated in inflammatory cytokine production[168] and the potential therapeutic effects of inhibitors of p38 are considerable. Use of selective inhibitors of p38 MAP kinase, such as SB 203580, shows that p38 MAP kinase regulates iNOS and COX-2 expression in murine macrophages.[169] However, little is known about activation of p38 MAP kinase and its role in regulation of human macrophage function. The possibility that p38 MAP kinase inhibitors might be beneficial in COPD has arisen from studies examining the effect of SB 239063 on LPS and bleomycin models of inflammation and pulmonary fibrosis.[170] SB 239063 reduced neutrophil infiltration, IL-6 expression, and MMP-9 activity in the airways. Oral administration of RWJ 67657, a pyrindinyl imidazole inhibitor of p38 MAP kinase, inhibited LPS-induced increases in plasma IL-6, IL-8 and TNFα in healthy human volunteers.[171] More recently, another p38 MAP kinase inhibitor, doramapimod (BIRB 796), inhibited a number of LPS-induced inflammatory responses in healthy volunteers.[172] There was no drug-related toxicity, which is surprising since p38 MAP kinases are involved in so many intracellular signalling processes.[161]

3.8.13 Phosphoinositide 3-Kinase Inhibitors

Phosphoinositide 3-kinase (PI3K) catalyses the production of phosphatidylinositol-3,4,5-triphosphate which initiates a number of cytosolic events leading to cell growth, entry into the cell cycle, cell migration and cell survival.[173] A number of these events are proinflammatory. For example, sustained exposure to hydrogen peroxide increases expression of proMMP-2 via a PI3K signalling pathway,[174] and PI3Kγ in neutrophils regulates their migration and respiratory burst.[175] Consequently, selective PI3K inhibitors could suppress neutrophil- and MMP-derived lung damage in COPD.

3.8.14 Summary

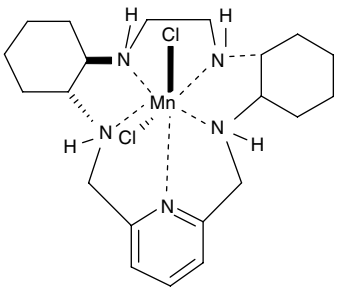
The relative contribution of the different inflammatory processes to the pathophysiology of COPD is at present unclear. Consequently, the therapeutic impact of targeting any specific aspect of inflammation remains to be elucidated. As a consequence, broad-spectrum anti-inflammatory agents, or inhibitors of intracellular signal transduction pathways that are pivotal to the inflammatory process, may have therapeutic advantage over more selective compounds.

3.9 Retinoids

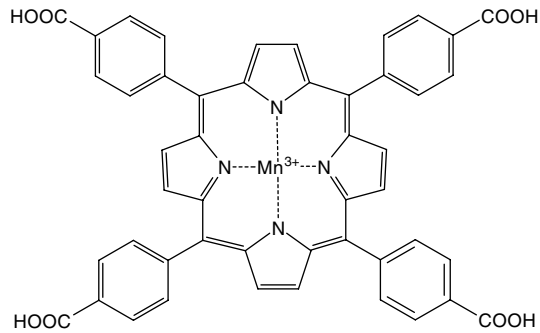
There is growing interest in retinoids as treatment for the alveolar destruction in COPD.[176] The principal activity of these compounds is expected to be reversal of tissue damage leading to halting of disease progression and improvement in lung function, and they represent the only current hope for a 'cure' for the emphysematous component of COPD. In rats, retinoic acid reverses elastase-induced emphysema,[177] suggesting that such compounds would encourage lung regeneration in COPD. All *trans*-retinoic acid inhibits MMP-9 and enhances TIMP-1 expression in bronchoalveolar lavage (BAL) cells from patients with COPD.[178] However, in a recent pilot study in patients with emphysema, 3-months treatment with all *trans*-retinoic acid did not improve lung function or structure, as measured by computed tomography (CT) scan.[179] Nevertheless, the drug was well tolerated, and this has encouraged planning of further trials with either increasing dosages or longer duration of treatment.

3.10 Antioxidants

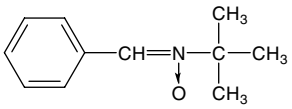
COPD is associated with increased levels of oxidant stress, and anti-oxidant therapy may combat this disease aspect and may impair disease progression.[180] *N*-acetylcysteine (NAC) is a widely used mucolytic agent that has antioxidant properties and acts as a substrate for synthesis of glutathione, the most abundant endogenous antioxidant[181] (figure



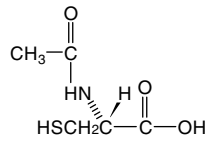
M40403



MnTBAP



N-*tert*-butyl-α-phenyl nitrone



N-acetylcysteine

Fig. 9. Chemical structures of antioxidants. Superoxide dismutase mimetics (upper two panels). *N*-tert-butyl-α-phenyl nitrone is a spin trap compound. *N*-acetylcysteine is an antioxidant with mucolytic properties.

9). Furthermore, long-term administration of NAC reduces exacerbations in patients with COPD[182] and decreases levels of markers of oxidative stress (e.g. hydrogen peroxide) in the exhaled breath condensate of patients with COPD.[183] Despite these antioxidant effects, NAC is not currently recommended in management of COPD.[2] A large multicentre trial of NAC on lung function, exacerbation rate, quality of life and cost utility in patients with moderate-to-severe COPD has been initiated to provide objective data to aid recommendations for treatment.[184] Results are expected in approximately 2 years time. The unpleasant taste of NAC compromises patient compliance and other anti-oxidant treatments are currently under investigation.

3.10.1 Superoxide Dismutase Mimetics

Manganese superoxide dismutase (MnSOD) is an endogenous cellular antioxidant. Gene therapy by introducing the *MnSOD* gene into mice protects against radiation-induced lung damage.[185] There are now several nonpeptidyl SOD mimetics such M40403,[186] which reduces tissue damage in animal models of inflammation,[187] and MnTBAP, which inhibits bleomycin-induced pulmonary fibrosis in mice[188] (figure 9). Another SOD mimetic, AEOL–10113, inhibits LPS-induced TNFα production by murine macrophages and interferon (IFN)-γ production by murine T cells *in vitro*,[189] which suggests that these compounds exhibit anti-inflammatory effects.

3.10.2 Spin Trap Compounds

Other antioxidants include electron spin trap agents such as *N*-tert-butyl-α-phenylnitrone (figure 9) that protect against hyperoxia-induced oxidative stress in mice.[190] Other compounds, for example the pyrrolopyrimidine U101033E, scavenge hydroxyl radicals and, hence, protect tissues from oxidative injury.[191] However, to our knowledge, none of these compounds are in clinical development for COPD.

3.11 'Mucoactive' Drugs

Hypersecretion of airway mucus is a pathophysiological feature of COPD and contributes to morbidity and mortality, especially in patients prone to chest infections[192] (figure 10). The hypersecre-

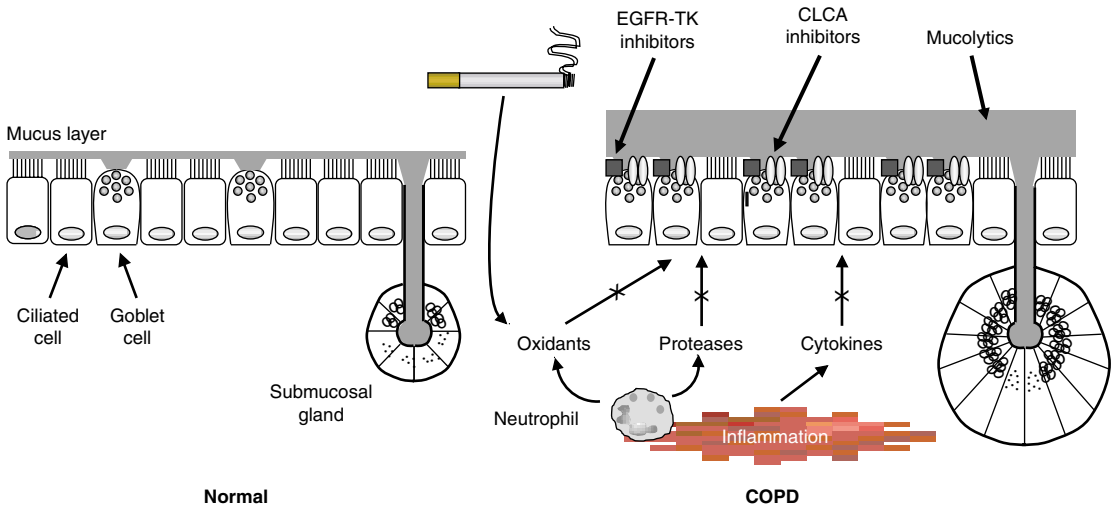


Fig. 10. Targets for inhibition of mucous hypersecretion in chronic obstructive pulmonary disease (COPD). The normal airway has a thin layer of mucus, many ciliated cells, few goblet cells and submucosal glands. In COPD there is a thicker mucus layer associated with increased secretion, the latter associated with goblet cell hyperplasia and submucosal gland hypertrophy. Oxidants, proteases and cytokines regulate goblet cell hyperplasia, although their relationship to gland hypertrophy is unclear. Goblet cell hyperplasia is associated with increased expression of epidermal growth factor receptors (EGFR; small square boxes) and calcium activated chloride channels (CLCA; two small ellipses close together). Antioxidants, antiproteases, cytokine inhibitors (X), EGFR tyrosine kinase (EGFR-TK) inhibitors, CLCA inhibitors and mucolytic drugs will each inhibit different aspects of mucous hypersecretion.

tion is associated with submucosal gland hypertrophy and goblet cell hyperplasia; the latter is currently considered the predominant feature of the hypersecretory phenotype. Aiding mucus clearance can alleviate the effects of mucous hypersecretion and, thereby, relieve symptoms. Reversal of the goblet cell hyperplasia may have long-term benefit on disease progression (figure 10).

3.11.1 Mucolytics

'Thinning' of viscous airway mucus with mucolytic drugs is one way of improving clearance, both by cough and by mucociliary transport. However, although numerous mucolytic drugs are available worldwide, their effectiveness in treatment of stable COPD has not been established.[193] Consequently, they are not generally recommended in current guidelines on management.[2] However, two rigourous meta-analyses demonstrate that treatment for at least two months with mucolytic drugs, especially *N*-acetylcysteine, reduces exacerbations and days of illness.[182,194] Cost-effective treatment would be in severe patients.[195] However, it is uncertain whether the beneficial effects of *N*-acetylcysteine (or the other drugs) are due to its mucolytic or antioxidant properties (or both).

3.11.2 Purinoceptor $P2Y_2$ Agonists

Activation of purinoceptor $P2Y_2$ receptors in the airway epithelium increases mucociliary clearance.[196] This effect is mediated via a combination of increased hydration of the mucus layer, via stimulation of chloride and water secretion, elevation of ciliary beat frequency, increased mucin secretion from goblet cells and increased surfactant secretion from type II pneumocytes. The natural ligand for these receptors is uridine triphosphate (UTP). However, UTP is rapidly metabolised and synthetic agonists are being developed.[197] One of these, diquafosol (INS365), is in clinical trial for chronic bronchitis.[196] The challenge to efficacy of $P2Y_2$ agonists in COPD is the balance between the benefits of enhanced mucus clearance, with expected improvements in symptoms and possibly exacerbation rates, and patient tolerability of short-term increases in cough and sputum production.

3.11.3 Drugs to Reverse the Hypersecretory Phenotype

Experimental studies have delineated many of the pathways that induce airway goblet cell hyperplasia and increased mucin synthesis.[198,199] The newest of these include epidermal growth factor receptor (EGFR) tyrosine kinase, calcium activated chloride channels (CLCA) and the antiapoptotic factor Bcl-2. Consequently, inhibitors of these and other factors may have long-term benefit on mucous hypersecretion in patients with COPD. Selective inhibitors of EGFR tyrosine kinase, such as gefitinib (ZD1839) are in clinical trial as anti-cancer agents but not yet for COPD. In contrast, talniflumate (MSI-1995), a putative inhibitor of the human CLCA1 channel, is currently undergoing clinical trials for respiratory disease.

3.11.4 Summary

Mucus hypersecretion contributes to pathophysiology of COPD most especially in patients who are prone to respiratory tract infections and possibly in elderly patients.[192] However, it is unlikely that compounds directed specifically against mucus hypersecretion will have therapeutic advantage over general anti-inflammatory therapy.

3.12 Defensins

Defensins are small cationic proteins with broad spectrum antimicrobial activity but which also have a role in innate immunity.[200] Patients with COPD who have a genetic variant in β-defensin-1 have a predominant chronic bronchitis phenotype with excessive sputum production,[201] presumably as a result of reduced antibacterial capacity. In addition, neutrophil defensins may be involved in epithelial repair.[202] Consequently, defensin-enhancing compounds would be expected to promote host defence and lung repair in COPD. However, it should be noted that neutrophil defensins may also cause injury and stimulate epithelial cells to produce neutrophil chemotactic factors.[203] Consequently, modulation of defensin expression should be viewed with caution.

4. Conclusions

Current treatment of COPD is symptomatic, with no drugs able to halt the relentless progression of airflow obstruction. Consequently, improved therapeutic interventions are required. However, only relatively recently has there been sufficient interest in COPD to generate the research data needed for better understanding of the airway inflammation and alveolar destruction that characterise this severe condition. Delineation of pathophysiological mechanisms has identified new disease targets, with consequent development of novel compounds with therapeutic potential. New drugs to aid smoking cessation are central both to reducing the incidence of COPD and to inhibit disease progression. Other therapeutic options include improvements to existing therapies, for example long-acting rather than short-acting bronchodilators, as well as combination therapy. There are new antiproteases, new anti-inflammatory interventions, new anti-hypersecretory compounds, and a range of selective inhibitors of specific extracellular mediators and intracellular signal transduction molecules. Many of these compounds are ready for investigating in the clinic. If asked to speculate on the most promising new therapy, we would suggest a combination of an antiprotease, for example a broad spectrum MMP inhibitor, and a retinoid. This combination might be expected to inhibit lung destruction and stimulate alveolar regeneration, leading to long-term reversal of symptoms and improvements in lung function and, hence, quality of life.

The challenge to transferral of new drugs from preclinical research to clinical management of COPD is the design of appropriate clinical trials. The current scarcity of well-characterised surrogate markers limits interpretation of the effect of drugs in short-term trials. At present, long-term studies in large numbers of patients will be needed to monitor changes to disease progression. Effective delivery of these new compounds to the lung will also have to be evaluated because it may be different than in asthma. A recent meta-analysis of the effectiveness of delivery of bronchodilators in patients with COPD showed little difference between inhaler de-

vices.[204] Similarly, there was little difference in conventional delivery of corticosteroids or bronchodilators to the airways of patients with asthma or COPD.[205] However, the new compounds may require specific delivery devices for optimal effect. Nevertheless, despite these problematic considerations, a number of new compounds are undergoing clinical trials, the results of which are awaited with great interest, not only in the hope of improvements to pharmacotherapeutic management of COPD but also as proof-of-concept to further understand of pathophysiology of inflammatory lung diseases.

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