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Review article

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Treatment of chronic obstructive pulmonary disease: current pipeline and new opportunities

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Abstract

Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder of the lungs that affects about 10% of the adult population and is currently the third leading global cause of death. COPD is the result of multiple, repeated and dynamic gene–environment interactions, starting early in life, that determine the lung function trajectory that a given individual follows over a lifetime. Increasing understanding of COPD pathogenesis has opened many new opportunities for drug development, including recently approved monoclonal antibodies that reduce inflammatory cytokine signalling by targeting the IL-4α receptor or the eosinophil-activating IL-5. Drugs targeting a range of other culprits involved in COPD, including neutrophils, alarmins and kinases, are also in clinical development. As the current pipeline of drugs in development for COPD matures, potential areas for novel therapies continue to emerge while lessons from ongoing trials such as patient stratification can be used to refine the design of future trials in this disease.

Sections

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem because it affects about 10% of the adult population and is currently the third global cause of death[1]. Typical symptoms of COPD include dyspnoea and cough (with or without sputum production); in addition, some patients suffer acute episodes of symptom worsening named exacerbations of COPD (ECOPD) that significantly worsen their health status and prognosis[1]. The hallmark pathophysiological feature of COPD is poorly reversible airflow limitation measured by forced spirometry, which is the result of chronic airway inflammation and remodelling as well as, in some patients, alveolar destruction (emphysema)[1]. The extent of these structural abnormalities varies greatly between individuals. COPD is usually a progressive condition, but the rate of lung function decline is not linear over time and varies between individuals[1].

COPD was traditionally considered a self-inflicted disease caused by tobacco smoking occurring in older 'susceptible' males and characterized by an abnormal inflammatory response that accelerates the physiological lung function decline that occurs with ageing[2,3]. However, research over the past decade has shown that there are risk factors other than smoking, including genetic, epigenetic and environmental risk factors, and that COPD is the result of multiple, repeated and dynamic gene (G)–environment (E) interactions through the lifetime (T) (GETomics; see Box 1) that determine the lung function trajectory over an individual's life (Fig. 1) and, eventually, their health status and prognosis[4–9]. As a result of this new understanding of the pathophysiology of COPD, it is now well established that COPD occurs in both men and women (albeit with a higher prevalence in men), as well as in older and younger subjects, and that it is not always progressive over time[5,7–9]. Likewise, COPD is now understood as a complex condition that involves various pulmonary morbidities (airway and parenchymal disease, whose presence and severity varies over time and between individuals[10]), as well as often extra-pulmonary multimorbidity (which recognizes a syndemic occurrence[11]) that contributes significantly to health status and prognosis[1,11]. Finally, the term aetiotypes has been introduced to highlight the various causes of COPD (including but not limited to smoking) such as lung development abnormalities, infections and exposure to various pollutants[1,12,13]. Of note, the pathogenesis of many of these new aetiotypes is largely unknown, and specific treatments are not available.

The current management of patients with smoking-related COPD includes pharmacological treatments with long-acting bronchodilators (either β_2 agonists (LABAs) and/or muscarinic antagonists (LAMAs)) with or without inhaled corticosteroids (ICSs) as an anti-inflammatory drug, preferably in a single inhaler[1], and non-pharmacological measures (including smoking cessation strategies, rehabilitation to improve the general conditioning of the patient, oxygen therapy if there is arterial hypoxaemia (that is, respiratory failure) and several endoscopic and surgical approaches). Recently, there has been progress towards a more personalized and precise pharmacological management strategy, and a strategy based on so-called 'treatable traits' has been proposed to this end[14–17]. For instance, two large randomized clinical trials (RCTs) have shown that triple therapy (LABA–LAMA–ICS) in a single inhaler reduces exacerbations and all-cause mortality[18,19], with the benefits of the ICS component being greater in patients with higher blood eosinophil count (BEC)[20], supporting the use of this blood biomarker to facilitate a precision approach to ICS use in the clinical management of COPD. Higher BEC is associated with a differential profile of inflammation in the lungs (greater type 2 inflammation; herein T2 inflammation) that is suppressed by ICS treatment[21,22]. Conversely, ICS treatment is less efficient in patients with less than 100 eosinophils per microlitre, who are at higher risk of developing pneumonia[21].

In this article we review the main pathophysiological mechanisms of COPD, discuss the pipeline of drugs currently in development, identify potential opportunities for the development of novel drugs and propose recommendations to consider in the design of future RCTs in COPD.

Pathophysiological mechanisms of COPD

Our understanding of the pathophysiology and natural history of COPD has changed significantly during the past decade[4–9]. This new understanding of COPD identifies two main pathophysiological mechanisms causing the disease: those related to impaired lung development in utero, infancy and/or adolescence and those related to an acceleration of lung function decline with age (Fig. 1). The former have begun to be investigated more recently and are less well understood than the latter, which are generally believed to include an abnormal, complex and sustained inflammatory response (both in the lungs and in the systemic circulation)[23]. Figure 2 shows the complexity of this inflammatory response, which, as discussed below, comprises two main types of response: neutrophilic inflammation (type 1 inflammation; herein T1 inflammation) and eosinophil-associated (T2) inflammation.

Neutrophilic inflammation (type 1)

Neutrophils are a type of leukocyte that are part of the innate immune system and provide a rapid response against pathogens through both phagocytosis and the secretion of preformed enzymes that are stored within cytoplasmic granules. Examples of bactericidal enzymes include neutrophil elastase, which is a serine protease, and myeloperoxidase (MPO), which is a haem-containing enzyme that promotes the production of reactive oxygen species. Neutrophils have a crucial role in physiological immune response in the lung, where they help to maintain a balance between host defence and tissue integrity. Peripheral airway neutrophil numbers are often increased in patients with COPD, particularly in those with more severe airflow limitation[24]. Cigarette smoking causes the release of neutrophil chemo-attractants, notably from the airway epithelium and macrophages that reside within the airway lumen[25], that encourage the development of pulmonary neutrophilia. Infiltrating neutrophils in the lungs release proteases such as neutrophil elastase that cause airway remodelling and destroy the alveolar walls (emphysema)[26,27].

α_1-Antitrypsin (AAT) is an anti-protease primarily produced in the liver by hepatocytes that protects the lungs against the activity of neutrophil elastase[28]. AAT deficiency is caused by mutations in the *SERPINA1* gene that reduce secretion of AAT. Insufficient AAT activity allows unrestricted neutrophil elastase-mediated lung tissue destruction, resulting in emphysema onset at an early age, particularly in individuals who also smoke. This genetic cause of COPD, which accounts for a minority of cases, highlights the role of neutrophil-derived proteases in emphysema development, and AAT replacement therapy has been shown to attenuate the rate of disease progression[29].

Macrophages have a homeostatic role in the lungs, where they engulf and clear inhaled microbes and particulate matter. Smoking increases lung macrophage numbers, which can promote neutrophil recruitment into the airways[25,30]. It has been proposed that the development and progression of COPD is largely due to a dysregulated and excessive innate immune response with increased numbers of macrophages and neutrophils that secrete pro-inflammatory

Box 1 | A new understanding of COPD: GETomics and the trajectome

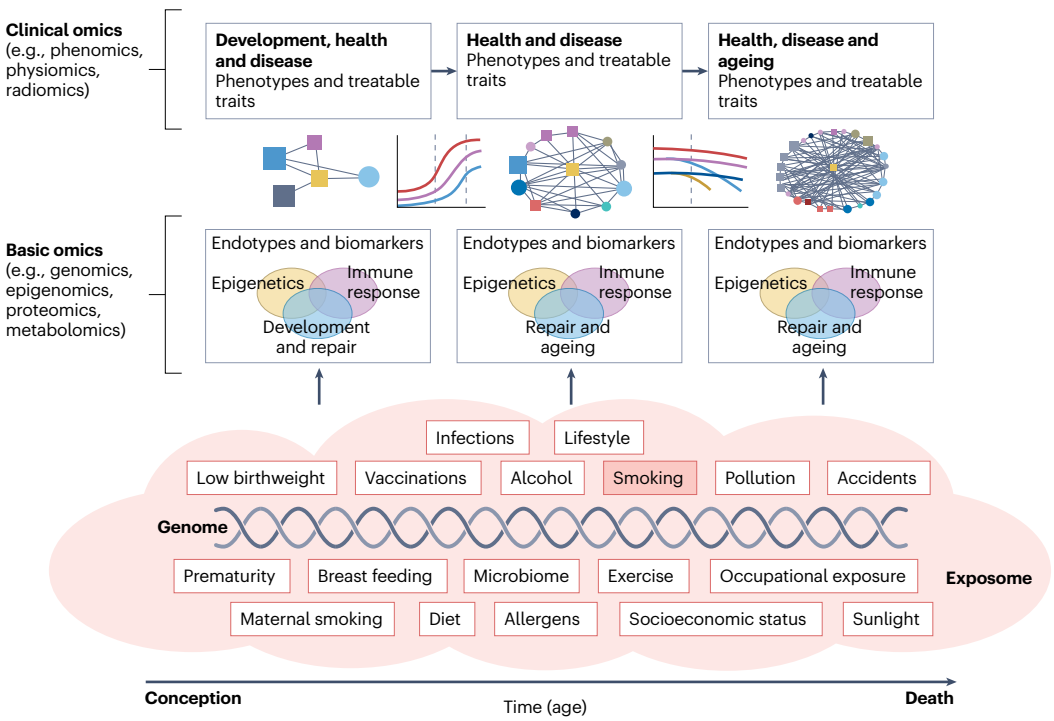
Chronic obstructive pulmonary disease (COPD) has been traditionally considered a self-inflicted disease by tobacco smoking occurring in so-called 'susceptible' older men and characterized by an enhanced rate of lung function decline with age[2,3]. This is now recognized to be an incomplete view of the pathogenesis of the disease[4,5,7,8] for several reasons.

First, about one-third of patients with COPD are never smokers[153,215], clearly indicating that there are other risk factors. In fact, a general population study in more than 11,000 participants[216] showed that there are many factors related to low lung function (including tobacco smoking) in different age 'bins', that these factors increase over time (that is, with age) and that they interact with one another (not only with lung function), hence increasing the complexity of the system progressively[154]. Accordingly, any drug intervention is likely to be more effective in younger individuals[217].

Second, more than 100 genes have been associated with low lung function and COPD, but their individual effect size is small, so several of them must coexist in the same individual to increase the risk of developing COPD[218]. As a result, studies are using polygenic risk scores (PRSs) to investigate the genetic background of COPD[218–222]. Of note, a recent publication showed that a PRS developed in adults with COPD can be identified in children with reduced lung function[155].

A third important factor in understanding COPD risk and progression is that epigenetic changes driven by smoking and exposure to other environmental factors also contribute to disease susceptibility[8,189,218,223]. Fourth, we now know that there is a range of lung function trajectories (see Fig. 1) that can occur in the population, collectively known as the trajectome[5,7,8], and that not all patients with COPD exhibit a decline in lung function with age greater than the physiological one, and they develop COPD because they never reached a normal peak lung function in early adulthood owing to both pre- and postnatal events that limited their normal lung development[4,9,206,224,225].

Based on all these observations, the term GETomics has been proposed to describe these complex and dynamic gene (G)–environment (E) interactions through the lifetime (T) of the individual[8] (see the figure). Throughout life, an individual is exposed to numerous environmental factors, collectively known as the exposome[8,226,227] (bottom panel in the figure). These factors can induce an immune response and/or interact with the genome to induce epigenetic modifications[192,223,228], producing different endotypes and biomarkers (middle panel in the figure). The biological effects and clinical outcomes of different G–E interactions depend not only on their specific characteristics, but also on the age of the individual at which the interaction occurs, as organs can be at different stages of development, maturation or ageing (shown here by the respective lung function trajectories[8] (see also Fig. 1)). Importantly, they also depend on the cumulative history of the individual's previously encountered G–E interactions (top panel in the figure, horizontal arrows). All of these interactions determine the health and/or disease status of the individual at various ages through life. In fact, we now know that COPD can occur in young people[1]. This new understanding of the pathophysiology of COPD can open new windows of opportunity for its prevention, early diagnosis and prompt therapy[8,9]. Figure reprinted with permission from ref. 8, Elsevier.



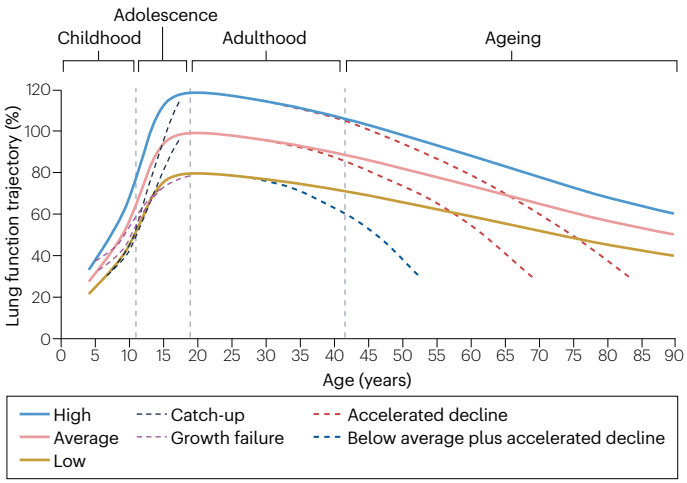


Fig. 1 | Potential lung-function trajectories from childhood to old age. The normal (pink) trajectory involves a lung development phase in infancy and adolescence, until lung function reaches its peak in early adulthood (20–25 years), slightly earlier in women[157]. Afterwards. lung function declines gradually over time owing to physiological lung ageing. This normal trajectory can be altered for better (above, shown in blue) or worse (below, shown in orange) because of many genetic and/or epigenetic and environmental factors[5,7–9]. Those above the normal trajectory are associated with better outcomes and healthier ageing[212–214], whereas those below the normal are associated with respiratory, cardiovascular and metabolic morbidity and premature death[6]. In adulthood and in elderly populations, accelerated lung function decline (dashed lines) may occur, often in relation to tobacco smoking or exposure to other environmental factors. Importantly, during childhood and adolescence, catch-up and growth failure might also occur, although the mechanisms underlying both are still unclear and warrant research. Reprinted with permission from ref. 9, Elsevier.

mediators and tissue-destructive proteases[25,30]. Furthermore, COPD macrophages display a reduced ability to phagocytose and kill pathogenic bacteria[31–33], enabling chronic bacterial infection that can further promote inflammation through a T1 immune response. This response involves T helper 1 (T_H1) $CD4^+$ lymphocytes, which classically respond to intracellular bacteria by producing cytokines (such as IL-12, IL-18, type I interferons and interferon-γ (IFNγ)) that, in turn, activate macrophages, natural killer (NK) cells and neutrophils. T_H17 responses (involving T_H $CD4^+$ cells producing IL-17) are also involved in neutrophil recruitment. A subset of patients with COPD display a bronchial epithelial *IL17* gene expression signature that is associated with increased airway neutrophils and macrophages, increased airway obstruction and functional small airway disease on quantitative chest computed tomography (CT), but a decreased response to corticosteroids that might be due to lack of association of the *IL17* signature with higher eosinophil or mast cell count, suggesting the need for targeted therapies[34].

Eosinophilic inflammation (type 2)

Eosinophils are a type of leukocyte involved in the T2 immune response, especially against parasites, with a role in some inflammatory processes such as allergies and COPD. Lymphocyte subsets (T_H2 and group 2 innate lymphoid cells (ILC2s)) secrete the cytokines IL-4, IL-5 and IL-13, which are expressed from a cluster of cytokine genes located at chromosome 5q31A, which also includes genes encoding IL-3 and granulocyte–macrophage colony-stimulating factor (GM-CSF) (*IL3* and *CSF2*)[35]. These cytokines provide activation and survival signals for mast cells, basophils and eosinophils[36]. There is evidence of mast cell activation in a subgroup of patients with COPD who also have other markers of T2 inflammation in the lungs[37]. This mast cell gene expression signature in COPD activation differs from the IgE activation gene expression observed in allergic asthma, suggesting that these are cytokine-activated mast cells. Furthermore, mast cell gene expression is downregulated by ICS[22]. Increased eosinophil counts are also present in the COPD subgroup of patients with a different profile of airway inflammation including other T2 components[20,38–41]. T2 airway inflammation can coexist with other abnormal immune responses in COPD such as neutrophilic inflammation[42,43].

The presence of eosinophilic airway inflammation often fluctuates over time, owing to both the natural circadian variation in eosinophil numbers and the dynamic nature of inflammation[44,45]. Repeated low eosinophil counts in the stable state are likely to represent an absence of T2 inflammation, whereas higher counts indicating T2 inflammation may show variation over time but nevertheless indicate a tendency towards T2 inflammation either in the stable state or in exacerbations[46–48]. Additionally, increased IgA and IgM levels are found in the bronchoalveolar lavage fluid (BALF) of patients with COPD with higher BEC. This suggests differences in adaptive immune response that potentially explain increased bacterial infections in patients with COPD with lower BEC[49,50].

IL-5. IL-5 has a central role in the differentiation and release of eosinophils from the bone marrow, promoting cell maturation and survival[36]. Conversely, mice that lack IL-5, or its receptor (IL-5RA), display several developmental and functional impairments in B cell and eosinophil lineages. In mice, IL-5 also regulates the expression of genes involved in proliferation, cell survival, maturation and effector functions of B cells[35]. Thus, IL-5 fulfils a pivotal role in innate and acquired immune responses and eosinophilia[51].

IL-4 and IL-13. IL-4 and IL-13 are two cytokines that share a functional signalling receptor chain (type II IL-4R, composed of IL-4Rα and IL-13Rα1), but IL-4 can also bind to the type I IL-4 receptor (IL-4R, composed of IL-4Rα and common γ-chain)[52]. IL-4Rα is present on various types of cell including $CD4^+$ and $CD8^+$ T cells, lung epithelial cells, B cells, macrophages, airway goblet cells and smooth muscle cells[53]. IL-13Rα1 is expressed by B cells, eosinophils, macrophages, lung epithelial cells, airway goblet cells and endothelial cells[53]. The signalling of IL-4 and IL-13 via the IL-4Rα–signal transducer and activator of transcription 6 (STAT6) pathway leads to the production of inflammatory mediators (histamines, leukotrienes) and cytokines (IL-4, IL-13 and IL-9) by basophils, eosinophils and mast cells that in turn trigger IgE production by plasma B cells, eosinophil infiltration, airway inflammation, bronchoconstriction and tissue damage[54]. Additionally, STAT6 signalling induces sonic hedgehog expression in the airway epithelium, leading to goblet cell metaplasia and enhanced mucus production and disruption of epithelial barrier integrity[55,56].

Epithelial alarmins

Alarmins are endogenous, constitutively expressed, chemotactic and immune-activating proteins or peptides that are actively released by various cell types including immune, epithelial and endothelial cells as a result of degranulation, cell injury or death, or in response to immune induction[57]. Epithelial alarmins are released by the airway epithelium

in response to inhaled microbes and particles[58]. Here we focus on the potential relevance of the epithelial alarmins IL-33 and thymic stromal lymphopoietin (TSLP) in patients with COPD.

IL-33. IL-33 is an alarmin that belongs to the IL-1 superfamily, located in the nucleus under physiological conditions. The full-length protein has 270 amino acids organized in two domains: an N-terminal nuclear domain and the C-terminal IL-1-like cytokine domain, separated by a divergent 'protease sensor' domain[58]. During inflammatory processes, the full-length protein can be cleaved by various proteases, producing smaller mature forms with higher biological activity[59].

IL-33 canonically binds to the ST2 receptor, which is a member of the Toll-like receptor (TLR)–IL-1R superfamily and is constitutively expressed by immune cells such as ILC2s, mast cells, eosinophils and regulatory T cells[59], and is also expressed on goblet cells and epithelial cells. ST2 stimulates the production of inflammatory mediators through the activation of transcription factors such as nuclear factor-κB (NF-κB), which leads to upregulation of TRAF6, IL-1 receptor-associated kinase 1 (IRAK1) or IRAK4, MAP kinases and AP-1. Treatments that target either IL-33 or ST2 have the potential to modulate both T2 and non-T2 inflammation as the ST2 receptor is expressed on cell types involved in T2 responses including ILC2s, eosinophils and mast cells, in addition

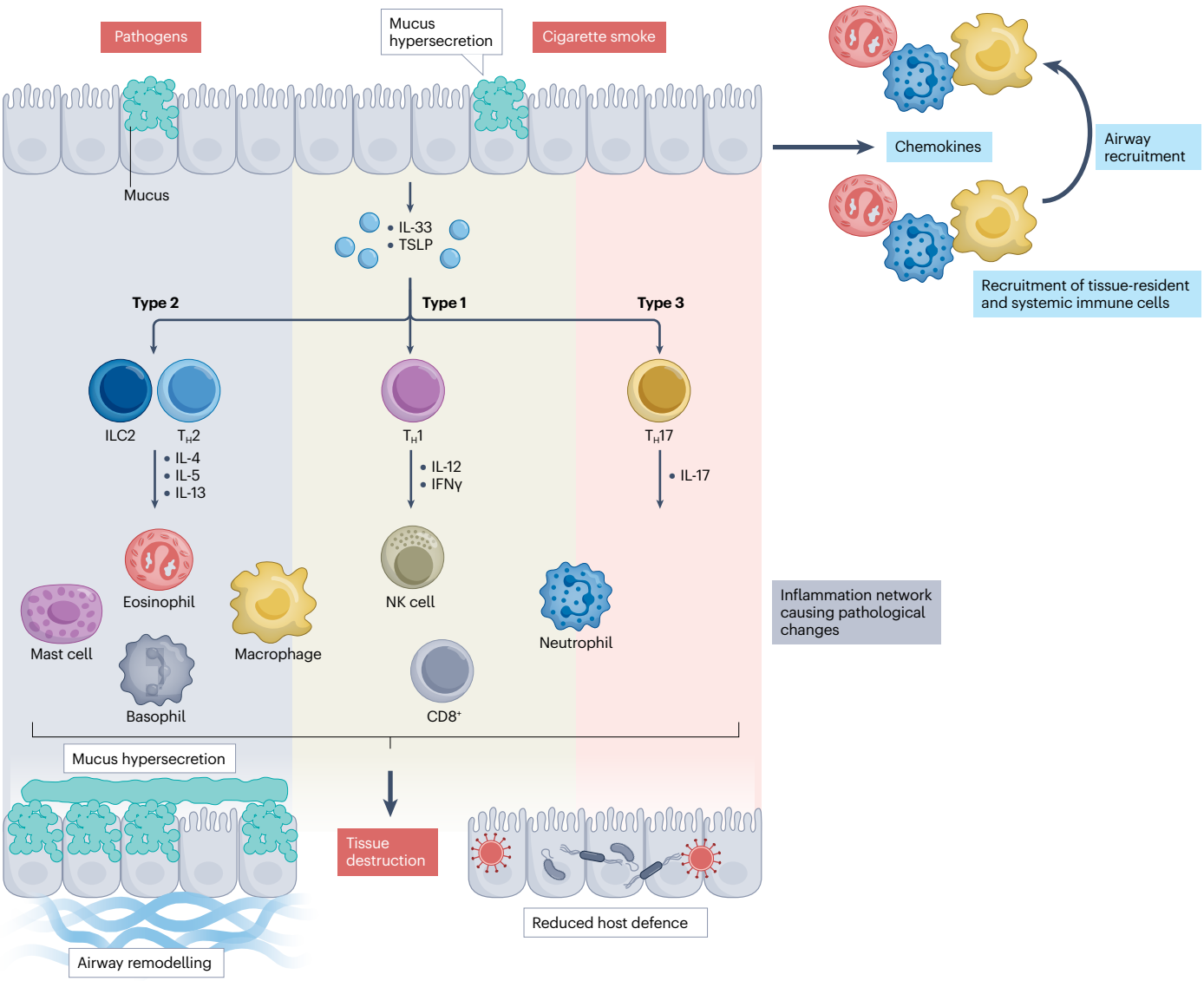


Fig. 2 | Overview of the inflammation network in COPD. Cigarette smoke (and other environmental pollutants) and infection cause chemokine and alarmin production. Chemokines cause the recruitment of inflammatory cells into the airways. Alarmins upregulate type 1, type 2 and type 3 (T helper 17 cell; T_H17 cell) responses, promoting the development of a complex inflammatory network that involves both the innate and adaptive immune systems. Type 1 and type 3 responses are common in chronic obstructive pulmonary disease (COPD), involving increased numbers of $CD8^+$ T cells and neutrophils. Type 2 responses are present in a subgroup of patients with COPD, involving the cytokines IL-4, IL-5 and IL-13 and increased numbers or activation of eosinophils and mast cells. The complex inflammation network causes pathological changes that are heterogeneous (varying between individuals). IFNγ, interferon-γ; ILC2, group 2 innate lymphoid cell; TSLP, thymic stromal lymphopoetin; NK, natural killer.

to non-T2 cells such as macrophages, $CD8^+$ lymphocytes and epithelial cells[59]. IL-33 has two forms: a reduced (IL-33red) and an oxidized (IL-33ox) form[60]. The oxidation of IL-33 involves a conformational change that prevents the binding of IL-33 to ST2. One study has reported that IL-33ox signals through the RAGE–EGFR signalling complex, which redirects epithelial cell fate, promoting a mucin hypersecretion phenotype at the expense of epithelial defence functions[61].

Animal models and experiments with cell lines have shown that chronic cigarette smoke exposure increases *IL33* gene expression levels in epithelial cells[62,63]. Subsequent viral exposure with cellular injury causes the release of IL-33 protein, potentially implicating this alarmin in the upregulation of inflammation during exacerbations[63]. Interestingly, smoke exposure was reported to decrease ST2 expression on ILC2s while increasing expression on macrophages and NK cells, which facilitated skewing of inflammation towards a T1 response[63]. Pulmonary IL-33 protein levels are higher in patients with COPD than in controls, with the highest levels being observed in those with severe or very severe COPD[63,64]. Whether the balance of IL-33ox versus IL-33red is altered in COPD has not been investigated. Interestingly, analysis of sputum supernatants from patients with COPD showed that IL-33 protein levels were higher in former than in current smokers, although IL-33 levels were still higher in current smokers with severe or very severe COPD than in non-smoking controls[64]. The explanation for these observations is not clear cut, as chronic smoke exposure upregulates epithelial IL-33 gene expression[62,63], but these protein studies suggest differences between current and former smokers with COPD. Airway epithelial IL-33 gene and protein expression levels were lower in current smokers versus never or ex-smokers across different COPD cohorts, although not all cohorts demonstrated these differences and there was considerable overlap in the expression levels between groups[65]. Consequently, the degree to which current smoking influences IL-33 activity in COPD remains unclear.

IL-33 expression in the epithelium is mainly confined to resting basal cells, with differentiation into mature epithelial cells resulting in a reduction or loss of expression[65]. Cigarette smoke reduces basal cell numbers owing to differentiation with an associated decrease in *IL33* gene expression, providing a mechanistic explanation for a reduction in IL-33 levels in current smokers[65]. These observations suggest that the potential efficacy of anti-IL-33 treatment in patients with COPD may be greater in former smokers than in current smokers[65].

Thymic stromal lymphopoietin. TSLP is an alarmin produced mainly by epithelial cells from multiple organs including the lung, skin and gastrointestinal tract. Other sources of TSLP are dendritic cells, keratinocytes, stromal cells, basophils and mast cells[66]. TSLP is considered a central regulator of the immune response to inhaled environmental insults, such as allergens, viruses and pollutants[67,68]. TSLP production can be induced by ligands that activate TLRs (2, 3, 8 and 9), by the pro-inflammatory cytokines TNF, IL-1α and IL-1β, and by the T2 cytokines IL-4 and IL-13 (ref. 66). Its production is NF-κB dependent and increases in response to a broad array of stimuli, including mechanical injury, infection, inflammatory cytokines and proteases such as trypsin and papain[66].

TSLP signals through a heterodimer of TSLP receptor (TSLPR) and IL-7 receptor-α, and uses the Janus kinase 1 (JAK1) and JAK2 signal transducer that subsequently activates either STAT5 (in haematopoietic cells) or STAT3 (in structural cells). TSLP influences various cell types, notably causing dendritic cells to induce naive $CD4^+$ T cell proliferation and T_H2 cell differentiation. Other key effects of TSLP on T2 inflammation include the activation of ILC2s and promotion of the development, function and recruitment of a subset of basophils to sites of T2 inflammation. TSLP also activates NK cells, $CD8^+$ T cells, B cells, regulatory T cells, eosinophils, neutrophils, monocytes, mast cells, macrophages, platelets, smooth muscle cells and sensory neurons[69,70].

Thus, similar to IL-33, TSLP potentially has broad inflammatory properties that are influenced by the inflammatory microenvironment. However, TSLP appears to be more important for the initiation of T2 immune responses. In summary, signalling by TSLP initiates a cascade of downstream inflammation, promoting T2 immune responses while also acting on a broad range of cell types[69,70].

Phosphodiesterases

Phosphodiesterases (PDEs) catalyse the hydrolysis of the intracellular second messengers cAMP and cGMP[71]. cAMP modulates the activity of transcription factors that promote inflammatory gene expression; for example, by interfering with the binding of NF-κB to promoter regions, PDE4 is expressed across multiple inflammatory cells and reduces cAMP levels upon activation, promoting multiple inflammatory pathways[72]. PDE3 modulates both cAMP and cGMP levels but has lower expression across immune cell types and so has a less prominent role in inflammation compared with PDE4 (ref. 73). However, PDE3 is more highly expressed in smooth muscle, which raises the potential for the development of PDE3 inhibitors as bronchodilators[74].

Kinases

Kinases facilitate cellular responses to extracellular signals that bind to cell surface receptors, including cytokines[75]. Kinases phosphorylate downstream molecules, thereby activating signalling cascades that modulate transcription factor activity. They are often expressed in multiple cell types, so the pharmacological inhibition of kinases involved in inflammation has the potential for a broad spectrum of cellular activity. However, many inflammatory genes are regulated by different kinase cascades, with the result that selective kinase targeting may be insufficient to control inflammation.

Members of the mitogen-activated protein kinase (MAPK) family promote inflammatory responses to various signals including TLR agonists, cytokines and oxidative stress[75,76]. There is evidence that the p38 MAPK pathway is activated in the lungs of patients with COPD[76–78]. JAKs are tyrosine kinases that bind to the cytoplasmic regions of cytokine receptors, activating inflammatory gene transcription through STAT proteins[75]. JAKs are the dominant kinases involved in cytokine signalling, and include JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) isoforms. Specific patterns of JAK isoform activation occur after cytokine receptor binding; for example, IL-5 signalling involves JAK2 only, whereas other cytokines recruit more JAK isoforms. The complex inflammatory pathways responsible for COPD, involving both T1 and T2 cytokines, supports the case to evaluate the therapeutic potential of JAK inhibitors in this condition.

IRAK4 is a threonine/serine kinase involved in TLR or IL-1 receptor signalling[79]. These receptors have a common intracellular domain that recruits the scaffold protein MyD88 after activation (by ligand binding). MyD88 facilitates the formation of a complex that involves IRAK4, resulting in the activation of downstream pro-inflammatory cascades including MAPKs and NF-κB. IRAK4 is also involved in IL-33 signalling[80].

Cystic fibrosis transmembrane regulator

Cystic fibrosis is caused by genetic mutations that alter the expression or function of cystic fibrosis transmembrane regulator (CFTR) through

mechanisms that include reduced ion channel function, decreased protein synthesis or impaired transport of CFTR to the cell membrane[81,82]. These abnormalities decrease chloride transport across the cell membrane, resulting in decreased airway surface liquid and mucociliary dysfunction. This leads to thick mucus secretions and increased susceptibility to infection, particularly to bacteria. In vitro evidence shows that cigarette smoke exposure causes dysfunction of wild-type CFTR[83]. Acquired CFTR dysfunction due to cigarette smoke exposure may arise through a reduction in mRNA expression and consequently protein levels[84], by protease-mediated degradation of CFTR protein[85] or by modification of CFTR structure and thereby function by components of cigarette smoke[86]. These studies suggest mechanisms by which chronic bronchitis symptoms in many patients with COPD may arise (at least partly) because of acquired (not genetic) CFTR dysfunction[83]. Indeed, clinical studies have shown that CFTR dysfunction in smokers is associated with increased symptoms of sputum production and the presence of bronchiectasis[87,88]. Recent reports clearly demonstrate that the presence of mucus plugs that obstructed medium- to large-sized airways in patients with COPD was associated with higher all-cause mortality compared with patients without mucus plugging on chest CT scans[89].

Oxidative stress

There is a high burden of oxidative stress in the lungs of patients with COPD, owing to continuous inflammation and tissue damage. The constituents of cigarette smoke itself also cause oxidation in smokers.

Nuclear factor erythroid 2-related factor (NRF2) is a transcription factor that regulates gene expression through the antioxidant response element pathway[90,91]. Oxidative stress signals promote NRF2 nuclear translocation, upregulating antioxidant gene expression[92]. Kelch-like ECH-associated protein 1 (KEAP1) acts as an antioxidant repressor by binding to NRF2 (ref. 90). Whereas the gene expression of NAD(P)H dehydrogenase quinone 1 (*NQO1*) and other antioxidant genes is upregulated in COPD, the activity of NQO1 is reduced in COPD alveolar macrophages, indicating a dissociation between gene expression and protein function under conditions of oxidative stress[38]. Indeed, the long-term effects of oxidative stress in the airways appear to lead to the reprogramming of COPD macrophages into a state characterized by mitochondrial dysfunction and metabolic exhaustion[93].

The inflammasomes form a family of multimeric intracellular protein complexes that control inflammation by activation of caspase 1 (ref. 94). The best-characterized inflammasome is formed by the Nacht, LLR and PYD domains-containing protein 3 (NLRP3), which is activated in response to various pathogens, particles, danger signals and oxidative stress[94]. Full activation of the NLRP3 inflammasome requires two sequential biological steps. The first ('priming step') increases pro-IL-1β and NLRP3 transcription, and the second ('activation step') induces inflammasome assembly, activation of caspase 1 and processing and release of the pro-inflammatory cytokines IL-1β and IL-18 (refs. 94,95). It has been described that patients with severe COPD present a primed NLRP3 inflammasome (that is, increased levels of *IL1B* mRNA) that can be activated during infectious events (production of IL-1β)[96].

Systemic inflammation

Increased levels of pro-inflammatory mediators and cytokines such as C-reactive protein (CRP), fibrinogen, IL-6 and IL-8 have been described in the serum of patients with COPD and cited as evidence of systemic inflammation. This is an important pathogenic mechanism contributing to multimorbidity in COPD[97], particularly if persistent over time[23]. Further, a longitudinal analysis of six inflammatory biomarkers in peripheral blood (white blood cell count, CRP, IL-6, IL-8, fibrinogen and TNFalpha) of 1,755 patients with COPD included in the ECLIPSE cohort found that, at baseline, 30% of patients did not show evidence of systemic inflammation whereas 16% had persistent systemic inflammation 1 year later. Importantly, persistent inflammation was associated with increased all-cause mortality (13% versus 2%, $P < 0.001$) and exacerbation frequency (1.5 versus 0.9 per year, $P < 0.001$)[23]. The potential effects of the new biologic drugs that are administered systemically will have to be characterized in future clinical trials.

Current COPD drug pipeline

Achieving disease improvement, stability and, eventually, remission is an important concept in chronic inflammatory diseases, and, in this context, there is a need for novel drugs that can modify the natural history of COPD, encompassing improved patient-reported outcomes, prevention of episodes of ECOPD, reduction in lung function decline and prevention of early mortality. As discussed below in detail, there is now a rich pipeline of drugs currently in development to achieve these goals (Table 1). Chronic inflammation triggered by cigarette smoking has been traditionally considered a key pathogenic mechanism of COPD. It is not surprising, therefore, that most research has focused, and still focuses, on anti-inflammatory drugs (Fig. 3). The current COPD pipeline

Table 1 | Selected drugs in clinical development for COPD

Drug	Company	Mechanism	Status
Anti-neutrophils			
Mitiperstat	AstraZeneca	Myeloperoxidase inhibitor	Phase II
Anti-eosinophils			
Mepolizumab	GlaxoSmithKline	Anti-IL-5 antibody	Approved by FDA
Benralizumab	AstraZeneca	Anti-IL-5Rα antibody	Phase III
T2 cytokine antagonists			
Dupilumab	Sanofi	Anti-IL-4α receptor antibody	Approved by the FDA and EMA
Anti-alarmins			
Astegolimab	Roche	Anti-ST2 antibody	Phase III
Itepekimab	Sanofi	Anti-IL-33 antibody	Phase III
Tozorakimab	AstraZeneca	Anti-IL-33 antibody	Phase III
Tezepelumab	AstraZeneca	Anti-TSLP antibody	Phase II
Phosphodiesterase inhibitors			
Ensifentrine	Verona Pharma	PDE3 and PDE4 inhibitor	Approved by the FDA
Tanimilast	Chiesi	PDE4 inhibitor	Phase III
Kinase inhibitors			
Frevecitinib	Kinaset Therapeutics	Pan JAK inhibitor	Phase I
AZD6793	AstraZeneca	IRAK4 inhibitor	Phase I
Mucus targeting			
GDC-6988	Roche	TMEM16A	Phase II

COPD, chronic obstructive pulmonary disease; IRAK4, IL-1 receptor-associated kinase 4; JAK, Janus kinase; PDE, phosphodiesterase; ST2, IL-33 receptor; TSLP, thymic stromal lymphopoetin.

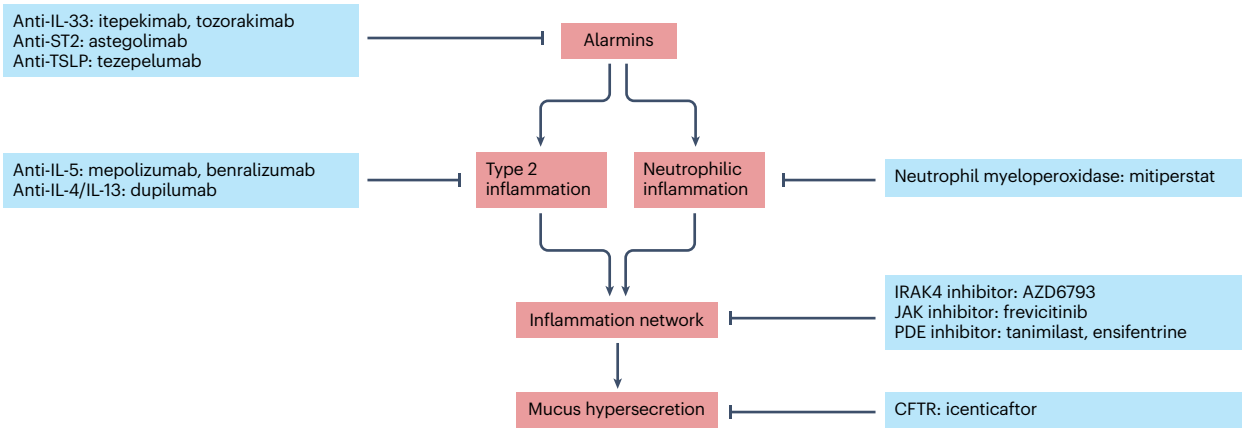


Fig. 3 | Pharmacological targets of drugs currently or recently in COPD clinical trials. Alarmin cytokines are released by various cell types including epithelial cells, causing both neutrophilic and type 2 inflammation. The alarmins thymic stromal lymphopoetin (TLSP) and IL-33, along with the IL-33 receptor (ST2), have been targeted by monoclonal antibodies. Monoclonal antibodies that target eosinophils (by blocking IL-5 signalling) or the IL-4 receptor-α (thus blocking IL-4 and IL-13 signalling) are able to reduce type 2 inflammation, which exists in a subset of patients with chronic obstructive pulmonary disease (COPD). Small molecules enable broader anti-inflammatory approaches that target multiple cell types. such as targeting IL-1 receptor-associated kinase 4 (IRAK4) inhibition (blocks cell activation), Janus kinase (JAK) inhibition (blocks cytokine signalling) and phosphodiesterase 4 (PDE4) inhibition (cAMP modulation). CFTR, cystic fibrosis transmembrane regulator.

has benefited from experience of the use of monoclonal antibodies (mAbs) to target alarmins and T2 pathway components in patients with asthma[98–101]. Historically, there have been failures of drugs designed to reduce neutrophil numbers in the lungs, in part due to safety concerns. Targeting neutrophil activation instead of cell numbers is an alternative approach, and developing broad anti-inflammatory small molecules is an approach that has been pursued historically and continues today. In recent years, there has been greater emphasis on precision medicine in the development of these novel drugs, with the aim to identify subgroups of patients who may eventually benefit the most.

Targeting neutrophilic inflammation

A clinical trial with a CXCR2 receptor antagonist aimed to reduce neutrophil lung recruitment to prevent progressive lung remodelling[102]. Unfortunately, it led to excessive inhibition of neutrophil function, with patients developing neutropenia and adverse effects. Despite this, the trial showed a clinically significant increase in the volume of gas exhaled in the first second of a forced spirometric manoeuvre (forced expiratory volume in 1 s (FEV_1), a measurement of lung function) in current smokers, somewhat supporting the validity of the conceptual construct[102]. Other attempts to block neutrophil recruitment or activation using mAbs directed against CXCL8, IL-1 receptor 1 and IL-17 also produced negative results[103–105]. The failure of these clinical trials may suggest that neutrophils do not play a prominent part in the pathophysiology of COPD, but there is a large body of evidence that associates increased neutrophil numbers and higher levels of neutrophil-related cytokines and chemokines with the presence and severity of COPD[30]. A plausible alternative explanation is that these historical clinical trials did not use a precision medicine approach targeting individuals with a high degree of neutrophil activity but recruited instead a broad range of patients with COPD.

COPD clinical trials of neutrophil protease inhibitors have also been negative so far[106,107]. Brensocatib (Brinsupri), an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP1), an enzyme responsible for the activation of neutrophil serine proteases, was associated with improved clinical outcomes in patients with bronchiectasis[108] and was recently approved by the FDA for this indication. Although bronchiectasis is a heterogeneous condition, a characteristic feature is the presence of airway bacterial infection associated with increased neutrophilic airway inflammation[109]. Brensocatib warrants research in patients with COPD, noting that the COPD responder subgroup may be individuals with neutrophilic activation caused by bacterial infection.

MPO is a haem-containing enzyme stored in neutrophil granules that promotes the production of reactive oxygen species that cause toxicity to local cells. Mitiperstat is a small molecule inhibitor of MPO[110] currently in phase II evaluation in COPD, aiming to reduce inflammation associated with neutrophil activation.

Targeting eosinophilic inflammation

IL-5 inhibitors. Mepolizumab is a mAb directed against IL-5, and benralizumab targets a subunit of the IL-5 receptor (IL-5Rα). Both of these mAbs decrease BEC by reducing release of these cells from the bone marrow. Benralizumab also causes antibody-dependent cell-mediated cytotoxicity owing to targeting the receptor and may confer an advantage by directly causing depletion of eosinophils. Both mAbs have been evaluated in phase III, placebo-controlled, RCTs performed in patients with COPD with increased exacerbation risk, defined as two moderate or one severe exacerbation in the previous year.

Mepolizumab was recently approved by the FDA for patients with COPD and an eosinophilic phenotype. In the first two phase III studies of mepolizumab, the drug did not meet the primary end point of exacerbation rate reduction over 52 weeks versus placebo in the METREO study (in patients with BEC ≥150 cells/μl at screening or ≥300 cells/μl in the previous year) but did meet this end point in the METREX study (ratio 0.82; $P = 0.04$), using the same BEC criteria[99]. A pre-specified pooled analysis of these studies reported a greater effect in patients with higher BEC at baseline, with a 23% exacerbation rate reduction at ≥300 cells/μl, highlighting the need to select patients with greater

eosinophilic inflammation for such interventions. Indeed, a recent phase III trial (the recent MATINEE study) showed that in patients with COPD with ≥300 eosinophils per microlitre mepolizumab reduced the annualized rate of moderate or severe ECOPD by 21% when added to background triple therapy[111].

The phase III studies of benralizumab (GALATHEA and TERRANOVA) did not show a consistent exacerbation rate reduction (primary end point) in the predefined eosinophilic population with a BEC of ≥220 cells/μl before randomization[112]. A prespecified pooled exploratory analysis investigated potential responder subgroups and reported a 30% exacerbation rate reduction (95% CI for rate ratio 0.56–0.88) in the eosinophilic population with three or more exacerbations in the previous year and receiving triple inhaled therapy[113].

Overall, these studies of mAbs that target IL-5 signalling have shown increased treatment effects in subgroups with higher BEC, higher exacerbation rates and using triple therapy before study entry. In fact, following the results of the MATINEE study, the FDA has recently approved mepolizumab as an add-on maintenance treatment for adult patients with inadequately controlled COPD and an eosinophilic phenotype.

Depemokimab is a mAb directed against IL-5 that has demonstrated efficacy in asthma when administered at 6-monthly intervals[114]. Other biologic drugs are administered every 2–8 weeks. The longer duration of action of depemokimab offers practical advantages to patients, and this drug may be a useful future candidate to be evaluated in patients with COPD.

IL-4 and IL-13 inhibitors. Dupilumab is an IL-4 receptor-α antagonist that interferes with both IL-4 and IL-13 signalling. Dupilumab is licensed for the treatment of both severe asthma with evidence of T2 inflammation and atopic dermatitis[115,116]. The drug has recently received regulatory approval in Europe and the USA for COPD based on two phase III RCTs (BOREAS and NOTUS) that compared dupilumab (300 mg, twice weekly) with placebo over 1 year in patients with high exacerbation risk while already using triple inhaled therapy. Patients were required to have a BEC of ≥300 cells/μl at screening, enriching the study population for the presence of T2 inflammation. A history of chronic bronchitis was also an inclusion criterion, potentially enriching for individuals with IL-13-driven pathophysiology[117]. The studies reported 30–34% exacerbation rate reductions for dupilumab versus placebo ($P < 0.001$), with improvements in FEV_1 and quality of life[118,119]. Lung function improvements have also been observed with dupilumab in asthma RCTs[116] and can be explained by the inhibition of IL-13-induced airway pathophysiology including smooth muscle constriction and airway remodelling. Additionally, the lung function benefit of dupilumab in COPD appeared to be greater in individuals with higher levels of exhaled nitric oxide (FeNO). IL-13 upregulates the activity of inducible NO synthase, thereby increasing NO production[120]. Similarly, FeNO levels identify patients with severe asthma with IL-13-driven T2 inflammation who are a target group for dupilumab treatment[121]. A practical issue that limits the use of FeNO as a COPD biomarker is that levels are reduced in current smokers[122].

Collectively, the results from the dupilumab and mepolizumab programmes indicate that certain biologic treatments can be clinically safe and efficacious in certain subtypes of COPD, and open new avenues to explore novel biologic therapies in subgroups of patients with COPD[123]. Dupilumab is the first biologic treatment recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for the maintenance treatment of patients with COPD with chronic bronchitis and BEC >300/μl who, despite being treated with triple therapy, continue to present episodes of ECOPD[1]. Dupilumab and mepolizumab target different components of the T2 response, and the clinical or biomarker characteristics that predict a better response to one of these treatments over the other remain to be elucidated. Furthermore, it is likely that, as results from ongoing studies emerge, other biologics will enrich the therapeutic armamentarium available for the treatment of people with COPD[123].

Targeting alarmins

IL-33 inhibitors. Itepekimab is a mAb that targets IL-33. A phase II RCT in patients with COPD with two or more ECOPD in the previous year showed no significant effect of itepekimab versus placebo on exacerbation rates (the primary end point)[124], whereas there was an improvement in FEV_1 (secondary end point). A subgroup analysis reported a 42% exacerbation rate reduction with itepekimab in ex-smokers, with no benefit in current smokers (as mentioned above, IL-33 expression is decreased in current smokers), and FEV_1 improvement with itepekimab was also greater in ex-smokers. Itepekimab reduced BECs, likely owing to inhibition of IL-33-mediated ILC2 activation, thereby reducing IL-5 secretion, and IL-33 binding to ST2 on eosinophils[125,126]. Higher BECs were associated with a greater effect of itepekimab on FEV_1 but there was no relationship with exacerbation rate reduction. These findings point to potential responder subgroups characterized by smoking status and BEC. Larger phase III studies in which the focus is on former smokers are ongoing.

Tozorakimab is another mAb that targets IL-33 (ref. 127). In phase I studies, tozorakimab decreased serum levels of the endogenous IL-33–soluble ST2 (sST2) complex in healthy subjects and patients with COPD, indicating inhibition of the receptor binding of IL-33 (ref. 128). Later-phase COPD studies of this molecule are ongoing.

A phase II study of tozorakimab versus placebo was conducted in patients with COPD with one or more exacerbations in the previous 2 years[129]. At 12 weeks, the primary end point showed no significant effect of tozorakimab versus placebo on FEV_1 (24 ml; $P = 0.22$), although a benefit on lung function and COPDcompEX (a surrogate measure of exacerbations[130]) was observed in the subgroup with two or more prior exacerbations[129]. Patients with COPD with higher exacerbation risk are the focus of ongoing phase III studies.

Interestingly, a phase IIa RCT in patients hospitalized with coronavirus disease 2019 (COVID-19) reported a statistically significant reduced risk of death or respiratory failure with tozorakimab in individuals with higher serum IL-33–sST2 complex levels[131]. These results suggest that inhibition of IL-33 during severe viral infection may provide therapeutic benefit and could be relevant to the acute treatment and prevention of ECOPD, which is frequently caused by viral infections.

Instead of targeting IL-33, astegolimab is a mAb that targets the ST2 receptor. It has been evaluated in a small phase II RCT in patients with COPD with two or more exacerbations in the previous year[132]. Astegolimab had no significant effect on exacerbation rate or FEV_1, but significantly improved quality of life and demonstrated biological effects by reducing blood and sputum eosinophil counts. Phase III studies are ongoing. Interestingly, a dose-ranging phase II study of astegolimab in patients with asthma showed positive effects versus placebo on exacerbation rates over 54 weeks. The effect was consistent across a range of BECs including lower counts (<150 cells/μl)[133]. These results suggest a benefit of this molecule in patients with asthma without T2 inflammation, which is compatible with the knowledge of IL-33 signalling (already reviewed) and may have relevance to the ongoing COPD studies in patients with lower circulating eosinophil levels.

Overall, the phase II studies of mAbs targeting the IL-33 signalling pathway have provided promising results, and further elucidation of the possibility of differential effects in current versus ex-smokers will come from the phase III studies. IL-33 can promote a broad range of inflammatory responses, and it will be of interest to understand whether there is a differential effect in patients with COPD according to the level of T2 inflammation present.

Thymic stromal lymphopoietin inhibitors. Tezepelumab is a mAb that targets TSLP[70]. It is licensed for use in severe asthma, showing efficacy in individuals with and without evidence of T2 inflammation, although the greatest benefits were observed in individuals with the highest levels of T2 biomarkers[134]. The effect of tezepelumab in COPD has been evaluated in the phase II, placebo-controlled COURSE study conducted in patients with COPD taking inhaled triple therapy and with two or more moderate or severe COPD exacerbations in the previous year[135]. The rate of moderate or severe exacerbations over 52 weeks was not significantly reduced with tezepelumab versus placebo. However, prespecified subgroup analyses showed greater effects in patients with higher BEC, with ≥150 cells/μl identifying a threshold above which greater exacerbation prevention was observed. Overall, this study is suggestive of efficacy of tezepelumab in patients with COPD with increased exacerbation risk and BEC >150 cells/μl.

Inhaled TSLP-targeting mAb therapy is in clinical development for asthma owing to its potential to increase lung exposure compared with systemically administered mAbs plus a more convenient route of administration for patients. This approach may also be useful in COPD.

The positive data for tezepelumab in asthma, coupled with the promising phase II results for anti-alarmin mAbs in COPD, has encouraged the preclinical development of other anti-alarmin mAbs designed to have greater potency and/or longer duration of action. Additionally, mAbs with specificity for more than one antigen have been developed, targeting TSLP, IL-4 and IL-13. Such a combination of targets may increase the efficacy compared with that already demonstrated by mAbs in COPD.

Phosphodiesterase inhibitors

Orally administered PDE4 inhibitors (for example, roflumilast) are licensed for use in COPD and atopic dermatitis. However, a limitation of these drugs is the frequency of side effects, including nausea, weight loss and gastrointestinal disturbance, due to relatively high PDE4 expression in the brain and gastrointestinal tract[71,136]. Similarly to topically administered PDE4 inhibitors that have been developed for atopic dermatitis to reduce systemic exposure[136], inhaled PDE4 inhibitors are being developed for COPD, with tanimilast now in phase III development[137,138]. Earlier-phase studies showed a high degree of lung versus systemic exposure with approximately 2,000-fold higher tanimilast concentrations in sputum samples versus plasma[137]. Tanimilast also regulated the expression of multiple genes in sputum, including some involved in inflammation and oxidative stress pathways[139]. A phase II dose-ranging RCT did not show a significant treatment benefit for tanimilast versus placebo on exacerbations over 24 weeks, although a post hoc analysis identified a potential responder subgroup based on the presence of chronic bronchitis and higher BECs[138]. These characteristics have been incorporated into the inclusion criteria of ongoing phase III studies. Phase II data show that tanimilast does not display adverse effects associated with systemic PDE4 inhibitors.

Ensifentrine is approved for COPD by the FDA. The drug inhibits both PDE3 and PDE4, with PDE3 inhibition enabling smooth muscle relaxation[71]. Ensifentrine displays higher potency for PDE3 versus PDE4 in vitro, suggesting that this molecule may have a predominant bronchodilator action clinically[71]. Early-phase clinical trials demonstrated that nebulized ensifentrine causes significant bronchodilation with improvements in symptoms and quality of life[140,141]. In the ENHANCE-1 and ENHANCE-2 phase III studies, ensifentrine met the primary end point of significantly improving average FEV_1 over 12 h post-dose versus placebo at week 12 (ref. 142). Ensifentrine also improved quality of life and dyspnoea compared with placebo. The inclusion criteria did not enrich for individuals with high exacerbation risk, resulting in low exacerbation rates. The reduction in exacerbation rates with ensifentrine in these studies should consequently be interpreted with caution. The ENHANCE studies showed that ensifentrine was well tolerated, without the typical PDE4-related adverse effects. Ensifentrine has recently received regulatory approval from the FDA, but there remain important gaps in knowledge. The anti-inflammatory activity of ensifentrine in COPD remains unclear, and the ability of this drug to prevent exacerbations in individuals at high exacerbation risk needs to be investigated. Furthermore, the ENHANCE studies excluded patients treated with two long-acting bronchodilators or triple therapy, and so the benefits of ensifentrine in this large COPD subgroup have yet to be determined.

Kinase inhibitors

Clinical trials of oral and inhaled p38 MAPK inhibitors have failed to show consistent efficacy in RCTs in COPD, probably because targeting p38 MAPK with high selectivity does not affect other kinase signalling cascades that promote inflammation, often through overlapping downstream signalling mechanisms. Compounds that target multiple kinases in addition to p38 MAPK have been developed to overcome this issue, with the advantage of being delivered by inhalation to avoid systemic toxicity[143]. These drugs have not advanced beyond phase II studies.

Oral JAK inhibitors are licensed for use in rheumatoid arthritis, ulcerative colitis and atopic dermatitis. However, there are concerns about side effects including increased risk of cardiovascular events, cancer and opportunistic infections, particularly in older individuals[144]. Inhaled JAK inhibitors have been developed to reduce systemic exposure and thereby reduce the risk of these adverse events[145,146]. These drugs have shown anti-inflammatory effects on FeNO, a T2 biomarker, in early-phase asthma studies[145,146]. It is not yet clear whether inhaled JAK inhibitors also have significant activity on other inflammatory pathways in the lungs including T1 inflammation. However, oral JAK inhibitors have demonstrated activity on such pathways in other conditions, notably rheumatoid arthritis. This supports the case to evaluate inhaled JAK inhibitors in COPD, with the potential for a broad anti-inflammatory effect across a range of cytokine signalling pathways. However, the potential for JAK-related adverse effects will need to be monitored closely.

IL-1 receptor-associated kinase 4 (IRAK4) is a threonine/serine kinase that signals downstream of MyD88 and is involved in activation of pro-inflammatory cascades. A small molecule oral inhibitor of IRAK4 being developed for COPD treatment has entered phase I trials.

Cystic fibrosis transmembrane regulator modulators

Small molecule CFTR potentiators increase the ion channel activity of wild-type and mutant CFTR and can improve CFTR function under conditions of cigarette smoke exposure[86]. CFTR potentiators are used to treat patients with cystic fibrosis and may also have utility for the treatment of patients with COPD with mucus hyper-secretion[81,82].

A phase II RCT over 28 days of the CFTR potentiator icenticaftor was conducted in patients with COPD with chronic bronchitis[147]. There was no difference in the primary end point of lung clearance index, a measurement of peripheral airway function, but there was some evidence to support an effect on pre-bronchodilator and post-bronchodilator FEV_1. A subsequent phase II, placebo-controlled RCT evaluated icenticaftor over 24 weeks in patients with COPD with one or more exacerbations in the previous year and symptoms of chronic bronchitis who were being treated with inhaled triple therapy before study entry[148]. The primary end point (change in FEV_1 at 12 weeks) was not met. However, there were dose–response relationships for FEV_1 at 24 weeks and symptom scores at both 12 and 24 weeks, although the average improvements were relatively small.

TMEM16A is a chloride channel expressed on the surface of epithelial cells that represents an alternative target to CFTR[149]. Small molecules have been identified that can stimulate TMEM16A with the aim of increasing epithelial fluid secretion to aid mucus clearance[150]. An early-phase clinical trial (ClinicalTrials.gov ID NCT06603246) has commenced, which includes patients with COPD, to evaluate the effects of the TMEM16A potentiator GDC-6988.

Any future development of CFTR modulators for COPD needs to carefully consider the target population most likely to respond. Using the inclusion criteria of chronic bronchitis may include individuals with generally little or no sputum production, whereas potential responders may be individuals with a greater burden of mucus hypersecretion. Additionally, responses may vary according to the degree of CFTR dysfunction, both acquired and genetic, for which the development of predictive biomarkers is required. The heterogeneous nature of COPD requires refinement of clinical and biomarker strategies to develop modulators of mucus secretion. Recent observations linking mucus plugs in COPD with mortality, discussed above, should boost a renewed interest in the investigation of mucus-regulating or mucolytic therapies[151].

Oxidative stress

Cigarette smoking and inflammation increase the burden of oxidative stress in the lungs of patients with COPD[38,90,91]. Studies of anti-oxidant treatments that scavenge molecules involved in oxidative stress, such as *N*-acetylcysteine, have produced varying and often negative results in COPD, possibly owing to insufficient activity in relevant lung environments[91].

KEAP1–NRF2 protein–protein interaction (PPI) inhibitors bind to KEAP1 to prevent the interaction with NRF2, enabling NRF2 nuclear translocation and activation of antioxidant signalling pathways[38,90]. PPI NRF2 activators increase NQO1 activity and upregulate antioxidant gene expression[38]. These compounds also restore macrophage oxidative metabolism and cellular energetic function[93], which might explain the increased bacterial phagocytosis and killing, as well as increased efferocytosis, in COPD macrophages upon NRF2 activation[31], providing an intriguing mechanistic basis to support the further development of PPI NRF2 activators for COPD.

Selnoflast is an oral small molecule reversible antagonist of NLRP3. This drug is in early clinical development with studies launched in asthma and other inflammatory diseases[152]. This class of drug may have utility in targeting dysregulated innate immune responses due to inflammasome activation in COPD.

Opportunities for therapeutic intervention

Prevention of COPD has been traditionally based on avoiding smoking initiation and/or facilitating early smoking quitting. Given that tobacco smoking is the main environmental risk factor of COPD these are valid and important measures. However, now we know that about one-third of patients with COPD in the world are never smokers[153], and many different environmental risk factors have been identified for reduced lung function in various age 'bins', which increase with age and interact with one another[154]. Besides, very recent research has shown that a polygenic risk score (PRS) developed in adult patients with COPD can also be identified in children and adolescents[155], further supporting the concept of early-life origins of COPD[5,8,9]. This new understanding opens opportunities for prevention and early treatment of COPD[156]. On the other hand, the recognition of the biological and clinical complexity of 'adult' COPD also opens new windows of opportunity for drug development in young and older patients with COPD. All these opportunities are discussed below in more detail.

Abnormal lung development

At birth, normal human lungs are not fully developed. They grow and mature until they reach peak lung function at around 20–25 years (slightly earlier in females)[157]. Many early life events, both before and after birth, can alter this development and result in lower-than-normal peak lung function. Several studies have now shown that this occurs in about 4–12% of the general population[5] and that this is a risk factor for the development of COPD later in life[8,9]. Genetic, host (prematurity, low birthweight) and environmental factors (includes respiratory infections, for example, by respiratory syncytial virus (RSV), passive exposure to smoking, allergies and poor nutrition, among others) have been identified as potential mechanisms of poor lung development in infancy and adolescence[8,9]. Importantly, for still unknown reasons, about 15% of children originally travelling in a low lung function trajectory can regain a normal trajectory during infancy and adolescence (catch-up), whereas the remainder do not[158]. We speculate that genetic and host factors are likely to have a key pathogenic role in those children not able to catch up, whereas environmental factors (which may improve over time) may be relevant in those who indeed catch up. Yet, this is a hypothesis that requires research, as a better understanding of the mechanisms of catch-up may potentially help more children to regain a normal lung function trajectory early in life and, hypothetically, be explored also in older populations. To our knowledge, there is no drug being investigated in this setting currently. Yet, the identification of measures that promote normal lung development seems of great potential relevance. For instance, supplementation of vitamin A in pregnant Nepali women (Nepal being an area with a high prevalence of vitamin A deficiency in the population) results in better lung function in the offspring[159].

Chronic bronchitis

Chronic bronchitis is a prevalent condition that occurs in about 30% of patients with COPD[1]. Chronic bronchitis has been traditionally defined by the presence of chronic cough and sputum production for at least 3 months per year for 2 consecutive years, in the absence of other conditions that can explain these symptoms[1]. Today, chest CT scans are obtained frequently for various reasons in patients with COPD and often find previously unsuspected bronchiectasis, which can also contribute to these symptoms[160–163]. The co-existence of COPD and bronchiectasis requires research and, eventually, development of new therapies[164].

Cigarette smoking is the main risk factor for chronic bronchitis, but it can occur in never smokers, suggesting that other factors (inhalational exposure to dusts, biomass fuels, chemical fumes or domestic heating and cooking fuels, or gastro-oesophageal reflux) may be also involved[1]. Mucus plugging can be identified on chest CT in patients with

COPD despite a lack of chronic bronchitis symptoms and, importantly, this is associated with greater airflow obstruction, lower oxygen saturation and worsened quality of life and all-cause mortality[1,89]. Mucins are large glycoproteins. Two of them are produced by proximal airway surface goblet cells (MUC5AC) and by surface secretory cells found throughout the airways and submucosal glands (MUC5B)[1]. In patients with COPD, MUC5B levels markedly increase owing to submucosal gland hyperplasia[1]. Viruses, acrolein and many cytokines (IL-4, IL-13, IL-17, IL-23 and IL-25) also increase MUC5AC production[1]. Sputum MUC5AC has been associated more specifically with increased ECOPD frequency, increased symptoms and greater lung function decline[1].

Other than smoking cessation, specific treatments for chronic bronchitis are lacking. According to GOLD 2024 recommendations[1], novel therapeutic interventions could target one or more of the following goals: reduce the overproduction of mucus through targeting goblet cell activity, including by reducing inflammation; facilitate elimination of mucus by increasing ciliary transport; decrease mucus viscosity (novel mucolytics, CFTR potentiators); and facilitate cough mechanisms. Currently, effective treatment of chronic bronchitis in COPD is a clear unmet need and opportunity for the development of new drugs.

Chronic bronchial infection

It is now well established that the healthy lung harbours a large number of microorganisms, including bacteria, fungi and viruses, plus their respective metabolites, collectively known as the lung microbiome[165]. This healthy lung microbiome changes in patients with COPD. The term dysbiosis refers to a reduction in bacterial diversity, with reduction in beneficial bacteria and rise in symbiotic bacteria that may eventually become pathogenic. Dysbiosis occurs in patients with COPD with mild to moderate airflow limitation with decreased bacterial diversity, involving decreased abundance of *Prevotella* (which is predominant in the healthy lung microbiome) and increased abundance of *Streptococcus*, Lactobacillales, *Fusobacterium* and *Moraxella*[165,166]. Further, by integrating microbiome and metabolome analyses of BALF samples from patients with COPD, it has been shown that the presence of *Prevotella* and related metabolites is associated with fewer symptoms and better lung function, whereas the presence of *Streptococcus*, *Neisseria* and *Veillonella* and their related metabolites is associated with worse lung function and higher symptom burden[167]. Moreover, in patients with COPD with more severe airflow limitation, a predominance of proteobacteria and Firmicutes has been reported, including the following specific genera: *Haemophilus*, *Moraxella*, *Streptococcus*, *Rothia* and *Staphylococcus*[168–170].

Dysbiosis in COPD can drive the recruitment and activation of neutrophils[42]. A proteobacteria-dominant microbiome is associated with greater neutrophilic airway inflammation and increased mortality, suggesting an interaction between the pulmonary microbiome and inflammation that results in a worse prognosis[42,171]. Chronic bacterial infection has also been associated with more rapid lung function decline over time, possibly in relation to more frequent ECOPD episodes[172]. Likewise, elevated *Staphylococcus* relates to increased all-cause mortality, and *Staphylococcus* and *Pseudomonas* associate with exacerbations and greater disease severity[173]. Dysbiosis in COPD, therefore, constitutes a novel and potentially relevant therapeutic target to consider. In this setting, potential approaches include the use of chronic nebulized oral antibiotic treatment, sputum transplant (similar to faecal transplant used in some gastrointestinal diseases, which aims to restore a normal gut microbiome[174]) and/or nebulized probiotics.

Immune fitness

The term 'immunosenescence' refers to the innate and adaptive immune dysfunction that occurs with ageing[175]. Although the primary goal of active vaccination is the prevention of pathogen-specific infections, trained immunity-based vaccines may confer broad protection beyond the specific antigens they contain[176]. In particular, they may indirectly reprogramme innate cells to respond more efficiently to repeated infections, slow or reverse immune senescence by altering the epigenetic landscape, and leverage the pool of memory B and T cells to improve responses to new infections (that is, 'immune fitness')[177]. A more resilient immune system can contribute to healthier ageing[177].

Several vaccines are now available and recommended in adults with COPD[1], including those for flu, COVID-19, pneumococcus, shingles (*Herpes zoster*), Tdap (dTPa; pertussis, tetanus and diphtheria, if not vaccinated in infancy or adolescence) and RSV[178]. A large prospective study is ongoing to determine the prevalence and consequences of RSV infection in patients attending the emergency room because of ECOPD (NCT06735612), but a recent systematic review suggests that these patients often require hospitalization and have in-hospital mortality rates of 2.8–17.8% (ref. 178).

Exacerbations of COPD

A significant proportion of patients with COPD suffer acute episodes (<14 days) of increased symptoms, termed ECOPD[179]. These episodes have a significant impact on the health status and prognosis of the patient[1]. Hence, prevention and treatment of ECOPD are a fundamental goal of COPD management.

Currently available therapies reduce the frequency of ECOPD by about 30%, leaving a substantial number of remaining ECOPD. Why this is the case is uncertain: are they caused by biological mechanisms that are not targeted by current treatment? Are they not exacerbations of the disease we call COPD, but instead a worsening of symptoms in a patient with COPD due to other conditions (that is multimorbidity)[180]? In any case, because of their considerable clinical impact, prevention of ECOPD constitutes a large unmet medical need and a research priority. In this context the use of biologics such as benralizumab[101] and dupilumab[118] seems promising[123].

The treatment of ECOPD episodes themselves has not changed much in several decades and generally consists of nebulized short-acting bronchodilators, systemic steroids, antibiotics and supplementary oxygen. The only real therapeutic progress has been the use of non-invasive ventilatory support in patients with respiratory acidosis[1]. Thus, development of new therapeutic interventions to improve the therapeutic armamentarium available for ECOPD is a significant unmet need. In this context, it is of note that four distinct biological exacerbation clusters have been identified using sputum samples: bacterial, viral, eosinophilic-predominant and pauci-inflammatory (that is, no clear evidence of inflammation)[47,181]. The first three endotypes were associated with different biomarkers: sputum IL-1β, serum CXCL10 and BEC, respectively[181]. The future development of point-of-care methods to identify different pathogens and determine a panel of biomarkers of inflammation could enable rapid identification of ECOPD inflammatory subtypes for specific targeting in RCTs. In fact, the recently published ABRA trial showed that treatment with a single dose of benralizumab (see above) in patients with an acute ECOPD (or asthma) episode and a BEC of ≥300 cells/μl at the time of exacerbation achieves better 90-day outcomes than the current standard of care with prednisolone alone[182]. The recent

COPD-HELP study failed to reproduce these results with mepolizumab administered for 48 weeks in patients hospitalized because of ECOPD and with BEC of ≥300 cells/μl within the previous year[183]. There are important differences between these studies: the timing of the BEC differs, and the ABRA study used one dose whereas the COPD-HELP study provided treatment for 48 weeks. Further studies should elucidate the optimum strategies for such interventions during ECOPD with regard to biomarker measurements, phenotype of the patient and duration of treatment.

Multimorbidity

Patients with COPD often suffer other concomitant diseases, including cardiovascular, metabolic, osteo-muscular and psychological and/or psychiatric disorders (multimorbidity) that have a syndemic origin (see above)[11] and deserve identification and personalized treatment[1]. Discussion of the pharmacological management of these comorbid diseases is outside the scope of the present Review. However, it should be noted that the traditional focus on using inhaled treatments in COPD to target drug delivery to the lungs and limit the potential for adverse systemic effects may fail to address some of these comorbid conditions. In this setting, future COPD treatments may achieve better efficacy by systemic delivery if the pharmacological target is expressed both inside and outside the lungs. An example of this is the potential use of metformin or GLP1 agonists in patients with COPD for their potential respiratory and cardiovascular effects[184]. In fact, there is an increased risk of significant cardiovascular events during and immediately after an exacerbation, likely due to mechanisms such as increased systemic inflammation, reduced cardiac output owing to lung hyperinflation and arterial hypoxaemia[185]. Exploring the use of cardiovascular medication to reduce this risk during and after an episode of ECOPD could be beneficial[185].

Accelerated lung ageing

About 50% of patients develop COPD following an accelerated lung function decline[4] (Fig. 1). Accelerated lung ageing has been proposed as a key mechanism underlying this particular trajectory[186,187]. Ageing is a complex condition in itself[188]. Recently, 12 hallmarks of ageing have been proposed,[188] some of which have been identified in patients with COPD[189], specifically: telomere attrition[190,191], epigenetic alterations[192], loss of proteostasis[193], mitochondrial dysfunction[194,195], cellular senescence[196], stem cell exhaustion[197], chronic inflammation (see discussion above) and dysbiosis (see discussion above)[198]. Collectively, this highlights several novel areas in which to explore the potential development of new drugs, targeting ageing mechanisms in specific groups of patients. Of particular interest here is the potential use of senolytic therapy in patients with evidence of senescence[199].

Lung regeneration

The 2024 GOLD guidelines identify two goals for the management of clinically stable patients with COPD: relieve symptoms and reduce the future risk of ECOPD, disease progression and mortality[1]. Note that the possibility of 'curing' the disease by reverting the structural and physiological abnormalities that characterize COPD is not considered. Previous attempts to boost lung regeneration using retinoic acid failed[200] but, in our view, this ambitious goal deserves further research[201]. Perhaps with the new developments in stem cell therapy[202,203] or chimeric antigen receptor (CAR)-T cell therapy to modulate the abnormal inflammatory response of COPD[204,205] a targeted option could be explored in this setting too.

Glossary

Bronchiectasis
Disease characterized by permanent enlargement of parts of the airways of the lung.

Dyspnoea
Shortness of breath.

Goblet cells
A type of epithelial cell in the airways the primary function of which is to secrete mucins onto the internal surface of the respiratory tract.

ILC2s
Group 2 innate lymphoid cells; a subset of innate immune cells that have key roles in barrier immunity, especially at mucosal surfaces such as the lungs, gut and skin.

Mucins
A family of high molecular weight glycosylated proteins secreted by lung epithelial cells.

Neutrophil serine proteases
Enzymes produced by neutrophils that cleave peptide bonds in proteins.

Polygenic risk score
A number that summarizes the estimated effect of many genetic variants on an individual's risk of a disease.

Syndemic
The co-occurrence of diseases with shared mechanisms and risk factors that can help to explain the clustering of certain morbidities in chronic obstructive pulmonary disease.

Treatable traits
A clinical (phenotype) or biological (endotype) characteristic that contributes to the heterogeneity of chronic airway diseases.

Type 1 inflammation
(T_H1-mediated response). A type of immune response characterized by the participation of T helper 1 (T_H1) cells, cytotoxic T cells ($CD8^+$), macrophages, natural killer cells and neutrophils. Key participating cytokines are interferon-γ, IL-2 and TNF.

Type 2 inflammation
(T_H2-mediated response). A type of immune response characterized by the participation of T helper 2 (T_H2) cells, eosinophils, mast cells, basophils and B cells. Key participating cytokines are IL-4, IL-5 and IL-13.

Considerations for designing future RCTs in COPD

To optimize the chance of successful drug development of novel therapies for COPD, we propose that the following aspects are important in the design of future RCTs.

First, the biological heterogeneity of the disease should be considered. Improved understanding of disease mechanism and identification and validation of biomarkers related to these mechanisms could enable selection of patients most likely to benefit from a particular mechanism of action and allow the measurement of readouts that relate to the drug mechanism. Drugs that target inflammation or other mechanisms are highly likely to provide benefit to only a subset of patients owing to the clinical and biological heterogeneity and complexity of COPD. Such novel drugs should not be tested in 'all comers' with COPD, and the design of the successful phase III RCTs of dupilumab in COPD[118,119] show the advantage of targeting individuals using both clinical phenotype and biological endotype information to maximize the chance of treatment success.

Second, the clinical heterogeneity between individuals with COPD should also be considered. This includes the age of the individuals studied, with a particular emphasis on the need for RCTs in patients younger than 50 years, in whom any therapeutic intervention is likely

to be more effective than in older individuals[156], and a better understanding of the lung function trajectories that individual participants have followed or may follow in the future (Fig. 1). For instance, patients with an accelerated rate of lung function decline are more inflamed than those with low lung function that is stable over time[206]. Hence, a clinical trial of a potential anti-inflammatory treatment may be expected to benefit more participants following a rapid decline trajectory than those who have had a below normal (but stable) trajectory since early life. Thus, considering the lung function trajectory in trial inclusion criteria may help to avoid terminating the development of potentially useful drugs because they have been investigated in the wrong COPD subgroup. Given that spirometry is rarely measured in real life, the precise ascertainment of these different trajectories may be challenging in practice[9]. Yet, recent data identified blood-based biomarkers associated with different lung function trajectories[206] and lung function[207].

Finally, to optimize clinical trial design in COPD, it could also be important to consider clinical outcomes that go beyond the traditional ones (symptoms, lung function, exacerbations), potentially in combination, to create composite end points that increase the event rate for clinically relevant outcomes, as they can provide a more sensitive measurement of drug response and/or be more relevant to patients[208–210]. Additionally, recent advances in lung imaging (for example, quantification of mucus plugs) should encourage the use of CT scanning to phenotype patients for entry into RCTs and develop imaging measurements as end points[89,211].

Conclusions and outlook

COPD is a major public health problem that requires and deserves more attention and better treatments. The discussion above presents the current pipeline of drugs being developed for COPD, including positive results for dupilumab and mepolizumab, which target T2 inflammation. However, the exacerbation rate reduction achieved by these mAbs (approximately 20–30%) highlights that ECOPD may continue despite these treatments. T2 inflammation often exists alongside a dysregulated innate immune response, so broader anti-inflammatory treatments may be required. This may be achieved through anti-alarmin treatments or mAbs that target more than one molecule (for example, bispecifics). Small molecule approaches are still possible. However, identifying responder populations based on phenotype and endotype characteristics remains a challenge for all of these efforts.

There are several environmental risk factors for COPD, and many can interact with the genetic background of the individual over the life course (GETomics), which underlies the different lung function trajectories observed in the general population (the trajectome), some of which can have significant consequences for healthier ageing[6,212–214].

COPD can have early-life roots and occur in young individuals. This provides opportunities for prevention, early diagnosis and prompt, personalized and precise therapeutic intervention.

Different endotypes (that is, biological mechanisms) underlie different phenotypes (that is, clinical presentation) of COPD, resulting in a complex and heterogeneous disease with multiple components that differ between individuals and may change over time in the same individual. A better understanding of the key biological mechanisms involved in COPD pathophysiology will enable appropriate biomarkers to be developed that will facilitate optimal patient selection in future RCTs of novel drugs.

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