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Novel Anti-Inflammatory Approaches to COPD

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Abstract: Airway inflammation, driven by different types of inflammatory cells and mediators, plays a fundamental role in COPD and its progression. Neutrophils, eosinophils, macrophages, and $CD4^+$ and $CD8^+$ T lymphocytes are key players in this process, although the extent of their participation varies according to the patient's endotype. Anti-inflammatory medications may modify the natural history and progression of COPD. However, since airway inflammation in COPD is relatively resistant to corticosteroid therapy, innovative pharmacological anti-inflammatory approaches are required. The heterogeneity of inflammatory cells and mediators in annethe different COPD endo-phenotypes requires the development of specific pharmacologic agents. Indeed, over the past two decades, several mechanisms that influence the influx and/or activity of inflammatory cells in the airways and lung parenchyma have been identified. Several of these molecules have been tested in vitro models and in vivo in laboratory animals, but only a few have been studied in humans. Although early studies have not been encouraging, useful information emerged suggesting that some of these agents may need to be further tested in specific subgroups of patients, hopefully leading to a more personalized approach to treating COPD.

Keywords: anti-inflammatory drugs, COPD, inflammation, treatment

The Unmet Need for New Anti-Inflammatory Therapies for COPD

An aberrant inflammatory response that involves both innate and adaptive immunity characterizes COPD.[1] However, determining the precise role of specific cell types in the evolution of COPD is challenging.[2] While chronic inflammation is basically characterised by neutrophils and macrophages,[3] 20–40% of patients exhibit increased eosinophil numbers in blood and lung tissue.[4] Furthermore, neutrophilic inflammation is variably associated with concomitant eosinophilic inflammation in many patients.[5] T cells, B cells, dendritic cells (DCs) and epithelial cells are also involved in COPD.[5]

Corticosteroids (CSs) are the most often utilized anti-inflammatory medications in the treatment of COPD.[6] ICSs are indicated in COPD patients when there is an overlap with asthma or frequent exacerbations associated with high blood eosinophil counts (BEC).[7] Furthermore, CSs may play a cardioprotective role, reduce the risk of lung cancer, and possibly improve survival.[7] However, ICSs have little to no impact on the underlying inflammation in most COPD patients,[8] particularly in those who continue to smoke.[9]

The transcription of some anti-inflammatory genes is controlled by histone deacetylase (HDAC)2, which has been found to be downregulated by oxidative stress generated by cigarette smoke and activated neutrophils.[8,9] Another factor is the reduced glucocorticoid receptor (GR) expression in airway neutrophils, but not blood neutrophils, which has been found to be associated with the poor clinical response to ICS therapy in COPD patients.[10] Moreover, neutrophils from patients with COPD also showed an increase in GRβ levels,[11] which is thought to be a factor in the development of corticosteroid resistance because it is capable of inhibiting HDAC2 promoter activity.[12] Furthermore, several studies have revealed a connection between long-term ICS treatment and the incidence of pneumonia in COPD patients, mainly in those with lower BECs.[13]

Since CSs are less effective in neutrophil-driven pulmonary inflammation, the demand for therapies that act on this type of inflammation is increasing.[6,14]

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Over the past two decades, research has focused on discovering new targets capable of inhibiting the recruitment or activation of inflammatory cells involved in COPD and the development of drugs capable of blocking the inflammatory mediators released by these cells.[6] A complex network of inflammatory mediators, including chemokines, growth factors and lipid mediators, produced by the structural and inflammatory cells in the lung, are implicated in COPD and play a potential role in its pathogenesis.[15,16] Therefore, their inhibition is an important strategy to tamper the ongoing inflammatory process. Unfortunately, the results have often fallen short of expectations.

This narrative review aims to examine ongoing research to identify and develop possible new anti-inflammatory therapies for use in patients with COPD.

Search Strategy

A review of the literature published up to May 2023 was performed through the PubMed and Scopus databases to identify studies related to our stated objective of reviewing novel drugs under development for treating COPD. Thereafter, evaluation of the references of the selected articles identified other relevant publications. All authors participated in evaluation of the literature.

Inhibition of Recruitment and Activation of the Inflammatory Cells

Several small molecule inhibitors and biologic therapies are able, at least in experimental models, to prevent the recruitment and activation of the cellular components of inflammation.[6] Some of these have now been tested in COPD (Table 1). The development of other classes of drugs acting on targets that were considered potentially useful[17] was later abandoned because when tested on humans they proved to be poorly effective and/or induced major adverse effects. This is the case with the adenosine A_{2a} receptor agonists (regadenoson and UK432.097) due to unsatisfactory results and

Table 1 Therapies That Inhibit Recruitment and Activation of the Cellular Components of Inflammation in COPD

Class	Target	Drug	Clinical Development
PDE inhibitors	PDE4	Tanimilast	Phase 3
	PDE3/4	Ensifentrine	Phase 3
CXCR2 antagonists	CXCR2	Danirixin	Phase 2 (discontinued)
	CXCR1/2	Navarixin	Phase 2 (discontinued)
		Ladarixin	Phase 1
p38 MAPK inhibitors	p38α	CHF6297	Phase1/2
		Acumapimod	Phase 2
	p38α/β	Losmapimod	Phase 2 (discontinued)
		AZD7624	Phase 2 (discontinued)
	p38α/γ	RV568	Phase 2
	p38, Src and Syk kinases	PUR1800	Phase 1b
PI3K inhibitors	PI3Kδ	Nemiralisib	Phase 2 (discontinued)
	PI3Kγδ	AZD8154	Phase 1 (discontinued)
		RV1729	Phase 1
	Undisclosed	CHF6523	Phase 1
Selectin antagonists	E-, L-, and P-selectin	Bimosiamose	Phase 2 (discontinued)

(*Continued*)

Table 1 (Continued).

Class	Target	Drug	Clinical Development
Anti-IL-17A mAbs	IL-17A	CNTO 6785	Phase 2
Anti-IL-5 mAbs	IL-5	Mepolizumab	Phase 3
	IL-5Rα	Benralizumab	Phase 3
Anti-IL13/anti-IL4 mAbs	IL-13	Lebrikizumab	Phase 2
	IL-4R	Dupilumab	Phase 3
Anti-TSLP	TSLP	Tezepelumab.	Phase 2
Anti-IL-33 mAbs	IL-33	Itepekimab	Phase 3
		Tozorakimab	Phase 3
	ST2	Astegolimab	Phase 2

Abbreviations: CXCR2, CXC chemokine receptor 2; IL, interleukin; IL-4R, IL-4 receptor; IL-5Rα, IL-5 receptor α; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinases; PDE, phosphodiesterase; PI3K, phosphoinositide 3-kinase; ST2, tumour suppressor protein 2; TSLP, Thymic stromal lymphopoietin.

unwanted effects on the cardiovascular system,[18,19] anti-CXCL8 (ABX-CXCL) mAbs, which only slightly improved dyspnoea in COPD patients[20] probably because such drugs only block free CXCL8 and not the bound one, TNF-α inhibitors (infliximab and etanercept) that had no beneficial effects in patients with mild, moderate, or severe COPD[21,22] or for the treatment of acute exacerbations of COPD (AECOPDs),[23] likely because other proinflammatory cytokines drive the inflammatory process[24] and, furthermore, COPD patients had a significantly increased incidence of airway tumours and lung infections caused by TNF-α antibodies,[22] and anti-IL-1β mAbs (canakinumab and MEDI8986) because a lack of efficacy at least with regard to impact on the risk of AECOPDs, lung function, and HRQoL.[25]

Small Molecule Inhibitors

The main classes of small molecule inhibitors investigated for COPD include PDE inhibitors, CXCR2 antagonists, p38 MAPK inhibitors, PI3K inhibitors, and selectin antagonists.

Phosphodiesterase Inhibitors

There are 21 PDE genes in the human genome, which are organized into PDE families (PDE1 to PDE11), with many subtypes in each family.[26] PDEs catalyse the hydrolysis of cAMP and cGMP, thus controlling the intracellular levels of these cyclic nucleotides, their signalling pathways, and, ultimately, their biological responses.[26] Almost all cell types implicated in the pathophysiology of COPD are modulated by cAMP, which also controls the tone of the airway smooth muscle via the β_2-adrenoceptor (β_2-AR)-soluble adenylyl cyclase (sAC)-cAMP signalling pathway.[27] cGMP promotes vascular smooth muscle relaxation via the NO-soluble guanylyl cyclase-cGMP pathway[28] and is also implicated in eliciting bronchodilation in human small airways via the β_2-AR-sAC-cAMP pathway.[29] PDE4, PDE7, and PDE8 are cAMP-specific PDEs, while PDE5, PDE6, and PDE9 are cGMP-specific PDEs, and PDE1, PDE2, PDE3, PDE10, and PDE11 hydrolyse both cAMP and cGMP.[30]

PDE4 inhibitors are likely the most studied because PDE4 is the predominant PDE expressed in T-cells, eosinophils, neutrophils, monocytes, and macrophages, and therefore its inhibition may also have inhibitory effects upon both inflammatory and immune cells.[30] Nevertheless, only one drug in this class, roflumilast N-oxide, has been approved for treating severe COPD.[31] However, roflumilast is not widely used because of a narrow therapeutic window with a range of dose-limiting side effects in the gastrointestinal tract and the central nervous system.[32] The addition of roflumilast is only recommended for patients who continue to exacerbate despite triple therapy with LABA + LAMA + ICS therapy or for those with a BEC of <100 cells/μL, especially if they have chronic bronchitis and a FEV_1 <50%.[33]

Therefore, other PDE4 inhibitors have been developed to be administered by the inhaled route to potentially reduce these adverse effects.[34] Unfortunately, the development of most of the inhaled PDE4 inhibitors has been discontinued due to modest effects in patients with COPD.[35] This lack of beneficial effects may be because inhaled drugs are generally designed to be retained in the lung and have no effect on systemic inflammation.[36] However, adding the inhaled PDE4 inhibitor, tanimilast, to inhaled triple therapy reduced AECOPDs.[37] Tanimilast exerts specific immunomodulatory effects linked to a T2 endotype and CD141 overexpression in DCs which suggests that it may have complementary anti-inflammatory effects to ICSs.[38] Tanimilast is currently being evaluated in two Phase 3 studies that are investigating its efficacy and safety as an add-on to triple maintenance therapy in subjects with COPD and chronic bronchitis (NCT04636801 and NCT04636814).

PDE4 is divided into four subfamilies: PDE4A, PDE4B, PDE4C, and PDE4D. The genes in each subfamily can express between 3 and 11 proteins, resulting in at least 25 distinct PDE4 protein isoforms.[39] PDE4 isoforms are essential spatiotemporal regulators of cAMP signalling due to their distinct intracellular distribution patterns, dynamic activity regulation, and isoform-specific regulation.[40] PDE4 isoform selective inhibitors do not yet exist. Therefore, it will be important to create novel isoform specific PDE4 inhibitors also because this approach may help to reduce side effects.[39] However, due to the structural similarities and highly conserved sequences of the isoforms, designing PDE4 isoform selective inhibitors is difficult.[30]

Agents capable of simultaneously inhibiting PDE3 and PDE4 are also under development.[41] This approach induces additional or synergistic anti-inflammatory and bronchodilator benefits compared to PDE3 or PDE4 inhibition alone[42] (Figure 1). Furthermore, dual PDE3/4 inhibitors have been shown to improve mucociliary clearance.[43] Ensifentrine, a first-in-class inhaled "bifunctional" dual PDE3/4 inhibitor, exhibits both bronchodilator and anti-inflammatory activities.[43] The two Phase 3 ENHANCE (Ensifentrine as a Novel inHAled Nebulized COPD thErapy)-1 and −2 clinical trials, not yet published in full, demonstrated substantial improvements in lung function, a clinically significant reduction of approximately 40% in AECOPD rate following 24 weeks of treatment with favourable safety results, although the improvement in symptoms and quality of life reached statistical significance only in ENHANCE-1.[44,45] The reduction in exacerbations was associated with a numerical reduction in circulating inflammatory biomarkers (IL-6, IL-8 and CRP).[46] The fact that ensifentrine was able to reduce the frequency and risk of exacerbations in patients with eosinophils >150 cells/μL[44] is

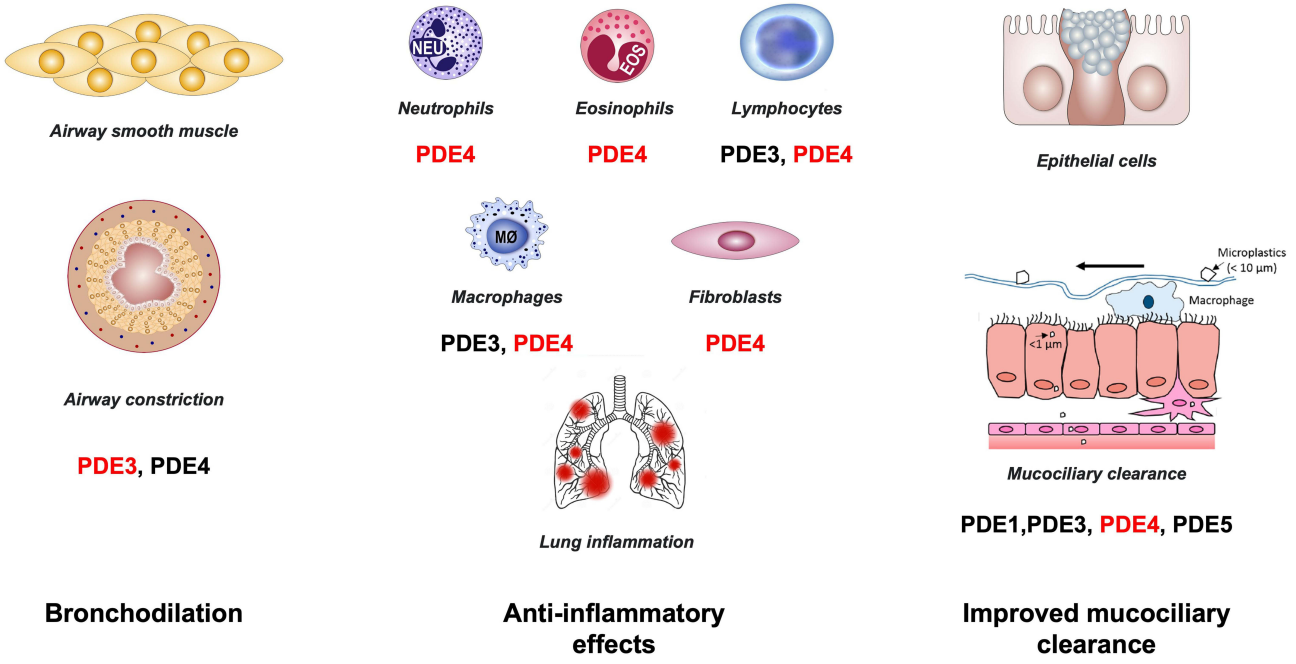

Figure 1 Effect of PDE inhibition in COPD. Combined inhibition of PDE3 and PDE4 provides additive and synergistic anti-inflammatory and bronchodilator effects when compared to PDE3 or PDE4 inhibition alone. It also improves mucociliary clearance. The primary PDE implicated in the activity of the given cell is shown in red.

fascinating because it suggests that in many patients, there would be no need to use ICSs. In ENHANCE-1, a higher percentage of patients were also under regular treatment for COPD (about 69% of subjects received LAMA or LABA and about 20% received ICS with concomitant LAMA or LABA), while in ENHANCE-2, this percentage was lower (about 55% of subjects received LAMA or LABA and about 15% received ICS with concomitant LAMA or LABA). Therefore, because few patients in these studies were on dual bronchodilation or triple therapy, it remains to be established what additional clinical benefit this drug brings to current standard of care.

Dual acting PDE4/PDE5 inhibitors, PDE4/PDE7 inhibitors, and PDE4/PDE1 inhibitors are also being investigated. The creation of pan-PDE inhibitors that can block a variety of PDE isoforms is another novel pharmacological approach being pursued.[41] An intriguing alternative is to create hybrid compounds with two or more pharmacophores, such as dual PDE4 inhibitors/muscarinic antagonists and dual PDE4 inhibitors/β_2-agonists.[41]

CXCR2 Antagonists

Due to their role in leukocyte chemotaxis, chemokines have long been thought to be involved in the onset and amplification of inflammatory reactions. One of the chemokine receptors, CXCR2, is expressed on a range of cell types and organs, which raises the possibility that these receptors have a wide functional involvement in the pathophysiology of COPD.[47] CXCR2 antagonists decreased neutrophil infiltration and tissue damage in the airways in pre-clinical models of cigarette smoke-induced acute neutrophilic inflammation in the lungs.[48] Some neutrophil CXCR2 antagonists have been investigated, but this drug class has only shown modest effects in patients with COPD, possibly due to redundancy in the chemokine network.[6] Navarixin, a dual CXCR1 and CXCR2 inhibitor, reduced inflammation and delayed the onset of the first exacerbation but also decreased the absolute neutrophil count, leading to the withdrawal of 18% of patients.[49] Danirixin, a selective CXCR2 antagonist, improved symptoms but its long-term administration caused a high incidence of AECOPDs and pneumonia, suggesting an adverse effect on host responses to infection.[50] Furthermore, in a small pilot study, there was no discernible difference between danirixin and placebo in terms of the % change from baseline in NETs, as determined by the histone-elastase immunoassay.[51] Ladarixin is another dual CXCR1 and CXCR2 antagonist that has been tested in a Phase 1 clinical trial (NCT04854642). It improved lung function and reduced neutrophilic airway inflammation in a corticosteroid-resistant model of cigarette smoke-induced influenza-A infection exacerbation.[52]

p38 Mitogen-Activated Protein Kinase Inhibitors

MAPKs significantly influence chronic inflammation. The p38 MAPK subgroup consists of four isoforms (α, β, γ, δ),[53] with p38α MAPK being suggested to have a significant impact on COPD.[26] It is increased in bronchial epithelial cells, macrophages and $CD20^+$ and $CD8^+$ lymphocytes in COPD lungs.[54] Several extracellular triggers cause the p38 MAPK pathway to become activated, leading to inflammatory gene transcription with increased cytokine and chemokine production, particularly interleukin 1β (IL-1β), CXCL8 (IL-8), and TNF-α, which are associated with the neutrophilic endotype of COPD[26] (Figure 2). Therefore, inhibiting p38 MAPK may be an effective treatment for patients with COPD.[6,53]

Some p38 MAPK inhibitors have been evaluated in patients with COPD. Losmapimod, an oral dual p38α/β inhibitor was not effective in reducing the moderate/severe COPD exacerbation rate in patients with blood eosinophils ≤2% and frequent exacerbations.[54] AZD7624, another p38α/β inhibitor, reduced the production of inflammatory mediators by primary human bronchial epithelial cells stimulated with polyinosinic: polycytidylic acid and lipopolysaccharide (LPS)-stimulated bronchoalveolar lavage fluid (BALF) macrophages to a greater extent than budesonide.[55] It was also more effective than budesonide in reducing IL-6 expression in bronchial epithelial cells, but without impacting AECOPD.[56] The inhaled narrow spectrum (p38α/γ) inhibitor RV568 improved lung function in a small 14-day clinical trial in COPD patients.[57] Acumapimod, a p38α inhibitor, improved FEV_1 compared to placebo in severe AECOPD.[58] It decreased the number of hospital readmissions due to COPD exacerbations.[59] CHF6297, a selective p38α inhibitor, has been evaluated for safety, tolerability, and pharmacokinetics in healthy participants and for its anti-inflammatory effects in patients with COPD (NCT02815488). However, the results of these studies have not yet been made public. A systematic review with meta-analysis that included 10 RCTs in patients with COPD concluded that p38 MAPK inhibition was safe when

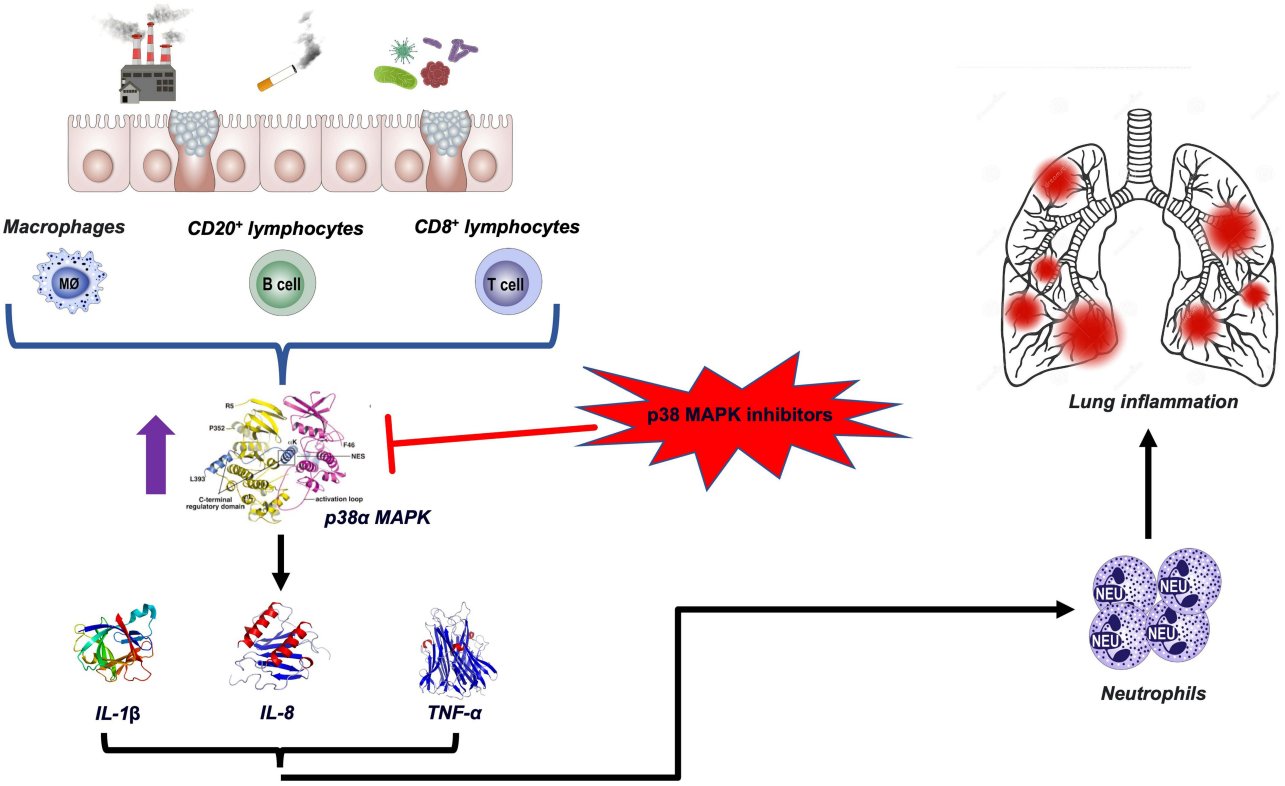

Figure 2 The role of p38 MAPK in the pathobiology of COPD. At the level of alveolar macrophages and other inflammatory cells, airborne pollutants, cigarette smoke, and microbial pathogens activate p38 MAPK. The p38 signaling pathway leads to increased cytokine and chemokine production, particularly interleukin (IL)-1β, IL-8, and tumor necrosis factor-α (TNF-α), which are associated with the neutrophilic endotype of COPD. Therefore, inhibiting p38 MAPK may be an effective treatment for patients with COPD.

compared with placebo, however this approach at best only caused a post-bronchodilator improvement in forced vital capacity.[59]

Oral administration of this class of drugs at safe doses is likely insufficient to induce significant clinical benefit.[60] However, inhaled p38 MAPK inhibitors may lead to a higher local drug concentrations in the lung. An alternative approach could be the development of selective inhibitors of the α-δ subgroups. However, it is now recognized that the transforming growth factor-activated kinase-1 and mixed-lineage kinase are hyperactivated due to p38 MAPK inhibitors' blocking of the upstream MAPK kinases, which in turn causes the c-Jun N-terminal kinase to become overactive.[61] These observations suggest a need to develop drugs that target downstream substrates in this signalling cascade.

Use of narrow spectrum kinase inhibitors, a new class of pharmaceutical agents that simultaneously targets key kinases involved in both innate and adaptive immune cell signalling, such as p38 MAPK, spleen tyrosine kinase (Syk), and Src family kinases (SFK), which include Src and lymphocyte-specific protein tyrosine kinase, is an additional option.[62] PUR1800 is a novel dry powder iSPERSE formulation of RV1162, a narrow spectrum kinase inhibitor, targeting p38 MAPK, Src and Syk kinases. In contrast to fluticasone propionate, it reduced TNF-α-induced cytokine release from primary bronchial epithelial cells of healthy volunteers and COPD patients.[63] The preliminary pharmacokinetic data indicate that PUR1800 results in low and consistent systemic exposure in COPD patients when administered via oral inhalation.[64]

Phosphoinositide 3-Kinase Inhibitors

PI3K is an enzyme that catalyses the production of phosphatidylinositol-3,4,5-triphosphate and is involved in the activation of macrophages and neutrophils, as well as the hyperphosphorylation and ubiquitination of HDAC2, thus influencing sensitivity of inflammatory cells to corticosteroids.[65] The function of this enzyme increases in patients with COPD.[65] Increased migratory speed and decreased directionality toward the cytokine gradient were seen with neutrophils

from patients with COPD, and these changes were reversed by PI3Kδ inhibition.[66] Furthermore, PI3Kδ inhibition reduces pro-inflammatory cytokine secretion and improves survival rates following infection.[67]

In a proof-of-concept trial, adding nemiralisib, an inhaled PI3Kδ inhibitor, to usual care was associated with a more effective recovery from AECOPDs and improved lung function but also resulted in cough.[68] However, in another trial, nemiralisib had no positive impact on lung function or relapses after an AECOPD.[69] Furthermore, this drug altered neutrophil migratory behaviour in stable patients with COPD, but not in those with AECOPD, despite improving lung function in the latter group.[70]

CHF6523 is another inhaled PI3K inhibitor, currently in clinical development and has been investigated for safety and tolerability in patients with COPD.[6] AZD8154, a PI3Kγδ inhibitor, has been tested in healthy volunteers,[71] while RV1729, another PI3Kγδ inhibitor, is being investigated in patients with COPD (NCT02140346). GSK045, a selective PI3Kδ inhibitor, and ZSTK474, a pan PI3K inhibitor, are other potential drugs for inhibiting PI3K in COPD.[6]

Selectin Antagonists

The selectin family consists of three members (E-, L-, and P-selectin). While L-selectin is constitutively expressed on circulating leukocytes, E- and P-selectin are expressed on the endothelium.[17] Selectins regulate inflammatory cell migration from the bloodstream into the lungs.[17] E-selectin, which is up-regulated on endothelial cells in the airways of COPD patients,[72] is required for the first attachment of neutrophilic granulocytes to endothelial cells in the airways.[73] Therefore, targeting these molecules may provide another approach to reducing inflammation in the lungs of patients with COPD.

Inhaled bimosiamose, a synthetic pan-selectin antagonist, decreased airway inflammation and improved lung function in patients with COPD, confirming the critical function of selectins in the movement of inflammatory cells.[74] Also, rivipansel, a pan-selectin antagonist, and uproleselan, a selective inhibitor of E-selectin, might be evaluated in the treatment of COPD.[6]

Developing inhibitors of selectin-ligand interactions in vivo is tricky because extremely potent inhibitors could have undesirable effects on healing processes, and weak inhibitors may not sufficiently act on the pathological processes of serious inflammatory diseases.[75] It has been suggested that a clinically effective inhibitor is likely to inhibit at least two selectins.[75]

Biologic Therapies

Anti-IL-17A mAbs, collectins, anti-IL-5 mAbs, anti-IL13/IL4 mAbs, anti-TSLP mAbs, and anti-IL-33 mAbs are among the biological therapies that have the potential to treat COPD.[24,76]

Anti-IL-17A mAbs

Along with IL-22, IL-17A and IL-17F are linked to an increase in neutrophils in the airways, which results in chronic inflammation and increased mucus production and smooth muscle mass in the airways.[76] To reduce neutrophil recruitment and airway inflammation, many anti-IL-17A and anti-IL-17 receptor A (IL-17RA) mAbs are being developed,[77] but CNTO 6785 is the only anti-IL-17A mAb that has been investigated in patients with COPD. It caused a small improvement in FEV_1 but did not interfere with the other primary or secondary endpoints.[78] Furthermore, more AECOPDs appeared in the CNTO 6785 arm than in the placebo arm at week 16. Brodalumab, which is a mAb that targets IL-17RA, secukinumab, a fully human anti-IL-17A of the immunoglobulin (Ig)$G_{1\kappa}$ isotype, and CCJM112, a novel fully human anti-IL-17A $IgG_{1\kappa}$ mAb that binds with similar affinity to both human IL-17A and IL-17AF, have not yet been tested in patients with COPD.[76]

Collectins

SP-A and SP-D are termed collectins because they contain collagen and are functional lectins.[79] By competing with LPS for CD14 binding on alveolar macrophages, SP-A and SP-D decrease TNF-α production.[79] Furthermore, they modify inflammatory cytokine production following macrophage activation by cytokines or pathogen-associated molecular patterns.[17] Pulmonary SP-D levels in COPD are lower than in smokers.[80] Supplementation with recombinant forms of SP-A and SP-D might correct collectin deficiencies in inflammatory respiratory disorders. The trimeric proteins SP-A and SP-D are available as small recombinant forms of human fragments

(rfhSP-A and rfhSP-D).[78] AT-100 is an engineered version of the endogenous human protein rhSP-D. Local treatment of rfhSP-D reduces inflammation, ceramide production, and epithelial cell death caused by cigarette smoke in mice,[81] but it has not yet been investigated in patients with COPD.

Targeting IL-5

As already mentioned, a subgroup of patients with COPD has elevated blood and airway eosinophils and elevated sputum IL-5 concentrations.[82] There is a relationship between IL-5 levels and the quantity of eosinophils in the sputum of COPD patients.[83] Moreover, there is proof that virus-induced AECOPD causes a rise in soluble IL-5Rα.[84] Blocking IL-5 may likely prevent or decrease eosinophil-mediated inflammation due to the fast death of eosinophils in the absence of IL-5.[76] Mepolizumab, a mAb that blocks IL-5, and benralizumab, an anti-IL-5Rα mAb, lower the rate of moderate and severe exacerbations in the highly selected population of individuals with COPD and higher levels of blood eosinophils[85,86] (Figure 3). However, substantial eosinophil clearance from the airways in many COPD patients does not result in appreciable clinical improvement.[87] This is probably because human lung-resident eosinophils are present independently of IL-5.[88] Nonetheless, both mepolizumab (NCT04133909 and NCT04075331) and benralizumab (NCT04053634 and NCT04098718) are still being investigated in patients having COPD exacerbations and higher levels of blood eosinophils.

Targeting IL13/IL4

IL-4 and IL-13 are cytokines that promote eosinophilic recruitment, IgE production, mucus hypersecretion, and airway fibrosis and remodeling.[89] They signal through a common receptor, IL-4Rα, expressed by airway epithelial cells[76] (Figure 3). IL-4 and IL-13 can drive eosinophilic inflammation through the production of chemoattractants such CC-chemokine ligand 26 from airway epithelial cells.[89] Patients with eosinophilic COPD and concomitant emphysema had significant levels of sputum matrix metalloprotease-12 (MMP-12), which is produced by alveolar macrophages when IL-13 is present.[76] Furthermore, it has been demonstrated that individuals with stable COPD or during an AECOPD have greater levels of group 2 innate lymphoid cells, which can produce IL-13.[90]

Lebrikizumab, a humanized mAb that binds to soluble IL-13 and inhibits activation of IL-4Rα and IL-13Rα1 heterodimers, has been examined in patients with COPD with a history of exacerbations despite using ICS and at least one long-acting bronchodilator inhaler drug (NCT02546700).[76] Although the complete results have not yet been made public, early data indicates that lebrikizimab did not affect the AECOPD rate compared to placebo. Consequently, the

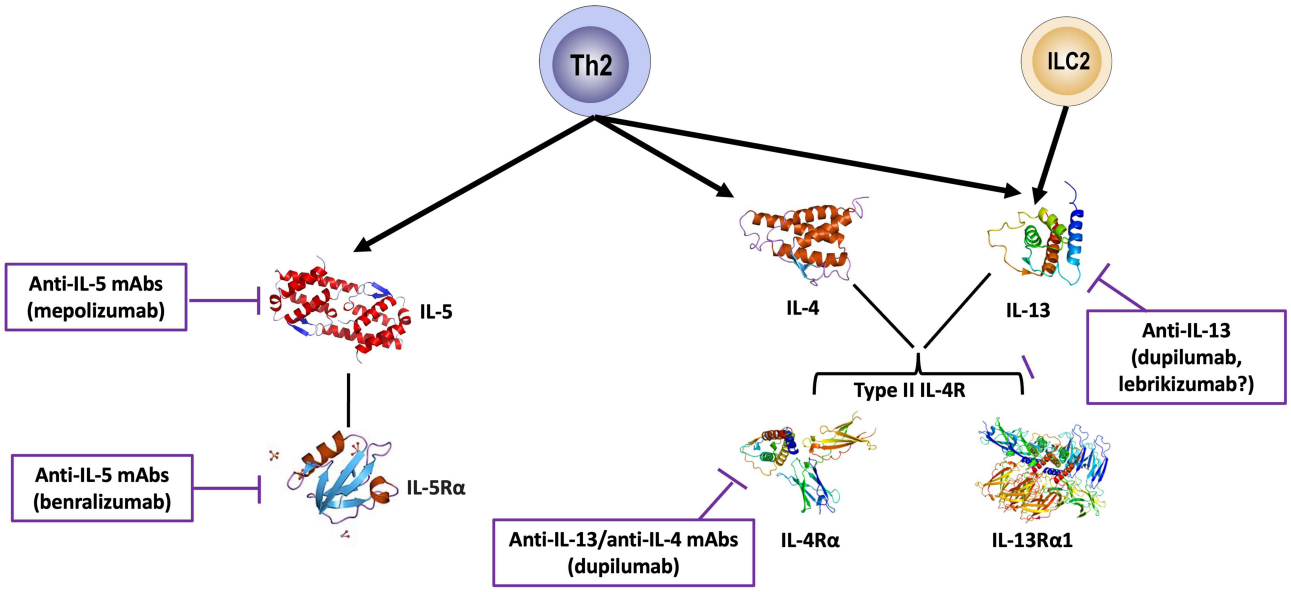

Figure 3 Monoclonal antibodies targeting T2 cytokines in COPD.
Abbreviations: ICL2, group 2 innate lymphoid cells; IL-4Rα, interleukin-4 receptor subunit α; IL-5Rα, interleukin-5 receptor subunit α; IL-13Rα, interleukin-13 receptor subunit α1.

clinical development of lebrikizumab for the treatment of patients with COPD has been halted indefinitely. Nevertheless, since IL-13 directly affects airway contractility and is critical for mucus production and remodeling[24] and airflow limitation and mucus hypersecretion are commonly treatable features in COPD, it would be interesting to conduct an RCT with lebrikizimab in patients belonging to the GOLD Group B, i.e. with COPD that is symptomatic but only slightly exacerbating.

A pivotal 52-week study, in which 939 adults aged 40 to 80 years with moderate-to-severe COPD and T2 inflammation, as measured by BECs ≥300 cells/μL, received dupilumab (n = 468) or placebo (n = 471), added to standard-of-care inhaled therapy, has shown that this biologic, a mAb that binds to IL4Rα and inhibits both IL-4 and IL-13 signaling, cut exacerbations by 30% compared with placebo ($p<0.001$).[91] The annualized rate of moderate or severe exacerbations was 0.78 with dupilumab and 1.10 with placebo. It also caused an increase in FEV_1 from baseline of 160 mL at 12 weeks compared with 77 mL for placebo ($p<0.001$), with the benefit versus placebo sustained through week 52. Furthermore, it improved patient-reported HRQoL as measured by SGRQ and reduced the severity of respiratory symptoms of COPD as measured by Evaluation Respiratory Symptoms: COPD (E-RS: COPD) Scale. Another phase 3 pivotal trial (NCT04456673) is also assessing the efficacy, safety, and tolerability of dupilumab in COPD patients with evidence of T2 inflammation, with data expected in 2024.

Targeting Thymic Stromal Lymphopoietin (TSLP)

TSLP, an IL-7-like cytokine, is an upstream epithelial alarmin that plays an important role in the regulation of T2 immunity.[76] TSLP operates on a variety of cells, including dendritic cells, T-cells, mast cells, innate lymphoid cells, and eosinophils, causing the production of a variety of interleukins, including IL-4, IL-5, and IL-13, which leads to airway eosinophilia and hyperresponsiveness. It is also capable of exerting multipotential pathogenic effects beyond T2 inflammation[76] (Figure 4).

TSLP is constitutively expressed in the airway smooth muscle of patients with COPD, where it probably interacts with and influences local immune cells.[92] In addition, viruses and T1 cytokines can induce COPD epithelial cells to overproduce TSLP,[93] suggesting that TSLP may play a role in AECOPD. However, it has been hypothesized that TSLP produced by DCs serves as a crucial molecular checkpoint to limit IL-1β-mediated effector responses through a negative feedback loop, potentially reducing the severity of the inflammatory response to injury.[94]

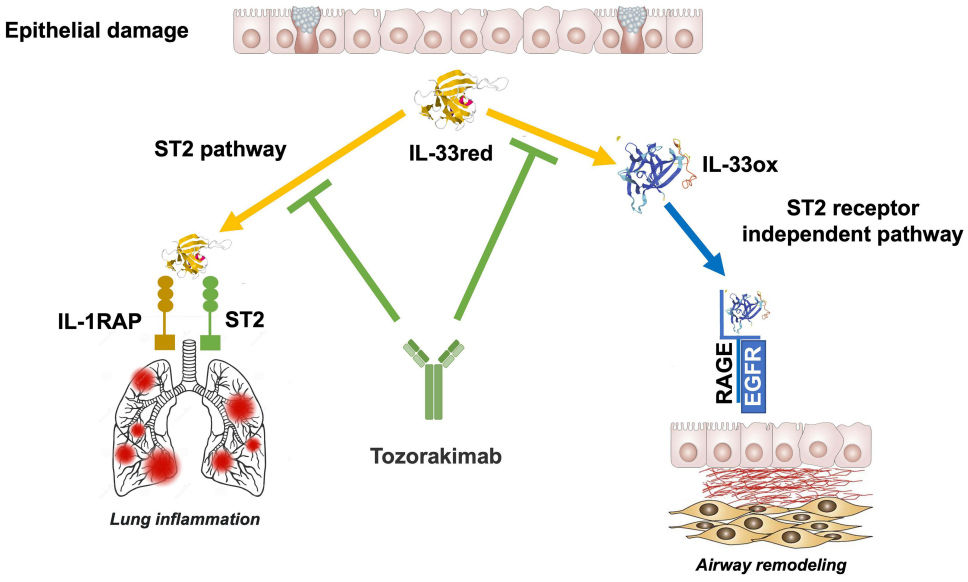

Figure 4 Targeting alarmins in COPD.
Abbreviations: DC, dendritic cell; EGFR, epidermal growth factor receptor; ILC2, group 2 innate lymphoid cells; IL-1RAP, IL-1 receptor accessory protein; IL-33red, reduced IL-33; IL-33ox, oxidated IL-33; MC, mast cell; RAGE, receptor for advanced glycation end products; ST2, suppression of tumorigenicity 2; TSLP, thymic stromal lymphopoietin; TSLPR, TSLP receptor.

Tezepelumab, a first-in-class human $IgG_{2/\lambda}$ mAb that binds to TSLP and inhibits its interaction with the TSLP receptor complex,[76] is currently under investigation as adjunctive therapy in preventing AECOPD (NCT04039113) and in reducing airway inflammation in patients with COPD (NCT05507242). Ecleralimab, an antibody fragment that is part of the $G_{1/\lambda}$ immunoglobulin isotype subclass and binds to TSLP, is being evaluated in a Phase 2 study in patients with COPD (NCT04882124).

Targeting IL-33

IL-33, a member of the IL-1 superfamily, is released in a reduced form ($IL\text{-}33^{red}$) from damaged epithelial cells and acts as an alarmin to notify the immune system of harm, thereby promoting the inflammatory response.[95] It exerts its biologically pro-inflammatory effects by activating its receptor, a heterodimeric complex composed of the IL-1 receptor accessory protein and tumor suppressor protein 2 (ST2)[96] (Figure 4).

IL-33 stimulates lung epithelial and endothelial cells to produce and release IL-6 and IL-8, resulting in an influx of neutrophils that damage lung tissue by producing elastases and proteases.[97] This, in turn, promotes pulmonary fibrosis and impairs lung function. Additionally, in non-atopic patients with COPD, IL-33 has been connected to the emergence of eosinophilic airway inflammation.[98]

Itepekimab, a human IgG_4 mAb targeting IL-33, added to the standard of care, did not significantly reduce the annualized rate of moderate-to-severe AECOPDs compared to placebo after 52 weeks of treatment.[99] However, it decreased the AECOPD rate and improved lung function in former COPD smokers. Itepekimab is under investigation in two Phase 3 trials to compare its efficacy to placebo on the annualized rate of mild to moderately severe AECOPDs in a 52-week placebo-controlled trial in former smokers with mild to moderately severe COPD (NCT04701983 and NCT04751487).

Astegolimab, an anti-ST2 mAb, did not significantly reduce the AECOPD rate but improved health status compared with placebo in patients with moderate-to-very severe COPD who were administered this drug subcutaneously in a 48-week RCT.[100] Two ongoing trials are evaluating the efficacy and safety of astegolimab compared with placebo in participants with COPD who are former or current smokers and have a history of frequent exacerbations (NCT05037929 and NCT05595642).

Tozorakimab (MEDI3506) is a human IgG_1 mAb that prevents IL-33 signaling. It possesses a higher affinity for the reduced form ($IL\text{-}33^{red}$) than soluble version of ST2 (sST2) and a rapid association rate comparable to that of sST2.[101] In primary human cells and in a humanized IL-33 murine model of airway inflammation, tozorakimab suppressed ST2-dependent inflammation.[100] It binds $IL\text{-}33^{red}$, blocking oxidation and, consequently, the action of the oxidated form ($IL\text{-}33^{ox}$) via receptor for advanced glycation end products/epidermal growth factor receptor.[102] Elimination of $IL\text{-}33^{ox}$ enhanced wound healing in vitro following epithelial injury. Tozorakimab is being investigated in several RCTs in patients with COPD. One of them (NCT04631016) will assess its efficacy and safety in patients with moderate to severe COPD and chronic bronchitis. Furthermore, two identical global Phase 3 studies (NCT05166889 and NCT05158387) are designed to evaluate the efficacy and safety of two different doses of tozorakimab administered for 52 weeks in patients with symptomatic COPD and a history of ≥2 moderate exacerbations or ≥1 severe AECOPD in the previous 12 months, despite receiving optimized treatment (triple therapy or dual therapy if triple therapy is not indicated or contraindicated) at a stable dose for at least 3 months before enrolment.

Targeting the Products of the Cellular Components of Inflammation

Several attempts have been made to develop therapies that target the products of the cellular components of inflammation. Some of these have been evaluated in humans (Table 2).

Matrix Metalloproteinase Inhibitors

MMPs are proteolytic enzymes that break down basement membrane and ECM proteins.[103] Consequently, these enzymes control airway remodelling, a critical pathogenetic aspect of COPD. Furthermore, proteolytic damage in the lungs can lead to elastin loss and emphysema formation, which are linked to reduced lung function in COPD patients. MMPs, particularly those derived from macrophages, have been linked to the development of COPD in several human and

Table 2 Therapies That Antagonize the Products of the Cellular Components of Inflammation in COPD

Class	Target	Drug	Clinical Development
MMP inhibitors	MMP-12	V85546	Phase 1 (discontinued)
		FP-025	Phase 1 (asthma)
	MMP-9	Andecaliximab	Phase 1
	MMP-9/12	AZD1236	Phase 2 (discontinued)
NE inhibitors	NE	Alvelestat	Phase 2 (AATD)
		CHF6333	Phase 1
		BAY 85-8501	Phase 2 (AATD)
		Lonodelestat	Phase 1 (cystic fibrosis)
		Unfractionated heparin	Phase 2b
DPP1 inhibitors	DPP1	GSK2793660	Phase 1 (discontinued)
		Brensocatib	Phase 3 (bronchiectasis)
AAT	AATD	AAT-MP	Phase 3
		INBRX-101	Phase 1
		Inhaled AAT	Phase 3
		Subcutaneous AAT	Phase 1
		VX-864	Phase 2

Abbreviations: AAT, α1-antitrypsin, AATD, AAT deficiency; DPP1, dipeptidyl peptidase 1; MMP, matrix metalloproteinase; NE, neutrophil elastase.

animal studies. MMPs have been shown to influence macrophage activation rather than working directly to destroy elastin, promoting inflammation and the disease course.[104,105] In addition to their activity on the ECM, MMPs can act on various other substrates.

In humans, there are 23 different MMPs.[103] MMP-9 and MMP-12 are those particularly involved in tissue remodelling and degradation of the ECM components and likely perpetuate and regulate lung inflammation when released by neutrophils and macrophages.[6] There is currently limited research investigating the use of MMP inhibitors in patients with COPD.[6] While V85546, a selective MMP-12 inhibitor, has completed Phase 1 clinical testing, AZD1236, a dual MMP-9/12 inhibitor, was ineffective in patients with moderate-to-severe COPD.[106] Andecaliximab, a recombinant chimeric IgG_4 mAb, has completed a Phase 1 clinical trial and is now being investigated in patients with COPD (NCT02077465). FP-025, an inhibitor of MMP-12, is currently being tested for efficacy in patients with asthma (NCT03858686), but to date no studies have been described in patients with COPD.

A novel series of compounds with single-digit nanomolar inhibition against MMP-12 have been discovered using the high-throughput screening by nuclear magnetic resonance technique.[107] Animals exposed to porcine pancreatic elastase but given MMP-12 inhibitors (MMP408, or lead agents compound 25, and 26) showed a substantial reduction in emphysema-like pathologies.

Drug repurposing might be an appealing technique for identifying current medicines with unique MMP inhibitory action. For example, doxycycline, a broad-spectrum antibiotic, has been shown to reduce MMP12 activity in vitro.[108] Despite its safety profile, antibiotic medication repurposing requires close monitoring to prevent the possibility of antibiotic resistance.

Neutrophil Elastase Inhibitors

NE is stored in neutrophil azurophilic granules and is released when neutrophils are activated by exposure to cigarette smoke or inflammation[107] It causes alveolar expansion and disintegration by proteolyzing lung tissues. Furthermore, NE induces airway epithelial cells to express *MUC5AC*, causing secretory cell hyperplasia and mucin synthesis.[109] Finally, NE stimulates macrophages, causing them to release active MMPs, which cause lung damage and emphysema, and proinflammatory cytokines, which cause inflammation.[110]

In individuals with COPD who have an overexpression of this enzyme, restoring the balance between NE and endogenous antiproteases by blocking NE might be a treatment option.

However, alvelestat, an orally available, potent, and selective inhibitor of human NE, did not induced changes in lung function or inflammation when added to budesonide/formoterol maintenance therapy in patients with COPD.[111] Furthermore, combined with tiotropium in patients with COPD, it failed to demonstrate a clinical benefit or an impact on biomarkers of tissue deterioration.[112] Nevertheless, a trial is investigating the effects of alvelestat on blood and sputum biomarkers in patients with PiZZ α1-antitrypsin deficiency (AATD) (NCT03636347).

Sivelestat is a NE inhibitor available only in Japan and South Korea to treat acute lung damage and acute respiratory distress syndrome in individuals with a systemic inflammatory response. Other NE inhibitors, such as BAY 85–8501, CHF6333, and lonodelestat, which could be useful in COPD, are currently in different stages of clinical development, but there is still no information on their effects on COPD.[6]

Interestingly, polysulfated glycosaminoglycans (GAGs) are potent anti-elastase drugs with multiple anti-inflammatory properties.[113] In one double-blind, placebo-controlled pilot research, inhaling unfractionated heparin, the prototypical drug in this class, as a COPD treatment resulted in enhanced lung function, highlighting the potential of GAG therapy for the treatment of chronic lung disorders.[114]

However, focusing solely on anti-NE activity does not appear to be sufficient to change the ongoing inflammatory state in the airways in a way that would alter the trajectory of clinical outcomes.[115] It has been suggested that employing combination therapy and/or multi-function drugs that have antiprotease and anti-inflammatory properties[115] or, alternatively developing an airway delivery system for these therapeutics, allowing activity not only on the free NE but also on the form bound to the extracellular vesicles found in the BALF of COPD patients[116] may be a more successful strategy.

Dipeptidyl Peptidase 1 Inhibitors

DPP1 transforms the neutrophil serine protease pool, including NE, cathepsin G, proteinase 3, into catalytically active forms and activates proteases in other immune cell types, such as chymases in mast cells.[117,118] Therefore, it may be a promising target for new drugs to treat COPD. GSK2793660, an irreversible DPP1 inhibitor, was stopped after a Phase 1 clinical study due to drug-related side effects and lack of impact on biomarkers.[119] This drug only decreased the activity of downstream serine proteases in 20% of the cases, although it suppressed most of DPP1. Brensocatib, an oral reversible DPP1 inhibitor, has been investigated for its effects in adult patients with non-cystic fibrosis bronchiectasis,[120] but its effects on COPD are unknown. Nevertheless, it has been proposed that limiting neutrophil protease activity before cell discharge into the circulation rather than at the inflammatory site, as well as blocking several inflammatory targets such as elastase, but also cathepsin G and proteinase-3, may be a crucial driver of success.[121]

Granzyme B Inhibitors

When released from the cytoplasmic secretory granules of $CD8^+$ T lymphocytes, granzyme B, which is a multifunctional serine protease and is also called α-1-antichymotrypsin (ACT), can start a cascade of DNA disruption that causes the apoptotic death of target cells, such as bronchial epithelial cells, which may lead to tissue damage and remodelling.[122] Furthermore, it increases inflammation by enhancing cytokine activity or sequestered growth factor release.[123] Thus, using targeted granzyme B inhibitors to treat COPD seems plausible. Serpina3n, a serine protease inhibitor that inhibits granzyme B,[124] an engineered extracellular granzyme B inhibitor in which the reactive center loop of human extracellular ACT is replaced with serpina3n,[125] VTI-1002, a first-in-class potent small-molecule inhibitor of granzyme B,[126] proteinase inhibitor 9 (PI-9), an endogenous GZMB inhibitor that can bind to GZMB in the cytosol of activated $CD8^+$

T cells,[127] serine protease inhibitor 6 (SPI-6), the mouse homolog of PI-9[128] are potentially interesting molecules but have not yet been investigated on humans. Furthermore, cefpiramide, a third-generation semi-synthetic cephalosporin antibiotic, and mupirocin, produced by *Pseudomonas fluorescens*, have the propensity to inhibit the active site of granzyme B[129] and may therefore be of value in treating COPD.

α_1-Antitrypsin Replacement Therapy

AAT modulates neutrophilic inflammation and inhibits proteases.[130] There is a proteolytic interplay between AAT, MMP and neutrophil elastase (NE) (Figure 5). In patients with AATD, augmentation treatment with pure intravenous AAT is essential, although it reaches the lung in a somewhat inactive state.[130] New intravenous formulations could solve this problem. AAT Modified Process (AAT-MP), with improved AAT purity, is in a 3-year Phase 3 trial (NCT01983241). INBRX-101, a recombinant human AAT Fc fusion protein that extends the half-life of AAT in blood by enabling it to be recycled, is under Phase 1 study (NCT03815396).

The inhaled route for AAT is also of interest as it can act directly on the target organ when administered in this way.[130] Inhaled AAT administered for 50 weeks significantly reduced the number of symptomatic exacerbations of Anthonisen type I, with a propensity to improve FEV_1 but without affecting the time to first exacerbation.[131] A trial is evaluating inhaled AAT in patients with AATD who have moderate or severe airflow limitation and have not experienced two or more moderate or one or more severe exacerbations of COPD during the past year (NCT04204252). Developing gene therapy to express AAT using various vector systems[130] or administering AAT treatment via the transepidermal route[132] are intriguing alternative approaches currently under investigation. A study is evaluating the safety and tolerability of subcutaneous AAT (NCT04722887).

Newer approaches that are predominantly in the preclinical phase tend to silence AAT production, enhance protein folding and secretion, or promote AAT degradation.[133] A folding corrector called VX-864 aims to increase Z-AAT secretion and activity. It is starting a Phase 2 study (NCT04474197) to show its safety and effectiveness in PiZZ patients.

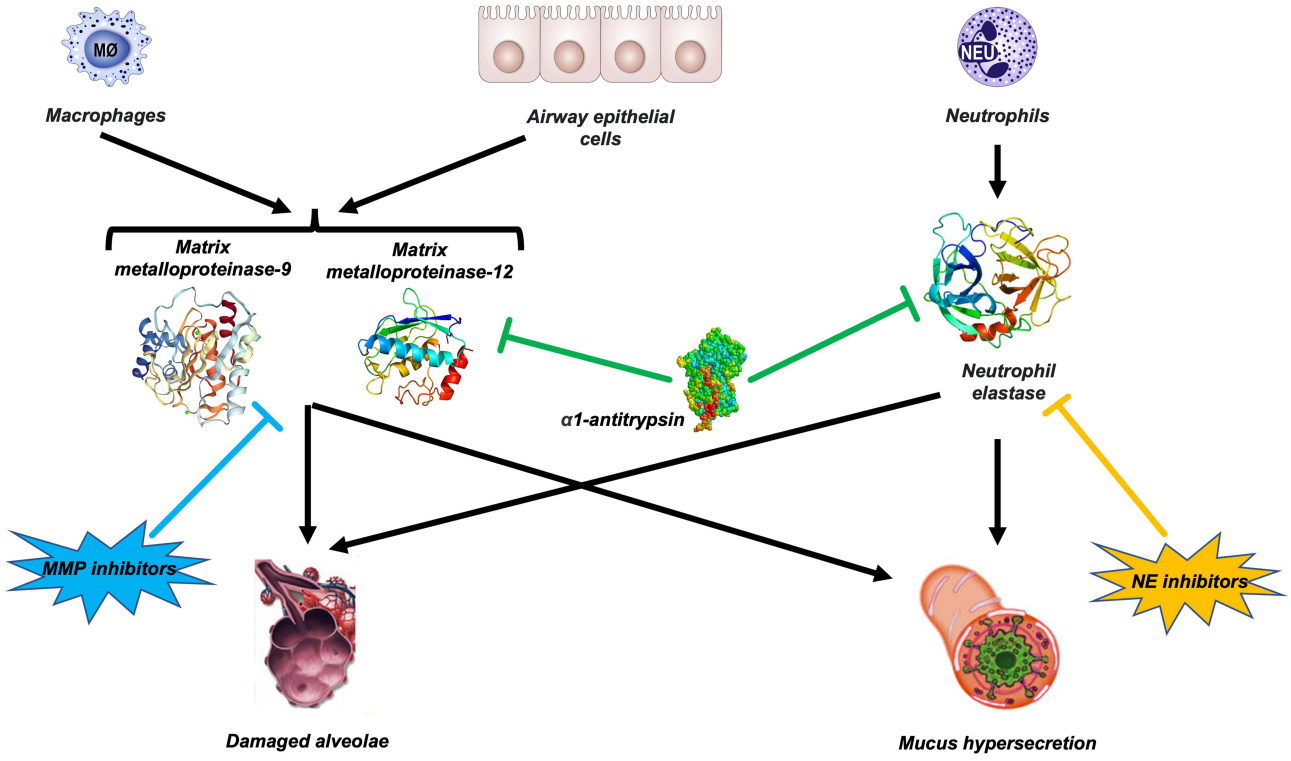

Figure 5 Proteolytic interplay between α1-antitrypsin (AAT), matrix metalloproteinases (MMPs) and neutrophil elastase (NE). Several proteases, including neutrophil elastase (NE) and MMP-9 and MMP-12, are involved in COPD. Therefore, inhibiting a single enzyme with a NE inhibitor or a MMP inhibitor may not have a significant therapeutic impact. AAT inhibits NE and reduces macrophage MMP-12 synthesis.

Targeting Neutrophil Extracellular Traps

Great attention has been given to the dysregulation of NETs that play an essential role in the innate immune system against infections. NETs have been identified in the airways of patients with COPD with chronic neutrophilic inflammation.[134] NETs result from the suicidal death of neutrophils during the attack of a pathogen or lesion, with the release of decondensed chromatin entangled with antimicrobial peptides to trap and capture pathogens to be an effective mechanism against invading microorganisms thus controlling overwhelming infections.[135] However, an aberrant and massive NET formation can directly induce epithelial and endothelial cell death, impairing lung function and accelerating disease progression.[6,136]

Interfering with the NETopathic inflammation pathways could help develop innovative therapeutics for COPD.[135] Heparin, which interferes with neutrophil autophagy, suppresses histones, prevents platelets-histone interaction, and blocks high mobility group box-1, deoxyribonuclease, which acts on and cleaves DNA matrices, and reduces the infiltration of neutrophils hence playing role in inhibition/reduction of NETs, and hydroxychloroquine, which mediates MMPs-TIMPs interaction that helps in maintaining homeostasis of extracellular matrix, are potential anti-NET therapeutics.[6,135] However, also protease inhibitors, CXCR2 antagonists, macrolides, and DPP1 inhibitors are drug classes that can specifically or non-specifically target NET formation,[137] although a pilot study did not find an effect of the reversible CXCR2 antagonist danirixin on NET formation.[49] Blockade of IL-1β and IL-17 could also be a valid strategy for interfering with the NETopathic inflammation pathways.[135]

Conclusion

Finding therapies that can reduce COPD-related inflammation and prevent the disorder from becoming worse is crucial. Recent discoveries have resulted in developing novel drugs for several novel potential targets directly involved in the inflammatory process.[6,14] To date, most of these new therapies are in preclinical or early clinical development and the results from clinical trials in patients with COPD are eagerly awaited.[138] However, the redundancy of the actions of signal-transmitting mediators involved in the complexity of the inflammatory response in COPD suggests that there will likely be several failures of the different approaches discussed above.[139]

Since COPD is heterogeneous, with many endotypes and phenotypes reflecting different pathophysiological mechanisms, the endo/phenotypic characterization of the inflammatory profile of patients with COPD may allow the identification of a reasonably homogeneous population such that there is a high possibility that the disease being treated is driven by the specific target pathway of the drug being tested. This strategy involves defining more specific management approaches.[1] As recently highlighted by the Lancet commission, the new COPD therapies must be specific and target the exact biological pathways or endotypes responsible for disease manifestation to have the greatest impact and eventually abolish the disease.[1] Characterization of the heterogeneity of the inflammatory signature associated with COPD could pave the way for personalized medicine by identifying new and effective therapeutic approaches for COPD.[140] For this reason, many clinical trials are underway to characterize the impact of some novel molecules that act directly against the inflammatory process in treating distinct subgroups of COPD patients.[6]

Nevertheless, other possible approaches, such as stem cell-based regenerative therapy and derivative products[141] and modulators of cystic fibrosis transmembrane conductance regulator,[142] may indirectly modulate inflammation in COPD and do not require accurate endotypic precision. The scientific community eagerly awaits the results of this experimental and mainly clinical research in the hope of improving treatments for such a challenging disease.

Abbreviations

AAT, α1-antitrypsin, AATD, AAT deficiency; ACT, α-1-antichymotrypsin; AECOPD, acute exacerbations of COPD; AR, adrenoceptor; BALF, bronchoalveolar lavage fluid; BEC, blood eosinophil count; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CS corticosteroid; COPD, chronic obstructive pulmonary disease; CXCR, CXC chemokine receptor; DC, dendritic cell; DPP1, dipeptidyl peptidase 1; ECM, extracellular matrix; FEV_1, forced expiratory volume in the first second; GR, glucocorticoid receptor; HDAC.

Histone deacetylase; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; Ig, immunoglobulin; IL, interleukin; IL-4Rα, interleukin-4 receptor subunit α; IL-5Rα, interleukin-5 receptor subunit α; IL-17RA, IL-17 receptor A; IL-33^{ox}, IL-33 oxidated form; IL-33^{red}, IL-33 reduced form; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LPS, lipopolysaccharide; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MMP, matrix metalloprotease; NE, neutrophil elastase; NETs, neutrophil extracellular traps; PDE, phosphodiesterase; PI3K, phosphoinositide 3-kinase; RCT, randomized controlled trial; Rfh, recombinant form of human fragments; sAC, soluble adenylyl cyclase; SP, surfactant protein; Syk, spleen tyrosine kinase; ST2, tumor suppressor protein 2; sST2, soluble version of ST2; T, type; TNF-α, tumor necrosis factor-α; TSLP, thymic stromal lymphopoietin.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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