

REVIEW ARTICLE

Biologics and airway remodeling in severe asthma

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Funding information

Regione Campania; TIMING Project; University of Naples Federico II

Abstract

Asthma is a chronic inflammatory airway disease resulting in airflow obstruction, which in part can become irreversible to conventional therapies, defining the concept of airway remodeling. The introduction of biologics in severe asthma has led in some patients to the complete normalization of previously considered irreversible airflow obstruction. This highlights the need to distinguish a “fixed” airflow obstruction due to structural changes unresponsive to current therapies, from a “reversible” one as demonstrated by lung function normalization during biological therapies not previously obtained even with high-dose systemic glucocorticoids. The mechanisms by which exposure to environmental factors initiates the inflammatory responses that trigger airway remodeling are still incompletely understood. Alarmins represent epithelial-derived cytokines that initiate immunologic events leading to inflammatory airway remodeling. Biological therapies can improve airflow obstruction by addressing these airway inflammatory changes. In addition, biologics might prevent and possibly even revert “fixed” remodeling due to structural changes. Hence, it appears clinically important to separate the therapeutic effects (early and late) of biologics as a new paradigm to evaluate the effects of these drugs and future treatments on airway remodeling in severe asthma.

KEYWORDS

airway remodeling, biologics, biomarkers, immunotherapies, severe asthma

Abbreviations: AHR, airway hyperresponsiveness; ANGPT, angiopoietin; ASM, airway smooth muscle; BAL, broncho-alveolar lavage; β_c , common receptor β subunit; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; DC, dendritic cell; EBUS, endobronchial ultrasound; ECM, extracellular matrix; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; EPX, eosinophil peroxidase; Fc ϵ RI, high affinity IgE; FeNO, fractional exhaled nitric oxide; FDA, food and drug administration; FGF, fibroblast growth factor; GINA, global initiative for asthma; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLM, human lung macrophage; HLMC, human lung mast cell; HRCT, high-resolution computed tomography; IL, interleukins; IL-5R α , IL-5 receptor α ; ILC, innate lymphoid cell; i.v., intravenously; IfTSLP, long form TSLP; mAb, monoclonal antibody; MBP, major basic protein; MMP, matrix metalloproteinase; NET, neutrophils extracellular trap; NHR, nuclear magnetic resonance; NK cell, natural killer cell; NKT cell, natural killer T cell; PDGF, platelet-derived growth factor; PGD₂, prostaglandin D₂; RCTs, randomized clinical trials; sfTSLP, short form TSLP; TGF- β , transforming growth factor β ; TSLP, thymic stromal lymphopoietin; T2-high, type 2-high; T2-low, type 2-low; VDP, ventilation defect; VEGF, vascular endothelial growth factors.

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1 | INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease of the respiratory system that affects approximately 10% of adults.¹ A typical feature of asthma is a variable airflow limitation associated with symptoms such as dyspnea, cough, wheezing, and chest tightness.² The heterogeneity of the immunologic disorder is reflected in different phenotypes that differ in etiology, pathogenic mechanisms, symptoms, and severity.³ Based on airway inflammation, asthma has been subdivided into type 2-high (T2-high) and type 2-low (T2-low), although the latter form is rare in clinical practice.³⁻⁵ A similar distinction is made between eosinophilic and non-eosinophilic asthma (GINA 2021).⁶ Severe asthma is defined as asthma that is not well controlled despite the adherence to maximal optimized pharmacological therapy and treatment of contributory factors.⁷ Up to 6% of asthma patients have severe asthma, with a reduced quality of life, and increased risk of exacerbations, hospitalizations, and death.^{8,9}

In T2-high asthma, immunologic stimuli (e.g., allergens, and viral and bacterial superantigens) activate primary effector cells of allergic disorders (i.e., mast cells and basophils) through the engagement of specific IgE to release a plethora of interleukins (ILs) (e.g., IL-3, IL-4, IL-5, and IL-13).^{10,11} Eosinophils and their mediators contribute to the pathogenesis of IgE-mediated asthma and play pivotal roles in eosinophilic asthma. T2-low asthma is heterogeneous, incompletely defined and understood and presumably includes different phenotypes characterized by the involvement of mast cells, macrophages, neutrophils, and/or a mixture of these immune cells.^{3,5} Bronchial epithelial cell-derived alarmins (e.g., TSLP, IL-33, and IL-25) are upstream cytokines that initiate immunologic events culminating in airway remodeling.¹²⁻¹⁴ The latter is a complex process requiring a timely expression of fibrogenic¹⁵ and angiogenic factors causing profound structural alterations of the bronchial walls and blood vessels.^{16,17} These alterations contribute to the reduction of airway caliber and stiffening, resulting clinically in airflow limitations and respiratory symptoms.¹⁸

2 | AIRWAY REMODELING

Airway remodeling can affect both large and small airways¹⁹ and is characterized by structural changes including goblet cell metaplasia, subepithelial matrix protein deposition and fibrosis, overexpression of angiogenic factors, and hyperplasia/hypertrophy of airway smooth muscle cells.^{15-17,20-23} Increased deposition of extracellular matrix (ECM) proteins in the reticular basement membrane (RBM), lamina propria, and submucosa is a characteristic of asthmatic airways and contributes to the airway wall thickening and airflow obstruction.^{24,25} Collagen fibers, fibronectin, and tenascin are the most abundant elements of the ECM in the asthmatic lung.²⁶⁻²⁹ Aberrant accumulation of ECM proteins leads to alterations in tissue structure and function, contributing to airway remodeling in asthma.³⁰⁻³² ASM hypertrophy/hyperplasia (e.g., increased ASM mass) are features of asthmatic airway remodeling.^{18,33,34,35}

ASM cells in asthmatic individuals also produce increased amounts of collagen and fibronectin.^{36,37} The increase in the ASM mass contributes to bronchial obstruction,³⁸ loss of lung function,²¹ and greater susceptibility to external triggers.^{20,39,40} Airway remodeling has been implicated in irreversible airflow limitation with consequent poor symptom control and lack of response to treatment.^{21,41,42}

The airway epithelium is a key component of the innate immune system and the initiator of airway remodeling in asthma.¹⁴ A plethora of environmental insults (e.g., allergens, cytokines, microbial proteins, smoke extracts, and chemical and physical insults) damage and/or activate epithelial cells to release several cytokines, including TSLP,^{13,43} IL-33,^{14,44} IL-25/IL-17E,¹² TGF- β , and granulocyte-macrophage colony-stimulating factor (GM-CSF), which can recruit/activate dendritic cells (DCs), type 2 innate lymphoid cells (ILC2s), mast cells, eosinophils, and other immune cells.⁴⁵

Thymic stromal lymphopoietin (TSLP), constitutively expressed by human bronchial epithelial cells,⁴⁶⁻⁴⁹ can be rapidly released as a result of cell injury in response to a variety of inflammatory stimuli.^{46,50-54} TSLP is also released by DCs,⁵⁵ mast cells,⁵⁶ human lung macrophages (HLMs),⁵⁷ and fibroblasts.^{58,59} TSLP exerts its effects by binding to a high-affinity heterodimeric receptor complex composed of TSLPR and IL-7R α .¹³ There are two isoforms of TSLP: the long (lf) and the short (sf) isoforms; the former is also known as TSLP and its expression increases during inflammation.^{57,60} The sTSLP, constitutively expressed in epithelial cells, lung fibroblasts, and HLMs,^{57,61} is not upregulated by inflammation. For instance, house dust mites induce lfTSLP but not sTSLP in human bronchial epithelial cells.⁶² TSLP immunostaining is increased in the airway epithelium in asthmatic patients,⁴⁹ and its concentrations are increased in the broncho-alveolar lavage (BAL) fluid of asthmatics.⁴⁸ TSLP is overexpressed in the airways of severe asthma patients,⁴⁸ and bronchial allergen challenge of asthmatics increases the expression of TSLP⁺ cells in the epithelium and submucosa.⁴⁷

TSLP promotes allergic responses and airway remodeling⁶³ by acting on DCs,⁵⁵ thereby promoting the differentiation of naive CD4⁺ T cells into Th2 cells^{64,65} and by inducing the survival of ILC2s^{13,66,67} and the induction of epithelial-mesenchymal transition (EMT) in airway epithelial cells.⁶⁸ Human lung fibroblasts are also a significant source of TSLP.^{59,69} Through an autocrine mechanism, TSLP can activate human lung fibroblasts⁷⁰ to release type I collagen⁷¹ and promote the proliferation of ASM cells.⁷² TSLP has also been shown to cause goblet cell metaplasia and mucus production.⁷³⁻⁷⁵ TSLP activates human eosinophils,¹³ mast cells,^{56,76} and HLMs.⁵⁷ The multiple activating properties of TSLP on a plethora of immune and structural cells indicate that this cytokine plays a role in T2-high and T2-low asthma.

IL-33, an IL-1 superfamily alarmin released by airway epithelial cells and endothelial cells,⁷⁷ activates the ST2 receptor on several cells of the innate and adaptive immunity.⁷⁷ IL-33 activates ILC2s⁷⁸⁻⁸⁰ and induces type 2 cytokines (i.e., IL-5 and IL-13) in human mast cells,⁸¹ collagen, and fibronectin release from airway fibroblasts.^{82,83} IL-33 and superantigenic activation of human lung mast cells (HLMCs) induce the release of angiogenic and lymphangiogenic factors.⁸⁴ IL-33, alone and

in combination with IL-3, activates human basophils to release a wide spectrum of cytokines (i.e., IL-4, IL-13, CXCL8, and VEGF-A).^{85,86} IL-33 expression is associated with enhanced RBM thickness in bronchial biopsies of tissues severe asthmatic children.⁸³ In addition, it has been reported that airway remodeling is absent in ST2^{-/-} mice in a model of house dust mite (HDM)-induced asthma.⁸³ Collectively, IL-33 and IL-33/ST2 signaling pathways might be involved in both airway inflammation and asthma remodeling through the activation of several immune and structural cells.

IL-25, also known as IL-17E, is a unique cytokine of the IL-17 family produced by a subset of airway epithelial cells (i.e., brush cells).^{12,87,88} Airborne allergens, ATP, and viral infections upregulate IL-25 and its receptor IL-17RB in airway epithelial cells and submucosa.^{89,90} IL-25 activates ILC2s,⁹¹ modulates EMT of alveolar epithelial cells and local tissue remodeling,⁹² and upregulates cytokine expression in lung fibroblasts.⁹³ IL-25 drives lung fibrosis in several mouse models.^{92,94,95}

A plethora of cytokines (transforming growth factor β [TGF- β], platelet-derived growth factor [PDGF], fibroblast growth factor [FGF], epidermal growth factor [EGF], vascular endothelial growth factors [VEGFs]), and chemokines (e.g., CXCL2, CXCL3, IL-8/CXCL8) contributes directly and indirectly to airway remodeling in asthma.⁹⁶⁻⁹⁸ In particular, TGF- β , produced by macrophages and eosinophils, is a main mediator responsible for airway remodeling by inducing epithelial-mesenchymal transition (EMT).⁹⁹ IL-4 activates ASM cells, causing an increase in actin and collagen synthesis as well as TGF- β release by the bronchial epithelium.^{20,100} IL-5 promotes subepithelial and peri-bronchial fibrosis through the recruitment and activation of eosinophils, a major source of TGF- β .^{101,102} IL-13 induces the release of TGF- β from bronchial epithelial cells, which increases goblet cell metaplasia.^{20,103-106}

IgE itself could play a role in airway remodeling by stimulating the production of interleukins.¹⁰⁷ Several investigators have reported that human monomeric IgE, in the absence of cross-linking, can induce the release of cytokines (e.g., IL-4) and chemokines (e.g., CXCL8) from mast cells.^{108,109} Moreover, Roth et al have shown that in vitro incubation of serum containing IgE obtained from allergic asthmatics caused ASM proliferation and marked production of type I collagen.¹¹⁰

Similarly, a large number of cells of the innate and adaptive immune system contribute directly and indirectly to airway remodeling in asthma. Human eosinophil granules are armed with cytotoxic major basic protein (MBP), eosinophil peroxidase (EPX), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), and galectin-10 (also known as Charcot-Leyden protein).¹¹¹ ECP and MBP induce the release of preformed (histamine and tryptase) and de novo synthesized mediators (prostaglandin D₂: PGD₂) from human mast cells.¹¹²⁻¹¹⁴ Activated human eosinophils secrete LTC₄ and a wide array of type 2 cytokines (e.g., IL-5, IL-4, and IL-13) and TGF- β .^{96,115} Altogether, current data indicate that eosinophils play a globally pathogenic role in airway remodeling.

Macrophages (alveolar and interstitial) are the most abundant immune cell type in human lung¹¹⁶⁻¹¹⁸ and are involved in immune responses as well as tissue remodeling.¹¹⁹ HLMs contribute to airway

remodeling through the release of TGF- β , matrix metalloproteinases (MMPs), angiogenic (e.g., VEGF-A and ANGPT2), and lymphangiogenic factors (i.e., VEGF-C).^{57,120} HLMCs are important lung-resident immune cells involved in asthmatic airway remodeling.¹²¹ IgE- and non-IgE-mediated activation of HLMCs induces the release of several profibrotic cytokines (e.g., IL-13 and TNF- α), as well as inflammatory mediators (e.g., PGD₂ and tryptase).^{113,114} Tryptase induces fibroblast, endothelial and epithelial cell proliferation, further fueling airway remodeling in asthmatic individuals.¹²² Neutrophils have also been shown to produce MMP-9,^{123,124} angiogenic factors,¹²⁵ and neutrophil extracellular traps (NETs)¹²⁶⁻¹²⁸ and can be associated with severe asthma.¹²⁶

Angiogenesis is fundamental to providing the blood vessels to maintain tissue homeostasis,¹²⁵ whereas inflammatory angiogenesis is a critical factor in the development of a disease process.^{84,129,130} Blood vessel density and vascular area are increased in patients with asthma.^{16,17}

A recent study in a mouse model of asthma demonstrated dynamic changes in the respiratory microbiota at different stages of the disease. In particular, *Staphylococcus* and *Cupriavidus* were more abundant during airway remodeling.¹³¹ Additional studies are urgently needed to investigate whether the dysbiosis of airway microbiota could also play a role in the progression from allergic inflammation to airway remodeling in humans.

2.1 | Imaging of airway remodeling

The direct assessment of human airway remodeling can be performed in vivo on bronchial biopsies in asthmatic patients.^{115,132,133} Bronchial biopsies identify useful information on bronchial and pulmonary alterations, such as thickening of the bronchial tissue, infiltration and density of inflammatory cells, aberrant accumulation of elements of ECM, and ASM hyperplasia and hypertrophy.¹⁵ However, this procedure has several limitations that should be pointed out. First, it is not part of the routine clinical evaluation of asthmatic patients. Second, it does not easily facilitate serial biopsies in the same patient. Third, the results can be significantly influenced by the operator and the techniques used to assess tissue remodeling.

During the last decade, high-resolution computed tomography (HRCT) and nuclear magnetic resonance (NMR) are gaining a place as non-invasive techniques to examine different aspects of airway remodeling in asthma. Hoshino found increased airway wall thickening in asthmatics assessed by HRCT.¹³⁴ Bronchial wall thickness assessed by endobronchial ultrasound (EBUS) was increased in asthma patients than healthy controls.¹³⁵ Hartley et al found that the proximal airway wall area was increased in asthmatics compared to controls.¹³⁶ The loss of the peripheral pulmonary vasculature, also termed pruning, was associated with asthma severity.¹³⁷ Recently, Eddy and co-workers demonstrated that the total number of CT-visible airways was correlated to asthma severity.¹³⁸

Preliminary results derive from imaging studies that have evaluated the effects of biological therapies on airway remodeling

using HRCT. Hoshino et al reported that 16-week treatment with omalizumab reduced the airway wall thickness and the number of sputum eosinophils.¹³⁹ In another study, 48-week treatment with omalizumab reduced the airway wall area corrected for body surface, but no changes in percentage wall area, without changes in the luminal area.¹⁴⁰ In two studies conducted by Haldar et al^{141,142} on airway remodeling by HRCT, it was found that the biological treatment determined a greater variation in pre-/post-treatment luminal area compared to the placebo group. A recent study evaluated the impact of one-year mepolizumab therapy on airway remodeling through EBUS and HRCT. Improved airway remodeling (e.g., reduction in bronchial wall thickness) was better noticeable in invasive EBUS than in non-invasive HRCT.¹⁴³ In the phase 2 CASCADE study, tezepelumab increased the CT scan-determined lumen area across airway generations.¹³²

Hyperpolarized helium-3 MRI of the lung has demonstrated regional heterogeneity of lobar ventilation in asthma,¹⁴⁴ which is correlated with asthma severity.¹⁴⁵ MRI ventilation defects (VDP) are correlated to sputum eosinophilia in severe asthma¹⁴⁶ and are a predictor of exacerbation.¹⁴⁷ Collectively, studies with CT and MRI in asthma have shown some structural and functional changes in airways and pulmonary vasculature associated with more severe disease but are unable to differentiate between reversible and potentially irreversible changes.

Finally, fractional exhaled nitric oxide (FeNO) has been proposed to assess airway structure variations in asthma patients, especially in the distal airway. FeNO was associated with bronchial wall thickening in the third to the sixth generation of bronchial trees.¹⁴⁸

2.2 | Single-cell transcriptomics of airway remodeling

The human lung is a complex tissue which comprises more than 40 cell populations, including immune and structural cells.^{149,150} Previous investigations of airway remodeling in asthma were limited by the examination of a restricted profile of immune and structural cells. Next-generation sequencing technologies (RNA-Seq) are now available to identify transcriptomic map of the human lung.^{150,151} Transcriptomic analysis of flow cytometry-sorted cell population from the human lung and single-cell RNA-Seq (scRNA-Seq) allows reliable identification of even closely related cell population.¹⁵² scRNA-Seq also allows the identification of known or novel cell populations for which there are no reliable surface markers during health and disease.¹⁵³ scRNA-Seq has been recently employed to reveal ectopic and aberrant lung-resident cell populations in patients with pulmonary fibrosis.^{150,151} Recently, single-cell transcriptomic of mouse lung revealed a population of inflammatory memory neutrophils with specific molecular features in a model of allergic asthma.¹⁵⁴ Vieira Braga and collaborators used single-cell transcriptomics to chart the cellular landscape of airways and lung parenchyma in healthy and asthmatic lungs. These authors discovered a

novel subset of CD4⁺ T cells in asthmatic airway wall and a novel mucous ciliated cell in the airway epithelium that contributes to goblet cell hyperplasia.¹³³ We anticipate that the use of scRNA-Seq will provide fundamental information to chart the landscape of immunological and structural cells involved in airway remodeling in different pheno-endotypes of asthma and the effects of biologics in this heterogeneous disorder.

2.3 | Targeting airway remodeling

Experimental and human studies have demonstrated that glucocorticoids and certain anti-inflammatory drugs can reduce inflammation and morbidity in mild to moderate asthma. However, evidences of beneficial effects of inhaled (ICS) or oral (OCS) glucocorticoids on airway remodeling have not been demonstrated, with several reports showing contradictory results with ICS.^{17,155,156} The introduction of several biological immunotherapies (e.g., anti-IgE, anti-IL-5/IL-5R α , anti-IL-4R α , and anti-TSLP)^{2,157} has contributed to the development of a personalized medicine approach for the treatment of patients with severe asthma.¹⁵⁸⁻¹⁶¹ There is some evidence that these biologics can improve not only clinical symptoms but also certain features of airway remodeling and functional decline of FEV₁. It is important to emphasize that FEV₁ and other spirometric indices are only surrogate markers of airway remodeling in asthma and any improvement in FEV₁ after treatment with biologics could be attributable not only to the attenuation of any remodeling processes but also due to the changes in bronchial hyperreactivity, autonomic nervous system modulation and other factors. Finally, it will be important to evaluate the effects of biological immunotherapies in randomized clinical trials (RCTs) and real-life settings.^{162,163}

2.4 | Omalizumab

Omalizumab is a humanized IgG1- κ monoclonal antibody (mAb) that binds to the Fc fragment of IgE.¹⁶⁴ This mAb inhibits the binding of IgE to the high-affinity IgE (Fc ϵ RI) receptor on human mast cells, basophils,^{165,166} and DCs.¹⁶⁷ Several studies have documented the efficacy of omalizumab in improving allergic asthma and reducing symptoms and exacerbations¹⁶⁸⁻¹⁷⁰ also in children and pregnant women.¹⁷¹⁻¹⁷³ Although omalizumab did not cause FEV₁ improvement in RCTs,^{174,175} there is some evidence that this mAb can improve FEV₁ in real-life settings^{176,177} and can reduce the thickness of the basement membrane^{139,178} and fibronectin deposits in asthmatic airways¹⁷⁹ in addition to preventing exacerbation-induced inflammatory alterations in the airways. IgE-containing serum from asthmatic patients stimulated in vitro mesenchymal cell proliferation and accumulation of collagen and fibronectin. Both proliferation and matrix deposition were prevented by preincubation of the cells with omalizumab.¹¹⁰

2.5 | Mepolizumab

Mepolizumab is an IgG1- κ anti-IL-5 mAb approved as add-on treatment for severe eosinophilic asthma (SEA).^{180,181} IL-5 is the most important growth, differentiation, and activation factor of human eosinophils.¹⁸² This cytokine acts on eosinophils by binding to the specific IL-5 receptor (IL-5R), which consists of an IL-5 receptor α (IL-5R α) subunit and the common receptor β subunit (β c).¹⁸³ IL-5, together with IL-3 and GM-CSF,¹⁸⁴ is crucial for the maturation of human eosinophils in the bone marrow.^{57,183} IL-5 is mainly produced by type-2 ILC2s, Th2 cells, mast cells, invariant NKT cells, and eosinophils themselves.¹⁸² Human eosinophils can also be activated by IL-33⁷⁷ and TSLP.¹³

The efficacy and safety of mepolizumab have been demonstrated in several RCTs.^{185–188} The DREAM study, conducted with mepolizumab at 3 different doses administered intravenously (*i.v.*), showed the clinical efficacy but there were no statistically significant changes in FEV₁, although there was an improvement, compared to baseline, in FEV₁ in the mepolizumab group versus placebo.¹⁸⁵ In the MENSA study, the FEV₁ increase was rapid, starting from the first administration, and persisted over time.¹⁸⁸ Two additional studies showed a rapid and long-lasting improvement in pre-bronchodilator FEV₁ in the mepolizumab group compared to placebo.^{189,190} There is some evidence that mepolizumab can also improve FEV₁ in real-life settings.^{191–193}

Interestingly, some patients first enrolled in the COSMOS study and subsequently in the long-term COSMEX study, with a suspension of more than 12 weeks of mepolizumab between the two, reported a transient worsening of their symptoms and FEV₁, which rapidly improved upon reintroduction of mepolizumab.¹⁸⁷ A clinical trial (NCT03797404) is evaluating the effects on airway remodeling during mepolizumab treatment.

In a pioneering study, Flood-Page and collaborators examined the bronchial biopsies of mild atopic asthmatics, treated only with SABA, studied before and after treatment with three mepolizumab infusions.¹¹⁵ They demonstrated that the thickness and density of tenascin in the RBM, the airway TGF- β 1⁺ eosinophils, and the BAL concentrations of TGF- β 1 were increased in mild asthmatic patients compared to normal subjects. As expected, mepolizumab reduced bronchial eosinophil numbers but also TGF- β 1⁺ eosinophils, thickness and tenascin immunoreactivity, and the concentration of TGF- β 1 in BAL fluid.¹¹⁵

2.6 | Reslizumab

Reslizumab is a humanized IgG4- κ anti-IL-5 mAb developed by drafting technology from a rat mAb with high affinity against human IL-5.¹⁹⁴ Reslizumab binds to a small region corresponding to amino acids 89–92 of IL-5, which are critical for binding to IL-5R α .¹⁹⁵ Reslizumab administration results in clinical improvement in asthma and an increase in FEV₁ in patients with eosinophilic counts >400 cells/ μ l compared to placebo.^{195–200} Apparently contrasting

results have been reported on the effects of reslizumab on the improvement of FEV₁ compared to placebo. Although several studies reported that reslizumab significantly improved FEV₁ compared to placebo,^{196,199} other investigators found that reslizumab had no improvement in FEV₁ compared to those receiving placebo.¹⁹⁶ A real-life study recently confirmed the efficacy of reslizumab treatment in reducing the number of exacerbations and increasing FEV₁ 6 months after the beginning of treatment.²⁰¹ Further investigations are needed to evaluate the potential role of reslizumab on mechanisms implicated in the pathogenesis of airway remodeling in asthma patients.

2.7 | Benralizumab

Benralizumab is a humanized, afucosylated IgG1- κ mAb that targets the α subunit of the IL-5 receptor (IL-5R α) and it binds via the constant Fc fragment to the Fc γ R1IIa receptor for IgG expressed on natural killer (NK) cells, macrophages, and neutrophils, which results in eosinophil apoptosis via antibody-dependent cell-mediated cytotoxicity.²⁰² Several studies have demonstrated that benralizumab administration leads to subjective and functional clinical improvement in patients with SEA. RCTs reported an improvement in FEV₁ at 12 weeks from the beginning of treatment.^{203–205} A post hoc analysis conducted on SIROCCO and CALIMA data further documented that benralizumab promoted functional improvement even in patients with fixed airflow obstruction, an alteration found in approximately 16% of patients with severe asthma.²⁰⁶ A recent study extended the previous results by showing that benralizumab caused a rapid (4 weeks) improvement in FEV₁, which increased after 12 weeks and persisted throughout the period (24 weeks) of observation.²⁰⁵

Cachi and collaborators evaluated the effects of benralizumab on airway remodeling by examining biopsies from patients with SEA.²⁰⁷ Benralizumab reduced the number of eosinophils in the bronchial lamina propria and ASM mass compared to placebo. In the benralizumab group, there were no significant changes in the number of myofibroblasts compared to the control group. The effects of benralizumab on ASM mass were attributed to an indirect effect mediated by the depletion of local TGF- β 1⁺ eosinophils in the bronchial lamina propria.

Pelaia and collaborators emphasized the clinical efficacy of benralizumab in terms of lung function in real life after the first administration of this mAb.²⁰⁸ Padilla-Galo et al reported an improvement in FEV₁ after three months of treatment with benralizumab, which lasted up to six months.²⁰⁹ Similar results were obtained in a retrospective study.²¹⁰ The authors ascribed the rapid improvement of lung function to the early effects of the mAb on peripheral blood and bronchial eosinophils. Although these observations were obtained in small cohorts of patients, they emphasize that the improvement caused by benralizumab on lung function observed in real life is more evident compared to certain RCTs.^{73,203,204} Finally, clinical trials (NCT04365205, NCT03953300) are evaluating the effects of benralizumab on airway remodeling.

2.8 | Dupilumab

The Th2-like cytokines IL-4 and IL-13 and the heterodimeric IL-4 receptor (IL-4R) complexes that they activate play a key pathogenic role in asthma.²¹¹ Dupilumab is a human IgG4 mAb that targets the IL-4 receptor α chain (IL-4R α), common to both IL-4R complexes: type 1 (IL-4R α / γ c; IL-4 specific) and type 2 (IL-4R α /IL-13R α 1; IL-4 and IL-13 specific).²¹²

In several RCTs, dupilumab reduced the annualized rate of asthma exacerbations in patients with moderate-to-severe uncontrolled asthma compared to placebo.^{213–215} Dupilumab in patients with severe asthma caused rapid (2 weeks) and long-lasting improvement in FEV₁ versus placebo.^{214,215} Furthermore, the trend curves of FEV₁ post-bronchodilation showed a loss of function in the placebo group and no decrease in FEV₁ over time in the dupilumab group. Moreover, in a mouse model of asthma, dual IL-4/IL-13 blockade with dupilumab prevented eosinophil infiltration into lung tissue without affecting circulating eosinophils.²¹⁶ A real-life retrospective study demonstrated that 4 weeks of treatment were necessary to achieve a significant improvement in FEV₁ compared to baseline.²¹⁷ The VESTIGE study (NCT04400318), evaluating dupilumab effects on lung function and structural airway changes using functional respiratory imaging (FRI), is ongoing.

It should be noted that blood eosinophilia was reported in 4%–25% of patients in the dupilumab group compared to 0.6% in the placebo group.^{215,218} This paradoxical effect has also been reported in patients treated with dupilumab for moderate-to-severe atopic dermatitis.²¹⁹ However, transient early elevation of blood eosinophils in asthma, chronic rhinosinusitis with nasal polyps (CRSwNP) or atopic dermatitis patients on dupilumab declined to baseline levels over time.²²⁰

Additionally, indirect evidence of a combined anti-inflammatory effect as well as on tissue and structural cells can be derived from the observation that all of the abovementioned anti-Th2 cytokine or receptor antibodies have been shown to reduce the size of nasal polyposis in patients with CRSwNP.^{221–224}

2.9 | Tezepelumab

Tezepelumab is a human IgG2- λ mAb, which binds with high affinity to TSLP, an epithelial cell-derived cytokine implicated in the pathogenesis of different phenotypes of asthma.¹³ TSLP, a pleiotropic cytokine overexpressed in the airway epithelium of asthmatics,⁴⁹ exerts its effects by binding to a high-affinity heterodimeric receptor complex composed of TSLPR and IL-7R α .¹³ TSLP concentrations are increased in BAL fluid of asthmatics,⁴⁸ and bronchial allergen challenge increases TSLP expression in the asthmatic epithelium and submucosa. Importantly, serum concentrations of TSLP are increased during asthma exacerbations.²²⁵ Finally, TSLP induces the release of angiogenic and lymphangiogenic factors from HLMS.⁵⁷

TSLP can promote airway remodeling via the activation of human lung fibroblasts.⁷⁰

The FDA has recently approved tezepelumab for the treatment of severe asthma with no phenotype or biomarker limitations. Tezepelumab is the first biologic antagonizing an alarmin (i.e., TSLP), which plays a pivotal role in the pathogenesis of asthma.^{13,43} The phase II PATHWAY study showed that three different doses (70 mg, 210 mg, or 280 mg s.c. every 4 weeks) of tezepelumab reduced the number of annual exacerbation rates regardless of blood eosinophil count, with a significant increase in prebronchodilator FEV₁ at 52 weeks from the start of treatment compared to the placebo group.²²⁶ These results were extended in the phase III NAVIGATOR study in which tezepelumab (210 mg s.c. every 4 weeks) reduced asthma exacerbations at Week 52 and significantly improved FEV₁ regardless of peripheral blood eosinophils in adolescent and adult patients with severe uncontrolled asthma²²⁷ although there was a trend toward a better improvement with higher eosinophil counts in subgroup analysis.

Studies conducted in different animal models using TSLP antibodies have demonstrated that TSLP blockade reduces airway inflammation, TGF- β 1 levels, hyperreactivity, and airway remodeling.^{228–231} The phase II CASCADE study evaluated the effects of tezepelumab on airway remodeling by performing bronchoscopic biopsies in moderate-to-severe asthma patients.¹³² Tezepelumab caused a greater reduction from baseline to the end of treatment in airway submucosal eosinophils compared to placebo. There were no other significant changes either at the level of other immune cells (neutrophils, mast cells, and T cells) and at the structural level (e.g., RBM thickness and epithelial integrity). Interestingly, tezepelumab administration was associated with lower hyperresponsiveness to mannitol inhalation compared to placebo. The latter finding was confirmed in an independent study.²³² These preliminary results on the effects of tezepelumab on airway remodeling are of translational interest for several reasons. There is overwhelming evidence that fibroblasts are a source of TSLP^{58,59} and there is evidence that a functional TSLP signaling axis plays a role in fibrotic lung disease.⁵⁹ Figure 1 schematically illustrates the mechanisms of action of different biologics and their immunological and cellular targets in the context of airway remodeling.

3 | FUTURE PERSPECTIVES

3.1 | Astegolimab

Astegolimab is an IgG2 mAb that blocks IL-33 signaling by targeting ST2, the IL-33 receptor.⁷⁷ The phase 2b ZENYATTA study²³³ evaluated the safety and efficacy of astegolimab in patients with severe asthma. Astegolimab was safe, well tolerated, and effective in reducing the annualized asthma exacerbations at Week 54. Astegolimab did not show a significant benefit compared to placebo in the absolute change in FEV₁ at Week 54.

Add-on biologic treatments of severe asthma

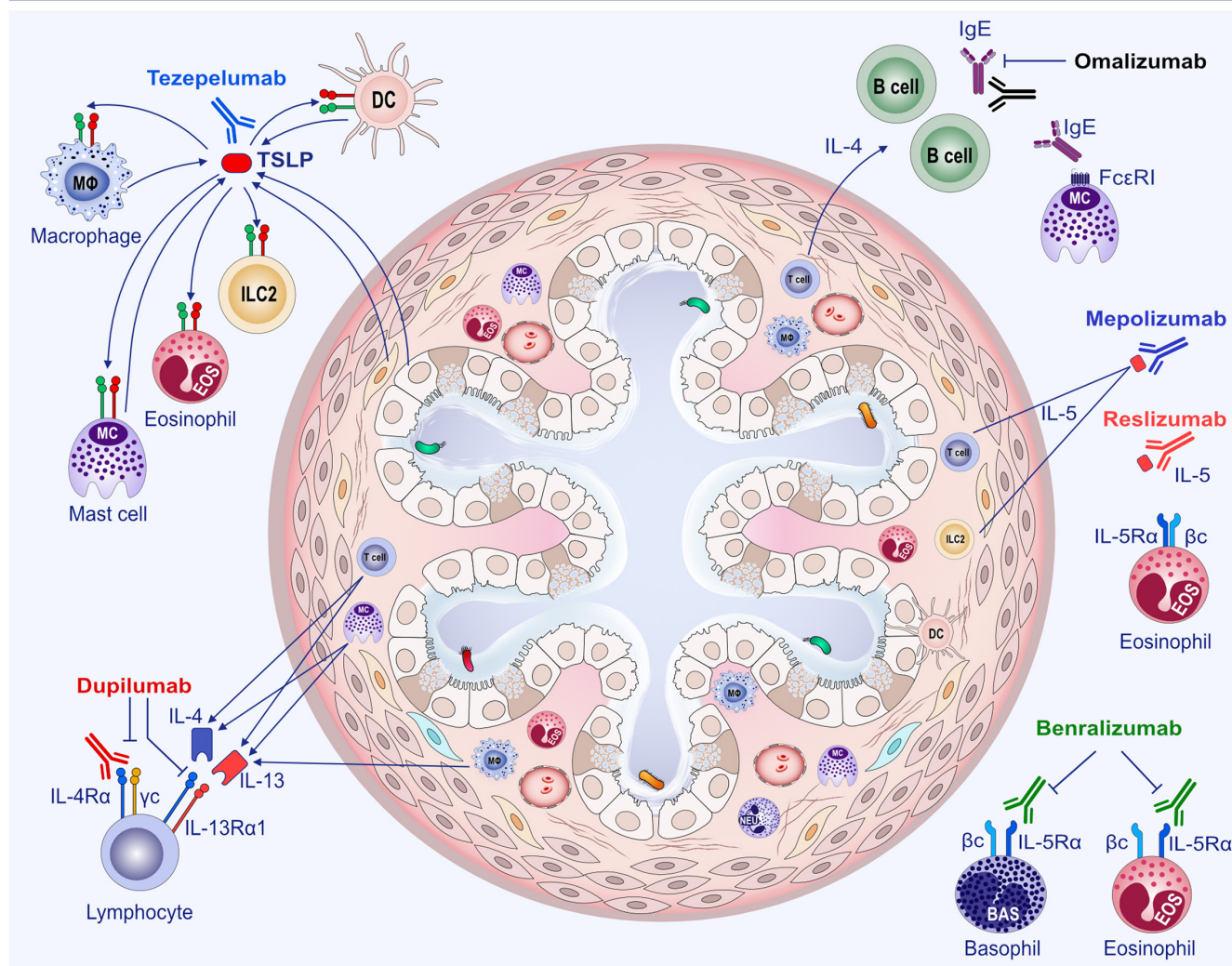


FIGURE 1 Monoclonal antibodies (mAbs) effective in the treatment of patients with severe asthma are listed, and their known immunological mechanisms are summarized. The targets of approved add-on biologic treatments of severe asthma include IgE (omalizumab), IL-5 (mepolizumab and reslizumab), IL-5 receptor (benralizumab), IL-4/IL-13 receptor complex (dupilumab), and TSLP (tezepelumab).

3.2 | Itepekimab

Itepekimab is a human IgG4 anti-IL-33 mAb. A phase 2 trial compared the safety and efficacy of itepekimab (300mg s.c. every 2weeks), dupilumab (300mg. s.c. every 2weeks), itepekimab plus dupilumab, or placebo in patients with moderate-to-severe asthma.²³⁴ The primary endpoint, loss of asthma control, was similar in the itepekimab (22%), combination (27%), and dupilumab (19%) groups and lower than in the placebo (41%) group. Prebronchodilator FEV₁ increased with itepekimab and dupilumab monotherapies but not with combination therapy. Itepekimab improved asthma control and quality of life compared to placebo and reduced peripheral blood eosinophils. The latter results are consistent with a role for IL-33 in the pathogenesis of asthma exacerbations and airflow limitations in asthma. Further investigations

are needed to investigate whether blockade of the IL-33/ST2 axis can modify airway remodeling in patients with asthma.

4 | CONCLUSIONS AND PERSPECTIVES

Immunotherapy with mAbs targeting IgE, several cytokines, or their receptors has revolutionized the treatment landscape for patients with severe asthma. mAbs that block IgE (omalizumab), the IL-5/IL-5Rα axis (mepolizumab, reslizumab, benralizumab), IL-4Rα (dupilumab), or TSLP (tezepelumab) can produce durable responses in the majority of patients with severe asthma.

Airway remodeling is a cardinal feature of bronchial asthma and is responsible for structural alterations of the airways and lung parenchyma, determining airway hyperresponsiveness and the

development of fixed airflow obstruction.¹⁵ Damaged epithelial barrier,^{235,236} subepithelial matrix proteins and collagen deposition,^{24,25,29} infiltration and activation of inflammatory cells,^{115,124,133} goblet cell metaplasia,²³ overexpression of inflammatory angiogenesis,^{16,17} and hyperplasia and hypertrophy of ASM cells^{18,33} are major features of airway remodeling in asthma.^{41,237}

At present, we have incomplete knowledge on the short- and long-term effects of biological therapies on airway remodeling in asthma. However, biological therapies targeting IgE, IL-5/IL-5R α , IL-4R α , TSLP, and IL-33/ST2 can improve not only clinical symptoms but also certain indirect features (e.g., FEV₁) of airway remodeling in asthma.^{215,226,238–241} These findings allow us to speculate that biologics could promote the resolution of allergic and non-allergic inflammation. Late phases of airway remodeling are associated with infiltration/activation of both profibrotic immune cells (e.g., mast cells, eosinophils, and macrophages) and structural cells (e.g., fibroblasts, myofibroblasts, ASM cells, and endothelial cells). Biologics may have late effects on immune and structural cells in addition to early effects on airway inflammation. The effects of each biologic on specific features of airway remodeling are summarized in Table 1.

Biologics are presently used for the treatment of patients with severe asthma who are likely to have a prolonged history of persistent and/or repetitive immunological insults. Repetitive or prolonged injury can lead to a pathological state of fibrosis associated with reduced lung function. Experimental studies indicate that there is a limited time window in which stopping inflammation avoids fibrosis.^{242,243} Beyond this time window, tissue remodeling inevitably occurs even if inflammation is resolved. In this circuit,

macrophages, the most abundant hematopoietic cells in the human lung parenchyma, can transition between different states, including proinflammatory, anti-inflammatory, and profibrotic states.²⁴⁴ Although there are no clinical and experimental data, we would like to speculate that perhaps early treatment of mild/moderate asthma with biologics might represent an innovative strategy to limit the irreversible airway remodeling of severe asthma.²⁴⁵ On the contrary, this preventive approach might reduce the direct and indirect heavy socio-economic consequences of severe asthma and their exacerbations thus counterbalancing the cost of biologic therapies.

There are several limitations in studying in vivo the effects of biological therapies on airway tissue remodeling in asthmatic patients. Bronchial asthma is a highly heterogeneous disorder and different forms of airway remodeling could likely underlie several asthma pheno-/endotypes.³ The quantitative identification of immune cells in the airway epithelium and submucosa should also take in consideration the functional heterogeneity of eosinophils,²⁴⁶ macrophages,^{57,118,133} mast cells,^{84,247–250} neutrophils,^{125,127,251} and basophils.^{85,86,125,252} Considering the technical and ethical difficulties to evaluate in vivo bronchial remodeling through invasive methods, particularly in patients with severe asthma, efforts are underway to identify peripheral blood biomarkers of airway remodeling in asthma.²⁴⁵

In conclusion, a deeper understanding of the immunological mechanisms of the formation of different forms of airway tissue remodeling in various asthma phenotypes is needed. The use of single-cell transcriptomics will be of paramount importance to chart

TABLE 1 Effects of biologics on specific features of airway remodeling

Biologics	Form	Target	Biological effects	Effects on airway remodeling
Omalizumab	Humanized IgG1- κ mAb	IgE	• $\downarrow$ circulating total IgE • Downregulation of FcϵRI receptors on basophils, mast cells, and DCs	• $\uparrow$ FEV₁ • $\downarrow$ RBM thickness • $\downarrow$ airway wall thickness in CT • $\downarrow$ fibronectin deposition • Prevents IgE-mediated ECM deposition in vitro
Reslizumab	Humanized IgG4- κ mAb	IL-5	Blockage of IL-5/IL-5R binding	• $\uparrow$ FEV₁
Mepolizumab	Humanized IgG1- κ mAb	IL-5	Blockage of IL-5/IL-5R binding	• $\uparrow$ FEV₁ • $\downarrow$ airway eosinophils and TGF-β1⁺ eosinophils • $\downarrow$ tenascin expression
Benralizumab	Humanized IgG1- κ mAb	IL-5 receptor (IL-5R α)	$\downarrow$ eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity (ADCC)	• $\uparrow$ FEV₁ • $\downarrow$ airway eosinophils • $\downarrow$ ASM mass
Dupilumab	Human IgG4 mAb	IL-4 receptor α chain (IL-4R α)	• Blockage of IL-4/IL-4Rα binding • Blockage of IL-13/IL-4Rα binding	• $\uparrow$ FEV₁ • prevents eosinophil infiltration into lung tissue in a mouse model of asthma
Tezepelumab	Human IgG2- λ mAb	TSLP	Blockage of TSLP/TSLPR binding	• $\uparrow$ FEV₁ • $\downarrow$ airway eosinophils • $\downarrow$ AHR to mannitol • $\downarrow$ airway inflammation • $\downarrow$ TGF-β1 • $\uparrow$ CT scan-determined lumen area

the cellular landscape and specific signaling networks of upper and lower airways in healthy and asthmatic subjects.^{133,154} The results emerging from these studies could help in the generation of new reliable diagnostic biomarkers and targeted therapeutic approaches to improve asthma treatment.

ACKNOWLEDGMENTS

We would like to thank Dr. Gjada Criscuolo for her excellent managerial assistance in preparing this manuscript and the administrative staff (Dr. Roberto Bifulco, Dr. Anna Ferraro, and Dr. Maria Cristina Fucci), without whom it would not be possible to work as a team. Open Access Funding provided by Università degli Studi di Napoli Federico II within the CRUI-CARE Agreement.

FUNDING INFORMATION

This work was supported in part by grants from the CISI-Lab Project (University of Naples Federico II), TIMING Project and Campania Bioscience (Regione Campania) to G.V.

CONFLICTS OF INTEREST

G.V., S.F., J.P., R.P., and G.S. have not potential conflicts of interest to declare. J.C.V. is a full time employee of the University of Rostock as a full time professor and chair of the Departments of Pneumology and Intensive Care Medicine has given independent advice, lectured for and received honoraria from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, TEVA, UCB/Schwarz-Pharma, Zydus/Cadila, has participated in advisory boards for Avontec, Boehringer-Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, MEDA, MSD, Mundipharma, Novartis, Regeneron, Revotar, Roche, Sanofi-Aventis, Sandoz-Hexal, TEVA, UCB/Schwarz-Pharma and has received research grants from the Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern, GSK, MSD. E.H. received grants and personal fees from AstraZeneca, Sanofi, Regeneron, Novartis, GSK, Circassia, Nestlé Purina, Stallergenes-Greer outside the submitted work. G.W.C. received honoraria for lectures, presentations, speakers from AstraZeneca, GSK, Novartis, Sanofi, Stallergenes, Greer, Hal Allergy, Menarini, Chiesi, Mylan, Valeas, Faes.

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REFERENCES

- Barnes PJ. Targeting cytokines to treat asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol*. 2018;18(7):454-466.
- GINA. 2021.
- Wenzel SE. Severe adult asthmas: integrating clinical features, biology, and therapeutics to improve outcomes. *Am J Respir Crit Care Med*. 2021;203(7):809-821.
- McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med*. 2019;199(4):433-445.
- Nair P, Surette MG, Virchow JC. Neutrophilic asthma: misconception or misnomer? *Lancet Respir Med*. 2021;9(5):441-443.
- Heaney LG, de Llano LP, Al-Ahmad M, et al. Eosinophilic and noneosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. *Chest*. 2021;160(3):814-830.
- Suehs CM, Menzies-Gow A, Price D, et al. Expert consensus on the tapering of oral corticosteroids for the treatment of asthma. A Delphi study. *Am J Respir Crit Care Med*. 2021;203(7):871-881.
- Settipane RA, Kreindler JL, Chung Y, Tkacz J. Evaluating direct costs and productivity losses of patients with asthma receiving GINA 4/5 therapy in the United States. *Ann Allergy Asthma Immunol*. 2019;123(6):564-572.e3.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43(2):343-373.
- Bartemes KR, Kita H. Dynamic role of epithelium-derived cytokines in asthma. *Clin Immunol*. 2012;143(3):222-235.
- Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol*. 2015;15(1):57-65.
- Borowczyk J, Shutova M, Brembilla NC, Boehncke WH. IL-25 (IL-17E) in epithelial immunology and pathophysiology. *J Allergy Clin Immunol*. 2021;148(1):40-52.
- Varricchi G, Pecoraro A, Marone G, et al. Thymic stromal lymphopoietin isoforms, inflammatory disorders, and cancer. *Front Immunol*. 2018;9:1595.
- Johansson K, McSorley HJ. Interleukin-33 in the developing lung—Roles in asthma and infection. *Pediatr Allergy Immunol*. 2019;30(5):503-510.
- Liu G, Philp AM, Corte T, et al. Therapeutic targets in lung tissue remodelling and fibrosis. *Pharmacol Ther*. 2021;225:107839.
- Hoshino M, Takahashi M, Aoike N. Expression of vascular endothelial growth factor, basic fibroblast growth factor, and angiogenin immunoreactivity in asthmatic airways and its relationship to angiogenesis. *J Allergy Clin Immunol*. 2001;107(2):295-301.
- Chetta A, Zanini A, Foresi A, et al. Vascular component of airway remodeling in asthma is reduced by high dose of fluticasone. *Am J Respir Crit Care Med*. 2003;167(5):751-757.
- Yick CY, Ferreira DS, Annoni R, et al. Extracellular matrix in airway smooth muscle is associated with dynamics of airway function in asthma. *Allergy*. 2012;67(4):552-559.
- Elliot JG, Jones RL, Abramson MJ, et al. Distribution of airway smooth muscle remodelling in asthma: relation to airway inflammation. *Respirology*. 2015;20(1):66-72.
- Doucet C, Brouty-Boyd D, Pottin-Clemenceau C, Jasmin C, Canonica GW, Azzarone B. IL-4 and IL-13 specifically increase adhesion molecule and inflammatory cytokine expression in human lung fibroblasts. *Int Immunol*. 1998;10(10):1421-1433.
- Pascual RM, Peters SP. Airway remodeling contributes to the progressive loss of lung function in asthma: an overview. *J Allergy Clin Immunol*. 2005;116(3):477-486. quiz 487.
- Bergeron C, Boulet LP. Structural changes in airway diseases: characteristics, mechanisms, consequences, and pharmacologic modulation. *Chest*. 2006;129(4):1068-1087.
- Hauber HP, Foley SC, Hamid Q. Mucin overproduction in chronic inflammatory lung disease. *Can Respir J*. 2006;13(6):327-335.

24. Hough KP, Curtiss ML, Blain TJ, et al. Airway remodeling in asthma. *Front Med (Lausanne)*. 2020;7:191.
25. Bourdin A, Neveu D, Vachier I, Paganin F, Godard P, Chanez P. Specificity of basement membrane thickening in severe asthma. *J Allergy Clin Immunol*. 2007;119(6):1367-1374.
26. Dolhnikoff M, da Silva LF, de Araujo BB, et al. The outer wall of small airways is a major site of remodeling in fatal asthma. *J Allergy Clin Immunol*. 2009;123(5):1090-7-1097.e1.
27. Chakir J, Shannon J, Molet S, et al. Airway remodeling-associated mediators in moderate to severe asthma: effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. *J Allergy Clin Immunol*. 2003;111(6):1293-1298.
28. Slat AM, Janssen K, Van Schadewijk A, et al. Expression of smooth muscle and extracellular matrix proteins in relation to airway function in asthma. *J Allergy Clin Immunol*. 2008;121(5):1196-1202.
29. Liu G, Cooley MA, Nair PM, et al. Airway remodelling and inflammation in asthma are dependent on the extracellular matrix protein fibulin-1c. *J Pathol*. 2017;243(4):510-523.
30. Roche WR, Williams J, Beasley R, Holgate S. Subepithelial fibrosis in the bronchi of asthmatics. *Lancet*. 1989;1(8637):520-524.
31. Mostaco-Guidolin LB, Osei ET, Ullah J, et al. Defective fibrillar collagen organization by fibroblasts contributes to airway remodeling in asthma. *Am J Respir Crit Care Med*. 2019;200(4):431-443.
32. Ito JT, Lourenço JD, Righetti RF, Tibério IF, Prado CM, Lopes FD. Extracellular matrix component remodeling in respiratory diseases: what has been found in clinical and experimental studies? *Cells*. 2019;8(4):342.
33. Howarth PH, Knox AJ, Amrani Y, Tliba O, Panettieri RA Jr, Johnson M. Synthetic responses in airway smooth muscle. *J Allergy Clin Immunol*. 2004;114(2 Suppl):S32-S50.
34. Prakash YS. Emerging concepts in smooth muscle contributions to airway structure and function: implications for health and disease. *Am J Physiol Lung Cell Mol Physiol*. 2016;311(6):L1113-L1140.
35. Yap HM, Israfi DA, Harith HH, Tham CL, Sulaiman MR. Crosstalk between signaling pathways involved in the regulation of airway smooth muscle cell hyperplasia. *Front Pharmacol*. 2019;10:1148.
36. Cheng W, Yan K, Xie LY, et al. MiR-143-3p controls TGF-beta1-induced cell proliferation and extracellular matrix production in airway smooth muscle via negative regulation of the nuclear factor of activated T cells 1. *Mol Immunol*. 2016;78:133-139.
37. Harkness LM, Weckmann M, Kopp M, Becker T, Ashton AW, Burgess JK. Tumstatin regulates the angiogenic and inflammatory potential of airway smooth muscle extracellular matrix. *J Cell Mol Med*. 2017;21(12):3288-3297.
38. Holgate ST. Pathogenesis of asthma. *Clin Exp Allergy*. 2008;38(6):872-897.
39. Cazes E, Giron-Michel J, Baouz S, et al. Novel anti-inflammatory effects of the inhaled corticosteroid fluticasone propionate during lung myofibroblastic differentiation. *J Immunol*. 2001;167(9):5329-5337.
40. Winkler T, Frey U. Airway remodeling: shifting the trigger point for exacerbations in asthma. *J Allergy Clin Immunol*. 2021;148(3):710-712.
41. Boulet LP. Airway remodeling in asthma: update on mechanisms and therapeutic approaches. *Curr Opin Pulm Med*. 2018;24(1):56-62.
42. James AL, Wenzel S. Clinical relevance of airway remodelling in airway diseases. *Eur Respir J*. 2007;30(1):134-155.
43. Marone G, Spadaro G, Braile M, et al. Tezepelumab: a novel biological therapy for the treatment of severe uncontrolled asthma. *Expert Opin Investig Drugs*. 2019;28(11):931-940.
44. Molofsky AB, Savage AK, Locksley RM. Interleukin-33 in tissue homeostasis, injury, and inflammation. *Immunity*. 2015;42(6):1005-1019.
45. Grainge C, Dennison P, Lau L, Davies D, Howarth P. Asthmatic and normal respiratory epithelial cells respond differently to mechanical apical stress. *Am J Respir Crit Care Med*. 2014;190(4):477-480.
46. Allakhverdi Z, Comeau MR, Jessup HK, et al. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potentially activates mast cells. *J Exp Med*. 2007;204(2):253-258.
47. Wang W, Li Y, Lv Z, et al. Bronchial allergen challenge of patients with atopic asthma triggers an alarmin (IL-33, TSLP, and IL-25) response in the airways epithelium and submucosa. *J Immunol*. 2018;201(8):2221-2231.
48. Li Y, Wang W, Lv Z, et al. Elevated expression of IL-33 and TSLP in the airways of human asthmatics in vivo: a potential biomarker of severe refractory disease. *J Immunol*. 2018;200(7):2253-2262.
49. Shikotra A, Choy DF, Ohri CM, et al. Increased expression of immunoreactive thymic stromal lymphopoietin in patients with severe asthma. *J Allergy Clin Immunol*. 2012;129(1):104, e1-9-111.
50. Smelter DF, Sathish V, Thompson MA, Pabelick CM, Vassallo R, Prakash Y. Thymic stromal lymphopoietin in cigarette smoke-exposed human airway smooth muscle. *J Immunol*. 2010;185(5):3035-3040.
51. Nakamura Y, Miyata M, Ohba T, et al. Cigarette smoke extract induces thymic stromal lymphopoietin expression, leading to T(H)2-type immune responses and airway inflammation. *J Allergy Clin Immunol*. 2008;122(6):1208-1214.
52. Kouzaki H, O'Grady SM, Lawrence CB, Kita H. Proteases induce production of thymic stromal lymphopoietin by airway epithelial cells through protease-activated receptor-2. *J Immunol*. 2009;183(2):1427-1434.
53. Lee HC, Headley MB, Loo YM, et al. Thymic stromal lymphopoietin is induced by respiratory syncytial virus-infected airway epithelial cells and promotes a type 2 response to infection. *J Allergy Clin Immunol*. 2012;130(5):1187-1196.e5.
54. Kato A, Favoreto S, Avila PC, Schleimer RP. TLR3- and Th2 cytokine-dependent production of thymic stromal lymphopoietin in human airway epithelial cells. *J Immunol*. 2007;179(2):1080-1087.
55. Lai JF, Thompson LJ, Ziegler SF. TSLP drives acute TH2-cell differentiation in lungs. *J Allergy Clin Immunol*. 2020;146(6):1406-1418.e7.
56. Kaur D, Doe C, Woodman L, et al. Mast cell-airway smooth muscle crosstalk: the role of thymic stromal lymphopoietin. *Chest*. 2012;142(1):76-85.
57. Braile M, Fiorelli A, Sorriento D, et al. Human lung-resident macrophages express and are targets of thymic stromal lymphopoietin in the tumor microenvironment. *Cells*. 2021;10(8):2012.
58. Kang JH, Yang HW, Park JH, et al. Lipopolysaccharide regulates thymic stromal lymphopoietin expression via TLR4/MAPK/Akt/NF-kappaB-signaling pathways in nasal fibroblasts: differential inhibitory effects of macrolide and corticosteroid. *Int Forum Allergy Rhinol*. 2021;11(2):144-152.
59. Datta A, Alexander R, Sulikowski MG, et al. Evidence for a functional thymic stromal lymphopoietin signaling axis in fibrotic lung disease. *J Immunol*. 2013;191(9):4867-4879.
60. Tsilingiri K, Fornasa G, Rescigno M. Thymic stromal lymphopoietin: to cut a long story short. *Cell Mol Gastroenterol Hepatol*. 2017;3(2):174-182.
61. Harada M, Hirota T, Jodo AI, et al. Functional analysis of the thymic stromal lymphopoietin variants in human bronchial epithelial cells. *Am J Respir Cell Mol Biol*. 2009;40(3):368-374.
62. Dong H, Hu Y, Liu L, et al. Distinct roles of short and long thymic stromal lymphopoietin isoforms in house dust mite-induced asthmatic airway epithelial barrier disruption. *Sci Rep*. 2016;6:39559.
63. Wu J, Dong F, Wang RA, et al. Central role of cellular senescence in TSLP-induced airway remodeling in asthma. *PLoS One*. 2013;8(10):e77795.
64. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol*. 2002;3(7):673-680.

65. Ito T, Wang YH, Duramad O, et al. TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med*. 2005;202(9):1213-1223.
66. Toki S, Goleniewska K, Zhang J, et al. TSLP and IL-33 reciprocally promote each other's lung protein expression and ILC2 receptor expression to enhance innate type-2 airway inflammation. *Allergy*. 2020;75(7):1606-1617.
67. Camelo A, Rosignoli G, Ohne Y, et al. IL-33, IL-25, and TSLP induce a distinct phenotypic and activation profile in human type 2 innate lymphoid cells. *Blood Adv*. 2017;1(10):577-589.
68. Cai LM, Zhou YQ, Yang LF, et al. Thymic stromal lymphopoietin induced early stage of epithelial-mesenchymal transition in human bronchial epithelial cells through upregulation of transforming growth factor beta 1. *Exp Lung Res*. 2019;45(8):221-235.
69. Brunetto E, De Monte L, Balzano G, et al. The IL-1/IL-1 receptor axis and tumor cell released inflammasome adaptor ASC are key regulators of TSLP secretion by cancer associated fibroblasts in pancreatic cancer. *J Immunother Cancer*. 2019;7(1):45.
70. Cao L, Liu F, Liu Y, et al. TSLP promotes asthmatic airway remodeling via p38-STAT3 signaling pathway in human lung fibroblast. *Exp Lung Res*. 2018;44(6):288-301.
71. Jin A, Tang X, Zhai W, et al. TSLP-induced collagen type-I synthesis through STAT3 and PRMT1 is sensitive to calcitriol in human lung fibroblasts. *Biochim Biophys Acta Mol Cell Res*. 2021;1868(10):119083.
72. Redhu NS, Shan L, Movassagh H, Gounni AS. Thymic stromal lymphopoietin induces migration in human airway smooth muscle cells. *Sci Rep*. 2013;3:2301.
73. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
74. Niimi A, Matsumoto H, Takemura M, Ueda T, Nakano Y, Mishima M. Clinical assessment of airway remodeling in asthma: utility of computed tomography. *Clin Rev Allergy Immunol*. 2004;27(1):45-58.
75. Awadh N, Müller NL, Park CS, Abboud RT, JM FG. Airway wall thickness in patients with near fatal asthma and control groups: assessment with high resolution computed tomographic scanning. *Thorax*. 1998;53(4):248-253.
76. Nagarkar DR, Poposki JA, Comeau MR, et al. Airway epithelial cells activate TH2 cytokine production in mast cells through IL-1 and thymic stromal lymphopoietin. *J Allergy Clin Immunol*. 2012;130(1):225-32 e4.
77. Afferni C, Buccione C, Andreone S, et al. The pleiotropic immunomodulatory functions of IL-33 and its implications in tumor immunity. *Front Immunol*. 2018;9:2601.
78. de Kleer IM, Kool M, de Bruijn MJ, et al. Perinatal activation of the interleukin-33 pathway promotes type 2 immunity in the developing lung. *Immunity*. 2016;45(6):1285-1298.
79. Leyva-Castillo JM, Galand C, Kam C, et al. Mechanical skin injury promotes food anaphylaxis by driving intestinal mast cell expansion. *Immunity*. 2019;50(5):1262-1275.e4.
80. Stier MT, Zhang J, Goleniewska K, et al. IL-33 promotes the egress of group 2 innate lymphoid cells from the bone marrow. *J Exp Med*. 2018;215(1):263-281.
81. Altman MC, Lai Y, Nolin JD, et al. Airway epithelium-shifted mast cell infiltration regulates asthmatic inflammation via IL-33 signaling. *J Clin Invest*. 2019;129(11):4979-4991.
82. Guo Z, Wu J, Zhao J, et al. IL-33 promotes airway remodeling and is a marker of asthma disease severity. *J Asthma*. 2014;51(8):863-869.
83. Saglani S, Lui S, Ullmann N, et al. IL-33 promotes airway remodeling in pediatric patients with severe steroid-resistant asthma. *J Allergy Clin Immunol*. 2013;132(3):676-685 e13.
84. Cristinziano L, Poto R, Criscuolo G, et al. IL-33 and superantigenic activation of human lung mast cells induce the release of angiogenic and lymphangiogenic factors. *Cells*. 2021;10(1):145.
85. Marone G, Borriello F, Varricchi G, Genovese A, Granata F. Basophils: historical reflections and perspectives. *Chem Immunol Allergy*. 2014;100:172-192.
86. Gambardella AR, Poto R, Tirelli V, et al. Differential effects of alarmins on human and mouse basophils. *Front Immunol*. 2022;13:894163.
87. Bankova LG, Dwyer DF, Yoshimoto E, et al. The cysteinyl leukotriene 3 receptor regulates expansion of IL-25-producing airway brush cells leading to type 2 inflammation. *Sci Immunol*. 2018;3(28):eaat9453.
88. Ualiyeva S, Lemire E, Aviles EC, et al. Tuft cell-produced cysteinyl leukotrienes and IL-25 synergistically initiate lung type 2 inflammation. *Sci Immunol*. 2021;6(66):eabj0474.
89. Yi L, Cheng D, Zhang K, et al. Intelectin contributes to allergen-induced IL-25, IL-33, and TSLP expression and type 2 response in asthma and atopic dermatitis. *Mucosal Immunol*. 2017;10(6):1491-1503.
90. Beale J, Jayaraman A, Jackson DJ, et al. Rhinovirus-induced IL-25 in asthma exacerbation drives type 2 immunity and allergic pulmonary inflammation. *Sci Transl Med*. 2014;6(256):256ra134.
91. Mjosberg JM, Trifari S, Crellin NK, et al. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CCR2 and CD161. *Nat Immunol*. 2011;12(11):1055-1062.
92. Xu X, Luo S, Li B, Dai H, Zhang J. IL-25 contributes to lung fibrosis by directly acting on alveolar epithelial cells and fibroblasts. *Exp Biol Med (Maywood)*. 2019;244(9):770-780.
93. Letuve S, Lajoie-Kadach S, Audusseau S, et al. IL-17E upregulates the expression of proinflammatory cytokines in lung fibroblasts. *J Allergy Clin Immunol*. 2006;117(3):590-596.
94. Hams E, Armstrong ME, Barlow JL, et al. IL-25 and type 2 innate lymphoid cells induce pulmonary fibrosis. *Proc Natl Acad Sci USA*. 2014;111(1):367-372.
95. Yao XJ, Huang KW, Li Y, et al. Direct comparison of the dynamics of IL-25- and 'allergen'-induced airways inflammation, remodelling and hypersensitivity in a murine asthma model. *Clin Exp Allergy*. 2014;44(5):765-777.
96. Halwani R, Al-Muhsen S, Al-Jahdali H, Hamid Q. Role of transforming growth factor-beta in airway remodeling in asthma. *Am J Respir Cell Mol Biol*. 2011;44(2):127-133.
97. Kardas G, Daszyńska-Kardas A, Marynowski M, Brząkalska O, Kuna P, Panek M. Role of platelet-derived growth factor (PDGF) in asthma as an immunoregulatory factor mediating airway remodeling and possible pharmacological target. *Front Pharmacol*. 2020;11:47.
98. Batra V, Musani AI, Hastie AT, et al. Bronchoalveolar lavage fluid concentrations of transforming growth factor (TGF)-beta1, TGF-beta2, interleukin (IL)-4 and IL-13 after segmental allergen challenge and their effects on alpha-smooth muscle actin and collagen III synthesis by primary human lung fibroblasts. *Clin Exp Allergy*. 2004;34(3):437-444.
99. Hackett TL. Epithelial-mesenchymal transition in the pathophysiology of airway remodelling in asthma. *Curr Opin Allergy Clin Immunol*. 2012;12(1):53-59.
100. Wen FQ, Liu XD, Terasaki Y, et al. Interferon-gamma reduces interleukin-4- and interleukin-13-augmented transforming growth factor-beta2 production in human bronchial epithelial cells by targeting Smads. *Chest*. 2003;123(3 Suppl):372S-373S.
101. Dolgachev V, Berlin AA, Lukacs NW. Eosinophil activation of fibroblasts from chronic allergen-induced disease utilizes stem cell factor for phenotypic changes. *Am J Pathol*. 2008;172(1):68-76.
102. Tanaka H, Komai M, Nagao K, et al. Role of interleukin-5 and eosinophils in allergen-induced airway remodeling in mice. *Am J Respir Cell Mol Biol*. 2004;31(1):62-68.

103. Booth BW, Sandifer T, Martin EL, Martin LD. IL-13-induced proliferation of airway epithelial cells: mediation by intracellular growth factor mobilization and ADAM17. *Respir Res.* 2007;8:51.
104. Malavia NK, Mih JD, Raub CB, Dinh BT, George SC. IL-13 induces a bronchial epithelial phenotype that is profibrotic. *Respir Res.* 2008;9:27.
105. Marone G, Granata F, Pucino V, et al. The intriguing role of interleukin 13 in the pathophysiology of asthma. *Front Pharmacol.* 2019;10:1387.
106. Ouyang Y, Miyata M, Hatsushika K, et al. TGF-beta signaling may play a role in the development of goblet cell hyperplasia in a mouse model of allergic rhinitis. *Allergol Int.* 2010;59(3):313-319.
107. Samitas K, Delimpoura V, Zervas E, Gaga M. Anti-IgE treatment, airway inflammation and remodelling in severe allergic asthma: current knowledge and future perspectives. *Eur Respir Rev.* 2015;24(138):594-601.
108. Pandey V, Mihara S, Fensome-Green A, Bolsover S, Cockcroft S. Monomeric IgE stimulates NFAT translocation into the nucleus, a rise in cytosol Ca^{2+} , degranulation, and membrane ruffling in the cultured rat basophilic leukemia-2H3 mast cell line. *J Immunol.* 2004;172(7):4048-4058.
109. Matsuda K, Piliponsky AM, Iikura M, et al. Monomeric IgE enhances human mast cell chemokine production: IL-4 augments and dexamethasone suppresses the response. *J Allergy Clin Immunol.* 2005;116(6):1357-1363.
110. Roth M, Zhao F, Zhong J, Lardinois D, Tamm M. Serum IgE induced airway smooth muscle cell remodeling is independent of allergens and is prevented by omalizumab. *PLoS One.* 2015;10(9):e0136549.
111. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. *Curr Opin Allergy Clin Immunol.* 2016;16(2):186-200.
112. Patella V, De Crescenzo G, Marinò I, et al. Eosinophil granule proteins activate human heart mast cells. *J Immunol.* 1996;157(3):1219-1225.
113. Marone G, Galdiero MR, Pecoraro A, et al. Prostaglandin D2 receptor antagonists in allergic disorders: safety, efficacy, and future perspectives. *Expert Opin Investig Drugs.* 2019;28(1):73-84.
114. Marcella S, Petraroli A, Braile M, et al. Vascular endothelial growth factors and angiopoietins as new players in mastocytosis. *Clin Exp Med.* 2021;21(3):415-427.
115. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest.* 2003;112(7):1029-1036.
116. Braile M, Cristinziano L, Marcella S, et al. LPS-mediated neutrophil VEGF-A release is modulated by cannabinoid receptor activation. *J Leukoc Biol.* 2021;109(3):621-631.
117. Byrne AJ, Mathie SA, Gregory LG, Lloyd CM. Pulmonary macrophages: key players in the innate defence of the airways. *Thorax.* 2015;70(12):1189-1196.
118. Balestrieri B, Granata F, Loffredo S, et al. Phenotypic and functional heterogeneity of low-density and high-density human lung macrophages. *Biomedicines.* 2021;9(5):505.
119. Balhara J, Gounni AS. The alveolar macrophages in asthma: a double-edged sword. *Mucosal Immunol.* 2012;5(6):605-609.
120. Staiano RI, Loffredo S, Borriello F, et al. Human lung-resident macrophages express CB1 and CB2 receptors whose activation inhibits the release of angiogenic and lymphangiogenic factors. *J Leukoc Biol.* 2016;99(4):531-540.
121. Varricchi G, Rossi FW, Galdiero MR, et al. Physiological roles of mast cells: collegium internationale allergologicum update 2019. *Int Arch Allergy Immunol.* 2019;179(4):247-261.
122. Compton SJ, Cairns JA, Holgate ST, Walls AF. The role of mast cell tryptase in regulating endothelial cell proliferation, cytokine release, and adhesion molecule expression: tryptase induces expression of mRNA for IL-1 beta and IL-8 and stimulates the selective release of IL-8 from human umbilical vein endothelial cells. *J Immunol.* 1998;161(4):1939-1946.
123. Ardi VC, Kupriyanova TA, Deryugina EI, Quigley JP. Human neutrophils uniquely release TIMP-free MMP-9 to provide a potent catalytic stimulator of angiogenesis. *Proc Natl Acad Sci USA.* 2007;104(51):20262-20267.
124. Ventura I, Vega A, Chacon P, et al. Neutrophils from allergic asthmatic patients produce and release metalloproteinase-9 upon direct exposure to allergens. *Allergy.* 2014;69(7):898-905.
125. Loffredo S, Borriello F, Iannone R, et al. Group V secreted phospholipase A2 induces the release of proangiogenic and antiangiogenic factors by human neutrophils. *Front Immunol.* 2017;8:443.
126. Varricchi G, Modestino L, Poto R, et al. Neutrophil extracellular traps and neutrophil-derived mediators as possible biomarkers in bronchial asthma. *Clin Exp Med.* 2021;22(2):285-300.
127. Cristinziano L, Modestino L, Antonelli A, et al. Neutrophil extracellular traps in cancer. *Semin Cancer Biol.* 2021;79:91-104.
128. Poto R, Cristinziano L, Modestino L, et al. Neutrophil extracellular traps, angiogenesis and cancer. *Biomedicines.* 2022;10(2):431.
129. Sammarco G, Varricchi G, Ferraro V, et al. Mast cells, angiogenesis and lymphangiogenesis in human gastric cancer. *Int J Mol Sci.* 2019;20(9):2106.
130. Varricchi G, Loffredo S, Bencivenga L, et al. Angiopoietins, vascular endothelial growth factors and secretory phospholipase A2 in ischemic and non-ischemic heart failure. *J Clin Med.* 2020;9(6):1928.
131. Zheng J, Wu Q, Zou Y, Wang M, He L, Guo S. Respiratory microbiota profiles associated with the progression from airway inflammation to remodeling in mice with OVA-induced asthma. *Front Microbiol.* 2021;12:723152.
132. Diver S, Khalfaoui L, Emson C, et al. Effect of tezepelumab on airway inflammatory cells, remodelling, and hyperresponsiveness in patients with moderate-to-severe uncontrolled asthma (CASCADE): a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med.* 2021;9(11):1299-1312.
133. Vieira Braga FA, Kar G, Berg M, et al. A cellular census of human lungs identifies novel cell states in health and in asthma. *Nat Med.* 2019;25(7):1153-1163.
134. Hoshino M, Ohtawa J, Akitsu K. Effect of treatment with inhaled corticosteroid on serum periostin levels in asthma. *Respirology.* 2016;21(2):297-303.
135. Gorska K, Korczynski P, Mierzejewski M. Comparison of endobronchial ultrasound and high resolution computed tomography as tools for airway wall imaging in asthma and chronic obstructive pulmonary disease. *Respir Med.* 2016;117:131-138.
136. Hartley RA, Barker BL, Newby C, et al. Relationship between lung function and quantitative computed tomographic parameters of airway remodeling, air trapping, and emphysema in patients with asthma and chronic obstructive pulmonary disease: a single-center study. *J Allergy Clin Immunol.* 2016;137(5):1413-1422.e12.
137. Ash SY, Rahaghi FN, Come CE, et al. Pruning of the pulmonary vasculature in asthma. The Severe Asthma Research Program (SARP) cohort. *Am J Respir Crit Care Med.* 2018;198(1):39-50.
138. Eddy RL, Svenningsen S, Kirby M, et al. Is computed tomography airway count related to asthma severity and airway structure and function? *Am J Respir Crit Care Med.* 2020;201(8):923-933.
139. Hoshino M, Ohtawa J. Effects of adding omalizumab, an anti-immunoglobulin E antibody, on airway wall thickening in asthma. *Respiration.* 2012;83(6):520-528.
140. Tajiri T, Niimi A, Matsumoto H, et al. Comprehensive efficacy of omalizumab for severe refractory asthma: a time-series observational study. *Ann Allergy Asthma Immunol.* 2014;113(4):470-475.e2.

141. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. *J Allergy Clin Immunol*. 2014;133(3):921-923.
142. Haldar P, Brightling C, Hargadon B. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2011;364(6):588.
143. Przybyszowski M, Gross-Sondej I, Zarychta J, et al. Late Breaking Abstract—the impact of treatment with mepolizumab on airway remodeling in patients with severe eosinophilic asthma. *Eur Res J*. 2021;58:PA894.
144. Zha W, Kruger SJ, Cadman RV, et al. Regional heterogeneity of lobar ventilation in asthma using hyperpolarized helium-3 MRI. *Acad Radiol*. 2018;25(2):169-178.
145. Mummy DG, Kruger SJ, Zha W, et al. Ventilation defect percent in helium-3 magnetic resonance imaging as a biomarker of severe outcomes in asthma. *J Allergy Clin Immunol*. 2018;141(3):1140-1141.e4.
146. Svenningsen S, Eddy RL, Lim HF, Cox PG, Nair P, Parraga G. Sputum eosinophilia and magnetic resonance imaging ventilation heterogeneity in severe asthma. *Am J Respir Crit Care Med*. 2018;197(7):876-884.
147. Mummy DG, Carey KJ, Evans MD, et al. Ventilation defects on hyperpolarized helium-3 MRI in asthma are predictive of 2-year exacerbation frequency. *J Allergy Clin Immunol*. 2020;146(4):831-839.e6.
148. Nishimoto K, Karayama M, Inui N, et al. Relationship between fraction of exhaled nitric oxide and airway morphology assessed by three-dimensional CT analysis in asthma. *Sci Rep*. 2017;7(1):10187.
149. Franks TJ, Colby TV, Travis WD, et al. Resident cellular components of the human lung: current knowledge and goals for research on cell phenotyping and function. *Proc Am Thorac Soc*. 2008;5(7):763-766.
150. Reyfman PA, Walter JM, Joshi N, et al. Single-cell transcriptomic analysis of human lung provides insights into the pathobiology of pulmonary fibrosis. *Am J Respir Crit Care Med*. 2019;199(12):1517-1536.
151. Adams TS, Schupp JC, Poli S, et al. Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. *Sci Adv*. 2020;6(28):eaba1983.
152. Paul F, Arkin YA, Giladi A, et al. Transcriptional heterogeneity and lineage commitment in myeloid progenitors. *Cell*. 2015;163(7):1663-1677.
153. Villani AC, Satija R, Reynolds G, et al. Single-cell RNA-seq reveals new types of human blood dendritic cells, monocytes, and progenitors. *Science*. 2017;356(6335):eaah4573.
154. Li Z, Feng Y, Liu H, et al. Single-cell transcriptomics of mouse lung reveal inflammatory memory neutrophils in allergic asthma. *Allergy*. 2022;77(6):1911-1915.
155. Riccioni G, Di Ilio C, D'Orazio N. Review: pharmacological treatment of airway remodeling: inhaled corticosteroids or antileukotrienes? *Ann Clin Lab Sci*. 2004;34(2):138-142.
156. Ward C, Reid DW, Orsida BE, et al. Inter-relationships between airway inflammation, reticular basement membrane thickening and bronchial hyper-reactivity to methacholine in asthma; a systematic bronchoalveolar lavage and airway biopsy analysis. *Clin Exp Allergy*. 2005;35(12):1565-1571.
157. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines—recommendations on the use of biologicals in severe asthma. *Allergy*. 2020;75(5):1023-1042.
158. Varricchi G, Marone G, Spadaro G, et al. Novel biological therapies in severe asthma: targeting the right trait. *Curr Med Chem*. 2019;26(16):2801-2822.
159. Ferrando M, Bagnasco D, Varricchi G, et al. Personalized medicine in allergy. *Allergy Asthma Immunol Res*. 2017;9(1):15-24.
160. Canonica GW, Ferrando M, Baiardini I, et al. Asthma: personalized and precision medicine. *Curr Opin Allergy Clin Immunol*. 2018;18(1):51-58.
161. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med*. 2022;386(2):157-171.
162. Roche N, Anzueto A, Anticevich SB, et al. The importance of real-life research in respiratory medicine: manifesto of the Respiratory Effectiveness Group: endorsed by the International Primary Care Respiratory Group and the World Allergy Organization. *Eur Respir J*. 2019;54(3):1901511.
163. Little RJ, Lewis RJ. Estimands, estimators, and estimates. *JAMA*. 2021;326(10):967-968.
164. Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med*. 2001;164(8 Pt 2):S6-S11.
165. Kawakami T, Blank U. From IgE to omalizumab. *J Immunol*. 2016;197(11):4187-4192.
166. MacGlashan DW Jr, Savage JH, Wood RA, Saini SS. Suppression of the basophil response to allergen during treatment with omalizumab is dependent on 2 competing factors. *J Allergy Clin Immunol*. 2012;130(5):1130-1135.e5.
167. Prussin C, Griffith DT, Boesel KM, Lin H, Foster B, Casale TB. Omalizumab treatment downregulates dendritic cell Ccrp50 expression. *J Allergy Clin Immunol*. 2003;112(6):1147-1154.
168. Alhossan A, Lee CS, MacDonald K, Abraham I. "Real-life" effectiveness studies of omalizumab in adult patients with severe allergic asthma: meta-analysis. *J Allergy Clin Immunol Pract*. 2017;5(5):1362-1370.e2.
169. Esquivel A, Busse WW, Calatroni A, et al. Effects of omalizumab on rhinovirus infections, illnesses, and exacerbations of asthma. *Am J Respir Crit Care Med*. 2017;196(8):985-992.
170. Pelaia C, Calabrese C, Terracciano R, de Blasio F, Vatrella A, Pelaia G. Omalizumab, the first available antibody for biological treatment of severe asthma: more than a decade of real-life effectiveness. *Ther Adv Respir Dis*. 2018;12:1753466618810192.
171. Adachi M, Kozawa M, Yoshisue H, et al. Real-world safety and efficacy of omalizumab in patients with severe allergic asthma: a long-term post-marketing study in Japan. *Respir Med*. 2018;141:56-63.
172. Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc*. 2017;38(4):250-263.
173. Namazy J, Cabana MD, Scheuerle AE, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. *J Allergy Clin Immunol*. 2015;135(2):407-412.
174. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154(9):573-582.
175. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;1:CD003559.
176. Hew M, Gillman A, Sutherland M, et al. Real-life effectiveness of omalizumab in severe allergic asthma above the recommended dosing range criteria. *Clin Exp Allergy*. 2016;46(11):1407-1415.
177. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. *J Allergy Clin Immunol Pract*. 2019;7(1):156-164.e1.
178. Riccio AM, Dal Negro RW, Micheletto C, et al. Omalizumab modulates bronchial reticular basement membrane thickness and eosinophil infiltration in severe persistent allergic asthma patients. *Int J Immunopathol Pharmacol*. 2012;25(2):475-484.
179. Zastrzezyńska W, Przybyszowski M, Bazan-Socha S, et al. Omalizumab may decrease the thickness of the reticular basement membrane and fibronectin deposit in the bronchial mucosa of severe allergic asthmatics. *J Asthma*. 2020;57(5):468-477.

180. FDA.GOV, 2019.
181. Varricchi G, Morjaria JB, Fuochi V, Polosa R, Caruso M. Mepolizumab in the management of severe eosinophilic asthma in adults: current evidence and practical experience. *Ther Adv Respir Dis*. 2017;11(1):40-45.
182. Varricchi G, Galdiero MR, Loffredo S, et al. Eosinophils: the unsung heroes in cancer? *Oncoimmunology*. 2018;7(2):e1393134.
183. Broughton SE, Nero TL, Dhagat U, et al. The betac receptor family - structural insights and their functional implications. *Cytokine*. 2015;74(2):247-258.
184. Borriello F, Galdiero MR, Varricchi G, Loffredo S, Spadaro G, Marone G. Innate immune modulation by GM-CSF and IL-3 in health and disease. *Int J Mol Sci*. 2019;20(4):834.
185. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651-659.
186. Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther*. 2016;38(9):2058-2070.e1.
187. Khurana S, Brusselle GG, Bel EH, et al. Long-term safety and clinical benefit of mepolizumab in patients with the most severe eosinophilic asthma: the COSMEX study. *Clin Ther*. 2019;41(10):2041-2056.e5.
188. Ortega H, Liu MC, Pavord ID. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2015;372(18):1777.
189. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med*. 2017;5(5):390-400.
190. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189-1197.
191. Sposato B, Camiciottoli G, Bacci E, et al. Mepolizumab effectiveness on small airway obstruction, corticosteroid sparing and maintenance therapy step-down in real life. *Pulm Pharmacol Ther*. 2020;61:101899.
192. Pelaia C, Crimi C, Pelaia G, et al. Real-life evaluation of mepolizumab efficacy in patients with severe eosinophilic asthma, according to atopic trait and allergic phenotype. *Clin Exp Allergy*. 2020;50(7):780-788.
193. Bagnasco D, Caminati M, Menzella F, et al. One year of mepolizumab. Efficacy and safety in real-life in Italy. *Pulm Pharmacol Ther*. 2019;58:101836.
194. Zhang J, Kuvelkar R, Murgolo NJ, et al. Mapping and characterization of the epitope(s) of Sch 55700, a humanized mAb, that inhibits human IL-5. *Int Immunol*. 1999;11(12):1935-1944.
195. Varricchi G, Senna G, Loffredo S, Bagnasco D, Ferrando M, Canonica GW. Reslizumab and eosinophilic asthma: one step closer to precision medicine? *Front Immunol*. 2017;8:242.
196. Bjermer L, Lemièrre C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150(4):789-798.
197. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184(10):1125-1132.
198. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799-810.
199. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355-366.
200. Bernstein JA, Virchow JC, Murphy K, et al. Effect of fixed-dose subcutaneous reslizumab on asthma exacerbations in patients with severe uncontrolled asthma and corticosteroid sparing in patients with oral corticosteroid-dependent asthma: results from two phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med*. 2020;8(5):461-474.
201. Wechsler ME, Peters SP, Hill TD, et al. Clinical outcomes and health-care resource use associated with reslizumab treatment in adults with severe eosinophilic asthma in real-world practice. *Chest*. 2021;159(5):1734-1746.
202. Ghazi A, Trikha A, Calhoun WJ. Benralizumab—a humanized mAb to IL-5R α with enhanced antibody-dependent cell-mediated cytotoxicity—a novel approach for the treatment of asthma. *Expert Opin Biol Ther*. 2012;12(1):113-118.
203. Bleecker ER, JM FG, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
204. Ferguson GT, JM FG, Bleecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2017;5(7):568-576.
205. Harrison TW, Chanez P, Menzella F, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. *Lancet Respir Med*. 2021;9(3):260-274.
206. Chipps BE, Hirsch I, Trudo F, Alacqua M, Zangrilli JG. Benralizumab efficacy for patients with fixed airflow obstruction and severe, uncontrolled eosinophilic asthma. *Ann Allergy Asthma Immunol*. 2020;124(1):79-86.
207. Chachi L, Diver S, Kaul H, et al. Computational modelling prediction and clinical validation of impact of benralizumab on airway smooth muscle mass in asthma. *Eur Respir J*. 2019;54(5):1900930.
208. Pelaia C, Busceti MT, Vatrella A, et al. Real-life rapidity of benralizumab effects in patients with severe allergic eosinophilic asthma: assessment of blood eosinophils, symptom control, lung function and oral corticosteroid intake after the first drug dose. *Pulm Pharmacol Ther*. 2019;58:101830.
209. Padilla-Galo A, Levy-Abitbol R, Oliveira C, et al. Real-life experience with benralizumab during 6 months. *BMC Pulm Med*. 2020;20(1):184.
210. Menzella F, Ruggiero P, Galeone C, Scelfo C, Bagnasco D, Facciolo N. Significant improvement in lung function and asthma control after benralizumab treatment for severe refractory eosinophilic asthma. *Pulm Pharmacol Ther*. 2020;64:101966.
211. Keegan AD, Zamorano J, Keselman A, Heller NM. IL-4 and IL-13 receptor signaling from 4PS to insulin receptor substrate 2: there and back again, a historical view. *Front Immunol*. 2018;9:1037.
212. Harb H, Chatila TA. Mechanisms of dupilumab. *Clin Exp Allergy*. 2020;50(1):5-14.
213. Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med*. 2013;368(26):2455-2466.
214. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388(10039):31-44.
215. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496.
216. Le Floch A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4R α antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75(5):1188-1204.

217. Renner A, Marth K, Patocka K, Idzko M, Pohl W. Dupilumab rapidly improves asthma control in predominantly anti-IL5/IL5R pre-treated Austrian real-life severe asthmatics. *Immun Inflamm Dis*. 2021;9(3):624-627.
218. Eger K, Pet L, Weersink EJ, Bel EH. Complications of switching from anti-IL-5 or anti-IL-5R to dupilumab in corticosteroid-dependent severe asthma. *J Allergy Clin Immunol Pract*. 2021;9(7):2913-2915.
219. Marcant P, Balayé P, Merhi R, et al. Dupilumab-associated hyper-eosinophilia in patients treated for moderate-to-severe atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2021;35(6):e394-e396.
220. Wechsler ME, Klion A, Paggiaro P, et al. Abstract: effect of dupilumab treatment on blood eosinophil levels in patients with asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic esophagitis (EoE), or atopic dermatitis (AD). *J Allergy Clin Immunol*. 2021;147:AB140.
221. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394(10209):1638-1650.
222. Pedersen E, Sondergaard B, Poulsen EF. Don't want to lose nursing hours on account of new education. *Sygeplejersken*. 1988;88(48):17.
223. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(10):1141-1153.
224. Canonica GW, Harrison TW, Chanez P, et al. Benralizumab improves symptoms of patients with severe, eosinophilic asthma with a diagnosis of nasal polyposis. *Allergy*. 2022;77(1):150-161.
225. Ko HK, Cheng SL, Lin CH, et al. Blood tryptase and thymic stromal lymphopoietin levels predict the risk of exacerbation in severe asthma. *Sci Rep*. 2021;11(1):8425.
226. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-946.
227. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800-1809.
228. An G, Wang W, Zhang X, et al. Combined blockade of IL-25, IL-33 and TSLP mediates amplified inhibition of airway inflammation and remodelling in a murine model of asthma. *Respirology*. 2020;25(6):603-612.
229. Chen ZG, Zhang TT, Li HT, et al. Neutralization of TSLP inhibits airway remodeling in a murine model of allergic asthma induced by chronic exposure to house dust mite. *PLoS One*. 2013;8(1):e51268.
230. Lin SC, Chou HC, Chen CM, Chiang BL. Anti-thymic stromal lymphopoietin antibody suppresses airway remodeling in asthma through reduction of MMP and CTGF. *Pediatr Res*. 2019;86(2):181-187.
231. Cheng Z, Wang X, Dai LL, et al. Thymic stromal lymphopoietin signaling pathway inhibition attenuates airway inflammation and remodeling in rats with asthma. *Cell Physiol Biochem*. 2018;47(4):1482-1496.
232. Sverrild A, Hansen S, Hvidtfeldt M, et al. The effect of tezepelumab on airway hyperresponsiveness to mannitol in asthma (UPSTREAM). *Eur Respir J*. 2021;59(1):2101296.
233. Kelsen SG, Agache IO, Soong W, et al. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2021;148(3):790-798.
234. Wechsler ME, Ruddy MK, Pavord ID, et al. Efficacy and safety of itepekimab in patients with moderate-to-severe asthma. *N Engl J Med*. 2021;385(18):1656-1668.
235. Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. *Am Rev Respir Dis*. 1993;147(3):697-704.
236. Holgate ST, Wenzel S, Postma DS, et al. Asthma. *Nat Rev Dis Primers*. 2015;1:15025.
237. Fehrenbach H, Wagner C, Wegmann M. Airway remodeling in asthma: what really matters. *Cell Tissue Res*. 2017;367(3):551-569.
238. Paganin F, Mangiapan G, Proust A, et al. Lung function parameters in omalizumab responder patients: an interesting tool? *Allergy*. 2017;72(12):1953-1961.
239. Caminati M, Cegolon L, Vianello A, et al. Mepolizumab for severe eosinophilic asthma: a real-world snapshot on clinical markers and timing of response. *Expert Rev Respir Med*. 2019;13(12):1205-1212.
240. Busse WW, Bleecker ER, JM FG, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med*. 2019;7(1):46-59.
241. Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):516-526.
242. Henderson NC, Rieder F, Wynn TA. Fibrosis: from mechanisms to medicines. *Nature*. 2020;587(7835):555-566.
243. Moretti L, Stalfort J, Barker TH, Abeyayehu D. The interplay of fibroblasts, the extracellular matrix, and inflammation in scar formation. *J Biol Chem*. 2022;298(2):101530.
244. Aran D, Looney AP, Liu L, et al. Reference-based analysis of lung single-cell sequencing reveals a transitional profibrotic macrophage. *Nat Immunol*. 2019;20(2):163-172.
245. Zhang J, Dong L. Status and prospects: personalized treatment and biomarker for airway remodeling in asthma. *J Thorac Dis*. 2020;12(10):6090-6101.
246. Mesnil C, Raulier S, Paulissen G, et al. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. *J Clin Invest*. 2016;126(9):3279-3295.
247. Varricchi G, de Paulis A, Marone G, Galli SJ. Future needs in mast cell biology. *Int J Mol Sci*. 2019;20(18):4397.
248. Varricchi G, Marone G, Kovanen PT. Cardiac mast cells: underappreciated immune cells in cardiovascular homeostasis and disease. *Trends Immunol*. 2020;41(8):734-746.
249. Varricchi G, Pecoraro A, Loffredo S, et al. Heterogeneity of human mast cells with respect to mrgprx2 receptor expression and function. *Front Cell Neurosci*. 2019;13:299.
250. Varricchi G, Loffredo S, Borriello F, et al. Superantigenic activation of human cardiac mast cells. *Int J Mol Sci*. 2019;20(8):1828.
251. Burn GL, Foti A, Marsman G, Patel DF, Zychlinsky A. The neutrophil. *Immunity*. 2021;54(7):1377-1391.
252. Vivanco Gonzalez N, Oliveria JP, Tebaykin D, et al. Mass cytometry phenotyping of human granulocytes reveals novel basophil functional heterogeneity. *iScience*. 2020;23(11):101724.

How to cite this article: Varricchi G, Ferri S, Pepys J, et al. Biologics and airway remodeling in severe asthma. *Allergy*. 2022;77:3538-3552. doi: [10.1111/all.15473](https://doi.org/10.1111/all.15473)