New Drug Therapies for COPD

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KEYWORDS

• COPD • Pharmacology • Bronchodilators • Antiinflammatory drugs • Antioxidants
• Protease inhibitors • Fibrosis • Lung regeneration

KEY POINTS

- It is proving a major challenge to produce new effective drugs for chronic obstructive pulmonary disease (COPD).
- Improved understanding of COPD pathophysiology, novel clinical trial designs, endpoints, imaging and biomarkers, noninvasive sampling, patient stratification, challenge models, and clinical trial designs is necessary to facilitate development of new drugs for COPD.
- Smoking cessation is fundamental and new approaches include antinicotine vaccines, cannabinoid receptor antagonists, and dopamine D3 receptor antagonists.
- Novel combinations of inhaled bronchodilators and corticosteroids are being introduced.
- Antiinfective drugs are important, with a recent focus on the viruses that commonly cause exacerbations.
- Antiinflammatory drugs are in development, including kinase inhibitors, chemokine receptor antagonists, inhibitors of innate immune mechanisms, and statins.
- Biologics used in rheumatoid diseases may also have a role; anti-IL-6 (tocilizumab) is promising.
- Antioxidants, mucolytics, antiproteases, and antifibrotics are all under active development.
- Aids to lung regeneration have potential to alter the natural history of COPD, including retinoids and mesenchymal stem cell therapy.

INTRODUCTION

New drugs for chronic obstructive pulmonary disease (COPD) have been largely based on existing classes of current therapies, involving new inhaled combinations of long-acting muscarinic antagonists (LAMAs), long-acting beta2-agonists (LABAs), and inhaled corticosteroids (ICS) (**Table 1**).[1] A useful reference source for new COPD medicines in development is the Pharmaceutical Research and Manufacturers of America (www.phrma.org). There is also an excellent series of topical articles on "The COPD Pipeline" provided by Nicholas J. Gross in the journal *COPD* (22 articles as of mid-2012). Although recent increases in knowledge of the inflammatory components contributing to COPD have led to many new targets for COPD treatment,[2] very few new classes of drugs are being licensed, making this a controversial area for new drug development.[3]

Clinical studies with new drugs for COPD have been difficult for several reasons[4]:

- The immunopathology of COPD is complex and variable (**Fig. 1**). Cigarette smoke has widespread effects beyond the respiratory system, involving the large airways (bronchitis), small airways (bronchiolitis), lung interstitium (emphysema and interstitial lung disease), pulmonary vasculature (pulmonary artery hypertension), and systemic complications.[5–7] Pathologic features such as mucus

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Table 1
Drugs to aid smoking cessation

Current treatments	First-line: • Nicotine replacement therapy • Bupropion • Varenicline (partial agonist for $\alpha 4\beta 2$ nicotinic acetylcholine receptors) Second-line: • Nortriptyline • Clonidine
New approaches	• Antinicotine vaccines: NicVAX, SEL-068 • Electronic cigarettes • Novel nicotine formulations: eg, inhaled aerosolized nicotine (ARD-1600) • Nicotine partial agonist: cytisine • Cannabinoid receptor 1 antagonists: taranabant • Dopamine D3 receptor antagonists: GSK598809 • Monoamine oxidase inhibitors: selegiline

hypersecretion, small airway fibrosis, and lung destruction (emphysema) are notoriously difficult to reverse with drugs.

- COPD may be caused by the innate immune response to oxidants and microbes, with accelerated aging and autoimmune features. Bacteria and viruses may become more important in more severe COPD.[8]
- Preclinical models need to be improved for in vitro and in vivo (animal) studies.[9]
- COPD patients are often elderly, frail, and have multiple diseases associated with smoking. Cardiovascular diseases, metabolic syndrome, and malignancies may be present. Hence, these patients may be on a variety of medications. These factors may mean that it is difficult to recruit patients when there are strict entry criteria.
- A new therapy is more likely to be effective when used early in the natural history of COPD, before irreversible disease has occurred. However, delays in diagnosis are common and the disease is notoriously underdiagnosed.
- Small proof-of-concept studies in humans are poorly predictive of efficacy in clinical practice. Some clinical development plans for COPD have been discontinued after large-scale clinical trials, including Viozan, recombinant DNase (Pulmozyme), and cilomilast (Ariflo).
- Challenge models looking at the effects of cigarette smoke,[10] ozone, or lipopolysaccharide have been developed. On the other hand, smoking cessation is part of COPD patient care, providing an interesting situation of withdrawal of the stimulus.[10–12] As a model of COPD exacerbations, live experimental challenge can be performed with human rhinovirus (HRV) in patients with COPD.[13] Novel large scale clinical trial designs for COPD are also needed.[14]
- There is a need to identify and validate endpoints that can capture the considerable heterogeneity of pulmonary and systemic features. Forced expiratory volume in 1 second (FEV_1) is a commonly used endpoint in most clinical COPD trials. However, recently, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study has demonstrated that the annual rate of change in FEV_1 in COPD is highly variable in different subjects.[15] In addition, given that the FEV_1 declines very slowly during the natural history of COPD, an estimated 1000 subjects per sample group must be followed for a minimum of 3 years to have sufficient power to detect a 50% improvement in disease progression.[16]
- Phenotypes of COPD need to be defined and validated in order to tailor drugs to individual patients; it is becoming increasing clear that "one size does not fit all" in COPD.[17] This was demonstrated clearly by recent trials such as the National Emphysema Treatment Trial (NETT), which showed a mortality benefit in only a subgroup of patients undergoing lung volume reduction surgery.[18] Of special interest are approaches that use CT.[7,19]
- Samples of varying invasiveness and from different compartments are required. Sputum gene expression looks promising,[20] although exhaled breath condensate has been disappointing,[21] and there are few studies with exhaled nitric oxide.[22] However, assessment by proteomics of epithelial lining fluid from the airway of COPD patients is feasible,[23] and bronchial brushings can be carried out to assess gene expression.[24]
- There is a need to identify and validate biomarkers that may predict potential responders for specific therapy.[25–27] Gene expression or transcriptomics of the airway in COPD is of special interest.[20,24]
- Current therapy is merely palliative; it is becoming clear that there must be more focus on preventative and regenerative therapies. However, these are ambitious targets for new drugs.

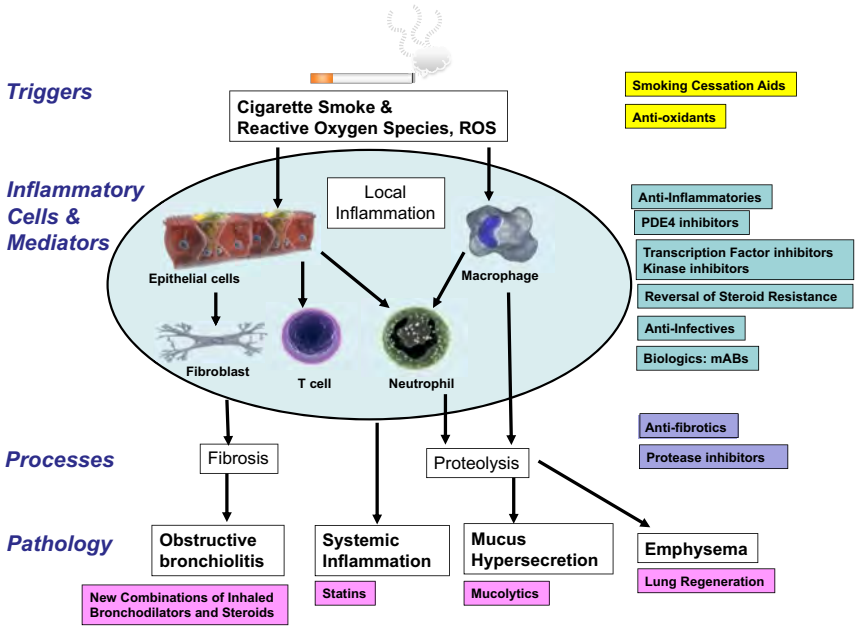

Fig. 1. Pathology, targets, and new drugs for COPD. An overview of some of the pathophysiologic processes involved in COPD, highlighting potential therapeutic targets for novel therapies. Cigarette smoke contains reactive oxygen species, particulates, and chemicals, which lead to a range of inflammatory effects: macrophage, epithelial cell, and CD8+ T cell activation. These cells in turn release neutrophil chemotactic factors. Numerous local inflammatory mediators are then released, along with proteases, which break down connective tissue in the lung, causing emphysema. Proteases are also important in stimulating mucus hypersecretion, which may manifest as chronic bronchitis. Profibrotic mediators are also released by epithelial cells, contributing to fibroblast proliferation and small airway fibrosis. Novel therapies include those aimed at local as well as systemic inflammation. The most ambitious target is to regenerate lung tissue in response to emphysema. mABs, monoclonal antibodies; PDE4, phosphodiesterase 4.

DRUGS TO AID SMOKING CESSATION

Smoking cessation is the first priority in the management of a COPD patient who smokes. To date, it is the only intervention shown to convincingly reduce the accelerated decline in pulmonary function and improve long-term prognosis (see **Fig. 1**, **Table 1**).[28,29] Success in quitting is increased by behavioral support in addition to a range of pharmacotherapies.[30] However, a recent systematic review has concluded that, in contrast to non-COPD smokers, neither the intensity of counseling nor the type of antismoking drug make a significant difference in smoking cessation results.[31]

The most widely used agents include nicotine replacement (in a variety of preparations), antidepressants such as bupropion and nortriptyline, and nicotine partial receptor agonists such as varenicline (which remains the most efficacious monotherapy for smoking cessation[32]). Cytisine, a partial agonist that binds with high affinity to the $\alpha 4\beta 2$ subtype of the nicotine acetylcholine receptor is effective in sustaining abstinence at 12 months.[33] Other approaches currently under investigation include nicotine vaccines (with the associated benefits of infrequent dosing and prolonged effect); however, large trials of the current front-runners (NicVAx and NIC002) have been disappointing.[34,35] Both agents stimulate the production of antibodies that bind to nicotine and prevent it from crossing the blood-brain barrier. Novel nicotine products that can be given via the inhaled, topical (in the form of a spray) or orally dissolving film route are also under development, and detailed in a recent review.[36] Compounds are also being explored to target other neurotransmitters implicated in nicotine dependence such as dopamine, γ- aminobutyric acid (GABA), and glutamate.[37] These include trials of monoamine oxidase inhibitors such as selegiline.[36] The cannabinoid receptor system is thought to inhibit indirectly the dopamine-mediated rewarding properties of food and tobacco, and cannabinoid receptor 1 antagonists are undergoing evaluation, although trials have so far been disappointing.[36] There is increasing popularity of electronic cigarettes, which deliver nicotine via an electronic

battery-powered device resembling a cigarette, despite no formal demonstration of the efficacy and safety of such devices. These devices have the potential advantage of tackling the psychological and physical components of nicotine addiction; therefore, several large prospective studies are now underway.[38]

INHALED BRONCHODILATORS AND CORTICOSTEROIDS

Inhaled Bronchodilators

The development of improved bronchodilators has focused on finding better inhaled LABAs and LAMAs (**Table 2**).[39–41] Novel classes of bronchodilator have been difficult to develop because they often have additional unwanted effects on vascular smooth muscle, producing postural hypotension and headaches. Until recently, all LABAs required twice-daily dosing, but newer once-daily agents, ultra-LABAs (ULABAs), such as indacaterol, olodaterol, vilanterol, and carmoterol are proving to be effective.[39,42–44] Aclidinium bromide is a new LAMA that has an acute onset of action (compared with tiotropium's slower onset of action) but has disappointed in trials to date.[45,46] Other LAMAs with a more rapid onset of action are in development. Glycopyrronium bromide/NVA237 has been shown to provide comparable effects to tiotropium.[47–49] Another company is soon to start phase III trials with nebulized LAMA, EP-101, a glycopyrrolate solution. Two single-molecule, dual-action bronchodilators, muscarinic antagonist and beta2-agonists (MABAs), are in phase I and II trials, including GSK961081.

Studies looking at the benefits of dual LABA or LAMA (salmeterol or formoterol with tiotropium) therapy have demonstrated greater bronchodilation and fewer symptoms when the drugs are combined, than with either agent alone.[50–52] New ULABAs allow for once-daily administration of LABA-LAMA combination inhaler, and a recent study has demonstrated significant benefits in FEV_1 using QVA149 (a combination of glycopyrronium bromide and indacaterol) versus indacaterol alone or placebo.[53] Aclidinium has been combined with formoterol as a LAMA and LABA combination.[46]

Attempts to combine existing classes of drugs with additional agents have proved less successful, as demonstrated by the arrested development of the novel D2 dopamine receptor–β2 adrenoreceptor agonist sibenadet (Viozan). The rationale for this agent was based on observations that sensory afferent nerves were key mediators of COPD symptoms such as breathlessness, cough, and excess sputum production, and advocates of Viozan hypothesized that that activation of D2-receptors on such nerves would modulate their activity.[54] Although initial short-term studies were promising, the duration of the bronchodilator effect diminished as studies progressed and no sustained benefit was reported in a 1-year large-scale trial.[55]

Table 2
Inhaled bronchodilators and corticosteroids and corticosteroid-related approaches

Ultralong-acting β2-agonists	Abadeterol AZD3199 Olodaterol (BI1744CL) Carmoterol Vilanterol (GSK642444) Indacaterol (QAB149)
LAMA	Aclidinium (LAS-34273) AZD8683 Umeclidinium (GSK573719) Glycopyrronium (NVA237)
Muscarinic antagonist and β2-agonist	AZD2115 GSK961081
LABA + LAMA	Formoterol + aclidinium Olodaterol + tiotropium Vilanterol + umeclidinium Indacaterol + glycopyrronium (QVA149)
ICS + Ultralong-acting β2-agonists	Beclomethasone + formoterol (Fostair) Fluticasone + vilanterol (Relovair) Mometasone + formoterol (Dulera) Fluticasone + formoterol (Flutiform) Mometasone + indacaterol (QMF149) Ciclesonide + formoterol
New corticosteroid-related approaches	Nonglucocorticoid steroids Selective glucocorticoid receptor agonists
Reversal of steroid resistance	Theophylline (histone deacetylase 2 activators) Phosphoinositide-3-kinase inhibitors LABAs and phosphodiesterase 4/ LABAs (via phosphoinositide-3-kinase inhibition)

ICS

Current United Kingdom and international guidance, despite little supporting evidence, recommend ICS for symptomatic patients with an FEV_1

lower than 50% and/or frequent exacerbations. These are usually prescribed in the form of a combination inhaler containing LABA. In reality ICS-LABA inhalers may be used inappropriately in an excessive number of COPD patients who do not meet the criteria outlined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[56] A Spanish study found a rate of inappropriate ICS use of 18.2%.[57]

A Cochrane review of the role of ICS included studies published up until July 2011.[58] This review concluded that long-term (>6 months) ICS use did not consistently reduce the rate of decline in FEV_1 in COPD patients. There was no statistically significant effect on mortality in COPD subjects, but long-term use of ICS did reduce the mean rate of exacerbations in those studies in which pooling of data was possible. In addition, there was slowing of the rate of decline in quality of life (measured by the St. George's Respiratory Questionnaire). There was an increased risk of oropharyngeal candidiasis and hoarseness with ICS use and, in the long-term studies, the rate of pneumonia was increased in the ICS group compared with the placebo group. Although ICS does seem to have some beneficial effects in COPD, when compared with long-acting bronchodilators, the latter agents seem to provide similar benefits to ICS or ICS-LABA combinations in exacerbation reduction without the side effects associated with ICS use.[59]

One alternative may be the use of nonglucocorticoid steroids. EPI-12323 is a once-daily, small molecule, inhaled nonglucocorticoid steroid and may not exhibit any of the classic side effects of glucocorticoid steroids. It may also be possible to avoid the unwanted side effects of glucocorticoids by selectively inducing transrepression genomic mechanisms (which are responsible for many desirable antiinflammatory and immunomodulating effects), whereas transactivation processes (associated with frequently occurring side effects) are simultaneously less affected.[60,61] An inhaled selective glucocorticoid receptor agonist is currently undergoing clinical trials.

For patients who remain symptomatic despite LABA-ICS combination, GOLD recommends triple therapy with LAMA, LABA, and ICS. The rationale behind this seems logical because all three agents work via different mechanisms on different targets, potentially allowing for lower doses of the individual agents to be used, accompanied by improved side-effect profiles. However, there has been a lack of sufficiently powered studies primarily addressing the benefits of triple therapy versus LABA-ICS therapy, or, indeed, versus dual LABA-LAMA therapy.[62,63] A single inhaler combining all three agents is currently in formational development, although the ICS to be used has not been confirmed. Once-daily ICS are now in development to allow future trials with once-daily triple-therapy combined inhalers. These inhalers may well improve compliance, but titration of individual component drug doses may prove difficult, and disease severity seems to affect the drug dose-response curve.[64]

Steroid Resistance

Interestingly, ICS do not seem to suppress inflammation in COPD. One hypothesis attributes this to the marked reduction in histone deacetylase 2 (HDAC2), the nuclear enzyme that corticosteroids require to switch off activated inflammatory genes,[65] rendering these patients resistant to the effects of ICS. The reduction in HDAC2 is thought to be secondary to oxidative stress, both independent of and by way of activation of phosphoinositide-3-kinase-δ (PI3Kδ).[66] Inhibition of PI3Kδ has recently shown to restore corticosteroid sensitivity in mice[66] and may hold therapeutic promise.[67,68] One group has shown that formoterol reverses oxidative stress-induced corticosteroid insensitivity via PI3Kδ.[68] Low-dose theophylline has shown to enhance the antiinflammatory effects of steroids during exacerbations of COPD[69] and seems to have the capacity to restore the reduced HDAC2 activity in COPD macrophages.[70] More recently, roflumilast has shown to augment the ability of formoterol to enhance glucocorticoid-dependent gene transcription in human airway epithelial cells.[71]

ANTIINFECTIVE AND ANTIINFLAMMATORY AGENTS

Antibiotics

The Lung Health Study of North America revealed that lower respiratory tract illnesses promote FEV_1 decline in current smokers (**Table 3**).[72] There is growing evidence that exacerbations accelerate the progressive decline in lung function in COPD patients.[73] Several lines of evidence now implicate bacteria as an important cause of exacerbations[74] and bacterial colonization is frequently found in patients with COPD.[75] It is associated with the frequency of exacerbations.[76] There seems to be a correlation between bacterial colonization of lower airways and elevated levels of inflammatory mediators.[77] Finally, patients with severe COPD who receive inappropriate antibiotic treatment are vulnerable to multidrug-resistant infections.[78]

It has become increasingly difficult to develop new antibiotics, so that there is a need for novel types of therapy. Bacteriophages are bacterial

Table 3
Antiinfective and antiinflammatory agents

Antibacterials	Antibiotics, antimicrobial peptides, bacteriophages, vaccines
Antivirals	Antivirals (eg, neuraminidase inhibitors for influenza) Vaccines for influenza, HRV, and respiratory syncytial virus
Agents acting on pattern recognition by the innate immune system	Toll-like receptor inhibitors 2, 4, and 9 NLR agonists or antagonists RLR agonists or antagonists
Antagonists of cell surface receptors	CXCR2 antagonists (AZD5069); GSK1325756 CCR2 antagonists (CCR2b antagonist: AZD2423) Chemoattractant receptor-homologous molecule expressed on Th2 cells antagonists LTB_4 receptor antagonists Selectin antagonists
Phosphodiesterase (PDE)-4 inhibitors	PDE4i: roflumilast, tetomilast Inhaled selective PDE4B inhibitor: GSK25066 Dual selective PDE inhibitors Novel combinations: PDE4 +7A inhibition PDE3 + PDE4 inhibition (RPL554)
Kinase inhibition	p38 mitogen-activated protein kinase inhibitors (inhaled GSK610677) JNK inhibitors Syk inhibitors JAK/STAT inhibitors: tofacitinib
Transcription inhibition	NF-κB inhibitors: IKK2 inhibitors PI3K-γ/δ inhibitors Peroxisome proliferator-activated receptor-γ antagonists (rosiglitazone) Cyclosporine-A (inhaled)
Combating systemic inflammation	Statins

viruses that are approximately 10 times more numerous than bacteria in nature. Although they have been used in Russia for many decades as antibacterial agents, they have been used less in Western medicine.[79] Lytic phages are highly specific to particular bacteria and are well tolerated, with no risk of overgrowth of intestinal flora. They may be administered by inhalation, so may be effective in the treatment of respiratory bacterial infections.

Antimicrobial peptides, including α-defensins, β-defensins, and cathelicidins, are produced from epithelial and other cells in the respiratory tract and play a key role in innate immunity and stimulating adaptive immune responses.[80] These peptides may also be considered potential future therapies.

Although the molecular mechanisms for these effects are not fully clear, 14- and 15-membered ring macrolide antibiotics have several antiinflammatory effects in addition to their antibacterial actions.[81] It has been shown that these drugs decrease the production of cytokines in the lungs.[82] A recent large clinical trial, with more than 1142 volunteers, randomized subjects to daily administration of 250 mg of azithromycin or placebo for 1 year.[83] The median time to the first acute exacerbation in the azithromycin group was increased by 92 days, and the frequency of exacerbations in the azithromycin group was significantly reduced. However, deafness was observed in the treatment group as an adverse event. Another long-term, placebo-controlled clinical trial examining macrolides in the prevention of acute exacerbations used erythromycin at a dose of 250 mg twice daily for 1 year.[84] A nonantibiotic macrolide such as EM704, derived from the structure of erythromycin, has been shown to inhibit neutrophilic inflammation, the release of TGF-β, and fibrosis in a bleomycin model of pulmonary fibrosis.[85] Such nonantibiotic macrolides may be delivered by inhalation during an exacerbation and will not affect antibiotic resistance patterns.

Recently, pulsed antibiotic prophylaxis has been trialed. Moxifloxacin has shown to reduce the odds of exacerbation in stable COPD subjects when given once a day for 5 days every 8 weeks for 48 weeks.[86] New pneumococcal vaccines are

also in development that may prove more effective than are their current counterparts.

Antivirals

With advances in diagnostic techniques for viruses, such as polymerase chain reaction, there is evidence that the most COPD exacerbations are associated with viral infections and that, of these, HRV is the most common cause[87] and can directly infect the lower respiratory tract.[88] Up-regulation of the HRV receptor, intercellular adhesion molecule 1, on epithelial cells occurs in COPD patients and this may cause predisposition to infection.[89] When infected, COPD primary bronchial epithelial cells elicit exaggerated antiviral therapies, especially in relation to HIV, development of resistance to proinflammatory response.[90] Although there have been remarkable strides in the development of antiviral therapies, especially in relation to HIV, development of resistance to viral therapy is a recurrent problem[91] and there are no effective antirhinoviral treatments to date. Recently, an important model of human RV16 challenge has been introduced as a model of exacerbations in patients with COPD.[13]

Respiratory syncytial virus (RSV) is increasingly recognized in adults with COPD[92] and it can persist in stable disease.[93] Treatment of RSV infection remains largely supportive, although a monoclonal antibody (MoAB) therapy against RSV F protein (palivizumab) is licensed for specialist use in restricted circumstances.[94]

Seasonal influenza is another important cause of exacerbations of COPD and there is the fear that an influenza pandemic could cause high mortality in patients with COPD.[95] It is important that all patients with COPD have adequate influenza immunization and that they be considered for early treatment in the event of an influenza-induced exacerbation of COPD. Apart from vaccines, there are two licensed antiviral agents against influenza: zanamivir and oseltamivir (Tamiflu).[96] Nevertheless, development of resistance is a major problem and new anti-influenza agents are being actively sought.[97]

Agents Acting on Innate Immunity

Cigarette smoke has long been known to increase the permeability of the respiratory epithelium, thus compromising the barrier function. Respiratory viruses have a particular predilection for respiratory epithelial cells and these can then initiate nonspecific inflammation. Once the respiratory physical barrier is penetrated, danger signals meet the next part of the immune system defense: the pattern recognition receptors (PRRs). Recently, there has been recent dramatic progress in the understanding of the molecular and cellular details of how the innate nonspecific immune system is activated.[98] PRRs are thought to be central to the activation of the innate immune system and they have the capacity to drive chronic lung inflammation,[99] repair processes, fibrosis, and proteolysis. A unified theory can be made of how the development of mild-to-moderate COPD, as well as exacerbations of COPD, is mediated through interaction of reactive oxidant species (ROS), viruses, and bacteria with the innate immune system.[100] Molecular signatures on ROS, viruses, and bacteria, as well as from dead and damaged cells, cause rapid activation of the family of PRRs. Pathogen-associated molecular patterns (PAMPs) are found especially in the nucleic acid of the viruses that infect the respiratory epithelium and in various cell wall and cytoplasmic components of bacteria.[101] A variety of damage-associated molecular patterns (DAMPs) has been proposed, including high-mobility group box 1, S100 proteins, heat shock proteins (HSP), and extracellular matrix hyaluronans.

ROS activate Toll-like receptor (TLR) 2[102] and TLR4 using MyD88 signaling,[103,104] but they can also cause damage to membrane lipids and to DNA and thus activate DAMPs.[105,106] The cell wall of gram-negative bacteria contains lipopolysaccharide that activates cell surface TLR4, whereas various other bacterial components activate different cell surface TLRs. In contrast, viral nucleic acid motifs activate TLR3, 7, and 9, which are found on the inner surface of the endosomal membrane.

PRRs undergo extensive cross-talk with TLRs,[101] scavenger receptors,[107] and receptor for advanced glycation end-products (RAGE).[91,108] In addition, there are TLRs on endosomes that recognize viral nucleic acids and cytoplasmic PRRs that consist of retinoic acid-inducible gene-1 (RIG-1)-like receptors (RLRs), and NOD-like receptors (NLRs). Activation of PRRs takes place in COPD on epithelial cells, neutrophils, macrophages, smooth muscle[109] fibroblasts, and other cells of the airways. Acute cigarette smoke activates MyD88, a common adapter protein that is involved in the signaling of several TLRs (including TLR2, 4, 7, 8, and 9).[104]

Therefore, blocking PRRs, including TLRs that recognize and are activated by PAMPs on oxidants and infectious agents, may be a potential way of modulating disease activity in COPD. There are now intensive efforts to develop TLR-agonists and antagonists for treatment of diseases like COPD that involve inflammation and infection.[110] Eritoran, a synthetic TLR4 antagonist, has been

shown to block influenza-induced lethality in mice, and may well provide a novel therapeutic approach for other infections.[111] PRRs activate a variety of signal transduction pathways, including NF-κB and mitogen-activated protein (MAP) kinase pathways, as well as type I interferon pathways in the case of viruses.[112] MyD88 offers another target for therapy.[104,113]

Chemokine Receptor Antagonists

CXC and CC chemokine receptors are thought to be involved in COPD inflammation due to their role in neutrophil recruitment. The concentrations of CXC chemokines, including CXCL5 and CXCL8, are increased during exacerbations and, because they all signal through a common receptor, CXCR2, specific antagonists of this receptor may be useful in treating exacerbations. A small molecule CXCR1/2 antagonist (AZD8309) shows promise in inhibiting sputum neutrophils, after inhaled endotoxin, by approximately 80%,[114] suggesting that this could be useful in exacerbations and has the advantage of oral administration. A proof-of-principle study revealed that SCH527123, a novel, selective CXCR2 antagonist, causes significant attenuation of ozone-induced airway neutrophilia in healthy subjects.[115] However, experimental inflammation by ozone challenge is chiefly CXCL8-dependent, transient, and fully reversible in contrast to the pathologic inflammation occurring in the airways of subjects with COPD, which depends on multiple mediators and is chronic and largely irreversible. This highlights the difficulty with current models. Interestingly, SCH527123 has now undergone phase 2 studies in subjects with moderate-to-severe COPD, during which there were beneficial effects on sputum neutrophil counts and FEV_1 (reported at the ERS in 2010).

Several other oral CXCR2 antagonists such as AZD5069 are currently in phase II trials and include secondary outcome measures of circulating blood neutrophil levels.

CX3CL1 binds exclusively to CX3C chemokine receptor 1 (CX3CR1), and is unregulated in the lung tissue of smokers with COPD, making this an attractive target.[38]

An inhaled CCR1 antagonist (AZD4818) failed to show benefit in COPD,[116] although a CCR2b antagonist (AZD2423) is currently in trials.

Chemoattractant Receptor-homologous Receptor Antagonism

Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) is a G-protein coupled receptor expressed by Th2 lymphocytes, eosinophils, and basophils. The receptor mediates the activation and chemotaxis of these cell types in response to prostaglandin D2 (PGD_2), the major prostanoid produced by mast cell degranulation typically in the initial phase of IgE-mediated reactions but also thought to occur at sites of inflammation, such as the bronchial mucosa. As such, selective PGD_2 receptor antagonists (CRTh2 antagonists) are mainly in development for asthma.[117]

LTB_4 Receptor Antagonists

Serum concentrations of LTB_4, a potent neutrophil chemoattractant, are increased in patients with COPD.[118] LTB_4 activates BLT_1-receptors, which are expressed on neutrophils and T lymphocytes. Although BLT_1-antagonists have a relatively small effect on neutrophil chemotaxis in response to COPD sputum[119] and they have not proved to be effective in treating stable COPD, it is possible that they would have greater efficacy if used acutely, due to observations that LTB_4 is especially elevated during COPD exacerbations.[7]

LTA4H has been proposed as another potential therapeutic target because it is the enzyme responsible for generation of LTB_4 from leukotriene A2. However, another role for LTA4H has been observed, whereby it degrades another neutrophil chemoattractant, namely proline-glycine-proline (PGP),[120] thus therapeutic strategies inhibiting LTA4H to prevent LTB_4 generation may not reduce neutrophil recruitment due to simultaneous elevation in PGP levels, once again demonstrating the complexity of manipulating inflammatory processes in COPD.

Selectin Antagonism

The selectin family is a group of adhesion molecules involved in the initial activation and adhesion of leukocytes on the vascular endothelium, which facilitates their migration into the surrounding tissue. In a phase II trial in 77 COPD subjects, 28 days of bimosiamose (an inhaled pan-selectin antagonist) led to a significant decrease in the sputum macrophage count, and decreased CXCL8 and matrix metalloprotease (MMP)-9, whereas most lung function parameters also showed a small numeric increase with no difference in adverse events.[121] Trials with longer treatment durations are now required and an anti-selectin MoAB (EL246) is currently under predevelopment.[122]

Phosphodiesterase Inhibitors

Theophylline has some PDE inhibitor activities and it as been used in the treatment of COPD for more

than 75 years. However, its use is limited by its narrow therapeutic range, side-effect profile, and drug interactions. Newer selective PDE inhibitors are anticipated to exhibit the beneficial effects of theophylline with an improved side-effect profile. PDE4 inhibitors have a broad spectrum of antiinflammatory effects and are effective in animal models of COPD. However, in human studies their effectiveness has been limited by side effects, such as nausea, diarrhea, and headaches.[123,124]

Development of selective orally active PDE4 inhibitors has predominantly involved cilomilast (Ariflo), roflumilast, and tetomilast in inflammatory bowel disease.[125] Cilomilast has been studied in five phase III studies: involving 2088 subjects on cilomilast and 1408 on placebo for 24 weeks.[126] Although an initial study was very encouraging in 424 patients with COPD assessed for 6 weeks,[127] benefits were not as great in a larger study for 6 months,[128] and cilomilast failed to convince in other phase III studies. As a result, the entire cilomilast program was terminated, providing a cautionary example of the difficulties in developing new drugs for COPD.

In contrast, roflumilast has proved more effective in long-term studies,[129–132] especially in decreasing exacerbations, and is now the first in this new class of agents licensed for treatment of severe COPD with bronchitis.[133,134] Roflumilast is given once daily (500 μg), but gastrointestinal adverse effects and weight loss are common on starting therapy. The Roflumilast in the Prevention of COPD Exacerbations While Taking Appropriate Combination Treatment (REACT) study aims to assess whether or not roflumilast will provide additional benefit when added to dual or triple therapy.[135] This will also go some way to confirming the safety of the drug and it's future use, although it may be that newer inhaled PDE4 inhibitors will prove preferable in terms of reduced side effects. To date, inhaled PDE4 inhibitors have been found to be ineffective.

Avoidance of targeting certain isoforms should help limit side effects because mouse studies have suggested that emesis is the result of PDE4D inhibition,[136] whereas PDE4B is the predominant subtype present in monocytes and neutrophils and is implicated in the inflammatory process. This insight has led to the design of PDE4 inhibitor modulators, which have one to two orders of magnitude less affinity for the PDE4D isoform, while maintaining other PDE4 inhibitory activities. However, more work is needed to confirm whether targeting specific subtypes really is more beneficial. In addition, mixed PDE4/7 inhibitors are under development that may have synergistic benefits. TPI 1100, which comprises two antisense oligonucleotides targeting the mRNA for the PDE4B/4D and PDE7A isoforms, has been shown to reduce neutrophil influx and key cytokines in an established smoking mouse model.[137] A final approach may be use of a PDE4 inhibitor in combination with other antiinflammatory drugs such as glucocorticoids[138] based on recent findings that these drugs together may impart clinical benefit beyond that achievable by an ICS or a PDE4 alone.[71]

Kinase Inhibitors

After decades of research on oral kinase inhibitors, a JAK inhibitor has been licensed in 2012 for the treatment of rheumatoid arthritis.[139] There is also progress with orally active Syk inhibitors in autoimmune disease. p38 (p38 MAP kinase) is activated by bacteria and viruses, as well as other inflammatory signals and, therefore, is another target for inhibition.[140,141] These phosphorylases are involved in cell-signaling cascades, which often result in the activation of proinflammatory nuclear transcription factors such as NF-κB. Several p38 MAP kinase inhibitors are now in clinical development, and the results of a phase II trial with losmapimod (an oral p38 MAP kinase inhibitor) were published last year. Although losmapimod did not have an effect on sputum neutrophils or lung function, there was a significant reduction in plasma fibrinogen levels after 12 weeks, and improvements in lung hyperinflation were noted.[142]

Other broad-spectrum antiinflammatory drugs in development include inhibitors of NF-κB and PI3K. However, there is much interaction between signaling pathways and it may be that a multipronged approach is required.[125,143] NF-κB inhibition can be attempted through a variety of approaches; namely by inhibiting the degradation of the inhibitor of NF-κB family of proteins (IκB), gene transfer of IκB or IκB kinase (IKK) inhibition. Several IKK inhibitors are in development.[38] PI3K inhibitors also have therapeutic potential,[144,145] and selective inhibition may restore glucocorticoid sensitivity.[146] There are drugs directed against both the δ- and γ-isoforms of PI3K,[147,148] as well as an inhaled dual γ/δ inhibitor.[149] In addition, peroxisome proliferator-activated receptor gamma (PPAR-γ) antagonists such as rosiglitazone may treat airway mucus hypersecretion.[150] Finally, new formulations of cyclosporine A (inhaled) are being developed for asthma and COPD.[151]

Statins

COPD is associated with a complex list of systemic manifestations, including systemic inflammation associated with cachexia and skeletal

muscle weakness.[152,153] COPD also has an extensive association with comorbidities, such as cardiovascular diseases,[154] and it is recognized that new drugs are required for COPD and these comorbidities.[155] This subset of patients with persistent systemic inflammation has been associated with poor clinical outcomes, irrespective of their lung impairment.[156] It is recognized that skeletal muscle weakness and wasting may also be amenable to therapy.[157,158]

This has encouraged the use of statins in COPD because they have a range of systemic antiinflammatory effects.[159] Statins increase survival in patients with peripheral arterial disease and COPD,[160] and may reduce COPD exacerbations.[161] Furthermore, retrospective studies have shown that statins reduce the risk of death in patients with COPD.[162–164] The benefit on all-cause mortality depends on the level of underlying systemic inflammation, as assessed using high-sensitivity C-reactive protein (hsCRP) measurements.[165] Various academic institutions are currently conducting studies looking at the effect of statins on the frequency of COPD exacerbations in patients with moderate-to-severe COPD who are prone to exacerbations, but may not have other indications for statin treatment. In addition, statins have been associated with a reduced risk of extrapulmonary cancers in patients with COPD.[166]

MISCELLANEOUS ADDITIONAL CLASSES OF NEW DRUGS

Antioxidants

Each inhalation of cigarette smoke contains a large burden of ROS,[167] as well as many different chemical components that cause lung toxicity (**Table 4**).[168] In addition, oxidants are generated endogenously from activated inflammatory cells. Manipulation of the oxidant–antioxidant balance, therefore, seems to be a logical therapeutic strategy and there is a range of novel targets.[169,170] Resveratrol is a cardioprotective antioxidant in red

Table 4
Miscellaneous additional classes of new drugs

Antioxidants	• Dietary antioxidants • N-acetyl-cysteine, N-acystelyn, N-isobutyryl-cysteine, erdosteine, procysteine, carbocysteine • Thiols, spin traps • Enzyme mimetics: superoxide dismutase, catalase and glutathione peroxidase • Polyphenols
Mucolytics	• N-acetyl-cysteine and carbocysteine • Epidermal growth factor receptor tyrosine kinase inhibitors
Protease inhibitors	• Neutrophil elastase inhibitors: sivelestat (ONO-5046), silanediol isosteres, AZD 9688 • MMP-9 & MMP-12 inhibitors • Broad-spectrum MMP inhibitors: ilomastat, marimastat
Antifibrotics	Agents used in idiopathic pulmonary fibrosis • Pirfenidone • Endothelin antagonists • PDE5 inhibitor: sildenafil • MoABs: anti-TGF-β, anti-FGF, anti-IL-13, anti-αvβ6 integrin (STX-100), anti-CCL2 (CNTO 888)
Drugs to combat cachexia and muscle wasting	Growth hormone releasing factor analogue (tesamorelin)
MoABs	• Anti-TNFα • Anti-IL-1β • Anti-IL-6 (tocilizumab) • Anti-CXCL8 (IL-8) • Anti-IL-17, anti-IL-13, anti-IgE • Anti-TGF-β
Drugs to slow aging	Sirtuin 1 activator (GSK2245840)
Lung regeneration	• Retinoids (γ-selective retinoid agonist, palovarotene) • Mesenchymal stem cell therapy • Gly-his-lys (GHK) tripeptide

wine, whereas stilbenes are dietary antioxidants from tomatoes, but may not achieve sufficient levels in established COPD. Interestingly, resveratrol is also a sirtuin (SIRT) activator and this property has been proposed to account for antiaging effects.[171] There are theories that COPD represents an accelerated form of lung aging,[172,173] and this concept suggests that antiaging molecules may have potential in COPD.[174] Other dietary components such as sulforaphanes and chalcones are potential therapeutic antioxidants in COPD.[175]

N-acetyl-cysteine (NAC) is a potent reducing agent capable of increasing intracellular glutathione levels. In addition, its mucolytic properties can improve sputum clearance in COPD. In preclinical studies, NAC attenuated elastase-induced emphysema in rats,[176] but later clinical studies have yielded mixed results. A Cochrane review reported the beneficial effects on exacerbation frequency of NAC in chronic bronchitis,[177] but this was later followed by a large multicenter trial in which NAC had no effect on exacerbation frequency or FEV_1 decline.[178] Carbocysteine may be more promising. The PEACE study revealed a significant decline in COPD exacerbations using 500 mg carbocysteine three times a day daily in Chinese patients with COPD.[179] Both of these agents are undergoing further studies in COPD.

Stable glutathione compounds, superoxide dismutase (SOD) analogues, and radical scavengers are in development. Enzyme mimetics are being developed that enhance the activity or expression of antioxidant enzymes such as SOD and glutathione peroxidase, which can neutralize cellular ROS. Nitrone spin-traps are potent antioxidants, which inhibit the formation of intracellular ROS by forming stable compounds, whereas thioredoxin is a redox sensor inhibitor. Hydrogen sulfide (H_2S) is a potent antioxidant and GYY4137 is a novel H_2S-releasing molecule that protects against endotoxic shock in the rat[180]; however, all these agents are still being assessed in animal models.

Mucoactive Drugs

Secretions can accumulate in airway lumens, exacerbating airflow obstruction and increasing susceptibility to infections in COPD. A variety of drugs has been developed to treat airway mucus hypersecretion, as well as mucoactive drugs,[181] in addition to NAC and carbocysteine mentioned above. These agents combat targets such as epidermal growth factor receptor, tyrosine kinase inhibitors, and human calcium-activated chloride channel (hCACL2). PPAR-γ is an exciting target for drugs to treat airway mucus hypersecretion.[150] Surfactant protein B has recently been found to be associated with COPD exacerbations.[182] It is important to stress that mucus can be both protective and harmful in different situations in COPD. In a study using inhaled recombinant DNAse to treat acute exacerbations of COPD, the study was terminated due to a trend toward increased mortality in the treatment arm.[183]

Proteases

α1-Antitrypsin deficiency is a genetic disease that illustrates the importance of proteases in causing a subtype of COPD.[134,135] There have been recent advances in provision of augmentation therapy for α1-antitrypsin deficiency.[184] Neutrophil elastase (NE),[136] MMP-9,[137] and MMP-12[185] have been implicated in the pathogenesis of COPD, and provide targets for novel therapies.[186]

A novel oral inhibitor of NE, AZD9668, underwent a 12-week dose-finding study in subjects with COPD treated with tiotropium, but failed to show benefit.[187,188] An inhibitory effect of heparin has been shown on neutrophil elastase release, which is independent of the anticoagulant activity of this molecule.[189] However, a phase II trial of O-desulfated heparin in subjects with exacerbations of COPD was terminated at the end of last year due to a lack of efficacy. Interestingly, heparin is also a known inhibitor of selectin-mediated interactions, but a phase II trial in COPD exacerbation patients with PGX-100 (2-O, 3-O desulfated heparin) also failed to demonstrate efficacy and was terminated early.[122]

Attempts to readdress the protease-antiprotease imbalance with synthetic MMP inhibitors have been attempted,[190] but the development of musculoskeletal syndrome with marimastat is a prominent adverse effect.[191] AZD1236, a novel more selective inhibitor of MMP-9 and MMP-12, has failed to demonstrate convincing clinical efficacy in two studies over 6 weeks.[192,193] The role of other proteases in COPD remains unclear, but inhibitors of cysteine proteases are under development.

Fibrosis and Remodeling

There have been dramatic advances in the understanding of lung injury and idiopathic pulmonary fibrosis (IPF).[194–196] This has resulted in a flurry of drug development, for which excellent reviews are available.[197,198] Inflammation and fibrosis are related processes, and COPD and IPF have some common features.[199,200] Airway inflammation, resulting in tissue injury can result in peribronchial fibrosis when lung injury exceeds the lung's ability to repair. The resulting airways become

narrowed, leading to airway obstruction. However, although these processes, inflammation, and fibrosis, may be closely related, it has also been postulated that fibrosis may occur alone in COPD. For example, in IPF there can be very little inflammation.[201] The process of fibrosis is prominent in the small airways as obstructive bronchiolitis, but excessive fibrosis may also contribute to emphysema. It has been recently recognized that fibroblasts and myofibroblasts may be resident cells, derived from bone marrow stem cells and blood-borne fibrocytes, or may be derived by epithelial to mesenchymal transition (EMT).[202,203] Therefore, strategies used to treat IPF (eg, pirfenidone) may be of benefit in COPD, but more research is needed in this area.[194,204]

A recent study has demonstrated that cigarette smoke induces EMT in differentiated bronchial epithelial cells via release and autocrine action of transforming growth factor-β1 (TGF-β1) as well as by enhancing oxidative stress, thus suggesting that EMT could participate in the COPD remodeling process of small bronchi such as peribronchiolar fibrosis.[205] Small-molecule inhibitors of TGF-β1 receptor tyrosine kinase have been developed: SD-208, however, has been shown to inhibit airway fibrosis in a model of asthma.[206]

Biologics: MoABs

Tumor necrosis factor α (TNF-α) has been implicated in the pathogenesis of COPD and seems to be a good therapeutic target. Indeed, an observational study in rheumatoid arthritis patients demonstrated that etanercept (a TNF-receptor antagonist) led to a reduction of 50% in the rate of hospitalization due to COPD exacerbations.[207] Although blocking TNF-α was not effective in stable COPD patients,[208–210] it is possible that administration during an acute exacerbation might be effective in view of the acutely increased TNF-α concentrations. However, there are major concerns that the TNF antibody infliximab increased the incidence of respiratory cancers in a COPD study (although this was not statistically significant),[208] and increased other types of cancer as well as infections in a study in severe asthma.[211] Future efforts may consider a more tailored approach using these agents in a subset of patients defined by an increased TNF-α axis. In addition, cachectic patients were found to have a small improvement in exercise capacity in post hoc analysis.[208] Inhibition of TNF-α production by inhibition of TNF-α converting enzyme is an alternative strategy.[38] A prominent effect of NF-κB and p38 MAP kinase inhibitor is the downstream inhibition of TNF-α synthesis.

An anti-CXCL8 (IL-8) MoAB was tested in COPD, but no improvement in health status or lung function was seen, possibly because the active bound form of CXCL8 was not recognized by the MoAB.[38] There is now special interest in assessing MoABs directed against IL-6, IL-1β, IL-17, IL-18, IL-1R, TGF-β, and granulocyte-macrophage colony-stimulating factor for effects in COPD. A humanized antibody against IL-6 receptors (tocilizumab) is effective in several other inflammatory diseases,[212] but there are no studies in COPD. Canakinumab, a MoAB to IL-1β, is already used in rare autoimmune diseases and is now in trials in COPD.[213] Th17 cells have recently been identified as a separate cell population that produce IL-17, which causes neutrophilia[214,215] and induce loss of HDAC2 and steroid insensitivity,[216] thus implicating another potential target, and phase II trials in psoriasis have been encouraging.[217,218] Finally, omalizumab, the anti-IgE MoAB approved for severe allergic asthma, has also now entered a study in a subgroup of COPD patients with elevated IgE levels.

Aging and Autoimmunity

COPD may be considered a disease of accelerated aging and geroprotectors are a novel therapeutic strategy.[219] SIRT1 and SIRT6 are attractive targets[220,221] because they can possess HDAC2 activity, protect against oxidative stress, and permit stabilization and repair of DNA. Another insight is that autoimmunity may have a role in COPD[222] and the immune system may be targeted against elastin[223] or epithelial cells.[224]

Lung Regeneration

Approaches to aid lung regeneration aim to correct the defect of emphysema and to replace destroyed lung interstitium. Human lungs have regenerative capacity, as demonstrated in Nepalese children given maternal vitamin A supplements.[225] This is not exclusive to children as demonstrated in an adult patient after pneumonectomy.[226] Attempts have been made to exploit this potential with new drugs to cause lung regeneration in COPD.[227–229]

Retinoids are known to promote alveolar septation in the developing lung and to stimulate alveolar repair in some animal models of emphysema. However, despite abrogation of elastase-induced emphysema in rats using all-trans retinoic acid,[230] subsequent attempts with retinoids and γ-retinoic acid receptor agonists in humans have been less promising.[231,232] The REPAIR study evaluated the effects of palovarotene (an oral γ-selective retinoid agonist) on lung density in

emphysema secondary to α1-antitrypsin deficiency. Although effects on the primary endpoint were not significant, there was a trend toward an improvement in most functional parameters in subjects taking palovarotene for a year. Another group conducted a 2-year trial with this agent and reported their findings at the ATS in 2011. There was no overall improvement in FEV_1 in COPD subjects on the drug; however, subgroup analysis revealed a significant reduction in the rate of decline in FEV_1 and TLCO in subjects with lower lobe emphysema.

Mesenchymal stem cells (MSCs) also offer exciting regenerative potential.[228,233] MSCs exhibit potent antiinflammatory and immunomodulatory activities both in vitro and in vivo. This finding has led to a trial assessing the safety and efficacy of an IV preparation of allogenic MSCs (Prochymal).[234] The therapy was well tolerated and, although there were no significant differences in lung function tests or quality of life indicators, an early significant decrease in levels of circulating C-reactive protein was observed in some subjects. Another approach taken with MSCs was to populate a biologic connective tissue scaffold (which has been stripped of HLA-antigen expressing cells), which can then be used to grow autologous tissue before surgical implantation.[235]

SUMMARY

For the future treatment of COPD, it should be possible to have improved current drugs, antiinfective and antioxidant therapy, coupled with novel approaches directed against the innate immune system. In terms of the processes involved in COPD, there is rapid advancement of knowledge of viral responses and fibrosis, steroid-insensitive inflammation, autoimmunity, aberrant repair, accelerated aging, and appreciation of systemic disease and comorbidities. There is the need to develop validated noninvasive biomarkers for COPD and to have novel challenge models in animals and humans.[71] More interest has recently focused on cigarette-challenge models in an attempt to understand the exact immunologic responses to an acute smoke exposure event, to understand better the chronic changes that result from smoking.[68] In terms of clinical trial designs, these are adapted for bronchodilation, the natural history, and the prevention and treatment of COPD exacerbations and comorbidities. As is the case with many diseases, combinations of therapies may be the key to effective COPD treatment and prevention, and they may need to be given early in the disease. To develop novel drugs for COPD, it is clear that long-term studies in specific phenotypic groups, giving targeted therapy based on companion biomarkers, are needed. This would ideally use inhaled agents delivered directly to the intended site of action, with minimal unwanted side effects.[35] Overall, there is need for extensive collaboration between scientists, clinicians, the pharmaceutical industry, and drug regulators to identify and provide better therapy for patients with COPD.

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