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MedImmune: Leading the revolution in respiratory medicine with biologics

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The main culprit of many debilitating respiratory, inflammatory and autoimmune diseases is an immune system that is out of balance. Working to restore that balance are the scientists of MedImmune, the global biologics research and development arm of AstraZeneca. By following the science around immune-mediated inflammatory diseases at the cellular and molecular level, MedImmune has built one of the richest, most diverse immunomodulatory portfolios in the industry, targeting asthma, COPD, idiopathic pulmonary fibrosis, lupus, multiple sclerosis, psoriasis and rheumatoid arthritis.

Asthma and COPD: Widespread use of inhaled corticosteroids (ICS) as monotherapy or in combination with long acting β_2-agonists in asthma has resulted in a pronounced reduction in the burden of the disease and in asthma-related mortality. In COPD, the appropriate diagnosis and treatment of patients is still a fundamental challenge and long-term use of ICS is only recommended for some high risk patients who are not sufficiently controlled with long-acting bronchodilators. However, the response to ICS is poor in the majority of patients and adverse effects include increased risks of infection, diabetes, and fractures. Asthma and COPD control is, therefore, often suboptimal, and many of the more severe patients continue to experience frequent acute exacerbations of their disease. Thus, there remains a substantial unmet need for treatments that achieve better symptom control and slow disease progression. Here, the use of specifically targeted and highly potent therapeutic monoclonal antibodies has the potential to modify disease and bring about life changing improvements to patients.

As with many other inflammatory diseases, asthma and COPD encompass several distinct patient phenotypes characterized by the shared presence of cellular and molecular biomarkers. Linking biomarkers with clinical phenotypes has greatly advanced our understanding of asthma pathophysiology and, importantly, facilitated the clinical development of our innovative targeted biologics. MedImmune is committed to the discovery of novel biomarkers and complementary or companion diagnostics to identify the patients who are most likely to respond to, and benefit from, a specific treatment. We have developed therapeutic monoclonal antibodies with significant potential for the treatment of patients with asthma and COPD. These "treatable traits" include eosinophilic disease, T_H2 high disease and epithelial-mediated pathologies (see Figure 1).

Eosinophilic disease: Increased eosinophils in the airways of patients with asthma correlate with increased disease severity, airway obstruction and susceptibility to exacerbations. Activated eosinophils release several toxic granule proteins that can damage lung tissue, induce airway hyper-responsiveness and mucus secretion as well as trigger exacerbations. Benralizumab, (https://www.youtube.com/watch?v=RPu6Vnp-WM8), is a humanized monoclonal antibody that binds with high affinity to interleukin (IL)- 5 receptor alpha and effectively depletes eosinophils and basophils via antibody-dependent cell-mediated cytotoxicity[1], through a different mechanism of action than that of the anti-IL-5 ligand approaches. Benralizumab is a potent eosinophil depleter inducing a complete removal of these cells in the bone marrow and peripheral blood of asthmatics, and an almost complete depletion within the airway mucosa and sputum[2]. Benralizumab has been well-tolerated and demonstrated clinical efficacy in a Phase IIb trial in patients with severe, uncontrolled asthma[3]. Benralizumab reduced the acute exacerbation rate in patients with high baseline blood eosinophils, (≥300 cells/μL), and resulted in significant improvements in lung function, (FEV_1), and health-related quality of life, (i.e. ACQ-6 score), compared with placebo.

Moreover, we recently announced that benralizumab achieved the primary endpoints in two pivotal Phase III trials in patients with severe, uncontrolled asthma, demonstrating significant reductions in annual asthma exacerbation rates compared with placebo (https://www.astrazeneca.com/media-centre/press-releases/2016/astrazeneca-announces-positive-results-from-benralizumab-phase-iii-programme-in-severe-asthma-17052016.html).

Eosinophilic inflammation is also associated with a sub-population of COPD patients. In a small Phase IIa study in patients with moderate to very severe COPD, with a history of previous exacerbations and sputum eosinophilia, benralizumab treatment resulted in a significant improvement in FEV_1. Although the primary endpoint of significantly reducing the exacerbation frequency was not met in this study, a pre-specified subgroup analysis revealed that benralizumab exhibited a trend towards a reduction in exacerbation rate for these patients with elevated blood eosinophils[4]. Patients with increased blood eosinophils also exhibited a significant improvement in COPD symptom scores[4]. Two phase III studies are currently underway examining the effects of eosinophil depletion in patients with COPD.

T_H2 high associated asthma: IL-13 is a cytokine that plays a significant role in mediating the key features of chronic severe asthma, including mucus metaplasia and hypersecretion, as well as having direct effects on airway smooth muscle contraction and hyperreactivity. MedImmune has developed a specific anti-IL-13 monoclonal antibody, tralokinumab, (https://www.youtube.com/watch?v=LB-wTJJmXFY), which has demonstrated clinical efficacy in a subset of severe uncontrolled asthma patients. Tralokinumab significantly reduced the frequency of acute exacerbations in patients with lung function reversibility and high serum periostin concentrations, a biomarker for IL-13 pathway activation. In patients with high periostin levels, tralokinumab also markedly improved FEV_1 and health-related quality of life, i.e. ACQ-6 score[5]. Tralokinumab is being further investigated in ongoing Phase III clinical trials of patients with uncontrolled asthma, along with the evaluation of the potential utility of serum dipeptidyl peptidase-4 and periostin as biomarkers of IL-13 pathway activation.

Modulating epithelial mediated inflammation: A growing body of evidence has linked epithelial-derived cytokines with innate lymphoid cell (ILC) function and exacerbations of disease. Thymic stromal lymphopoietin (TSLP), IL-25 and IL-33 are produced by epithelial cells in response to various pro-inflammatory stimuli, including allergens and viral infection, and exert potent effects on group 2 ILC function. TSLP is an upstream key initiator of allergic responses having direct effects on ILCs and dendritic cells, which result in the subsequent initiation of Th2 pathway activation. In an allergen challenge study of patients with mild atopic asthma, tezepelumab, a humanized anti-TSLP monoclonal antibody, attenuated the early allergen-induced bronchoconstriction and the late airway inflammatory response[6]. Treatment with anti-TSLP antibody also decreased blood and sputum eosinophils and reduced the fraction of exhaled nitric oxide (levels of which correlate with eosinophilic inflammation). These data are consistent with a key role for TSLP in allergen-induced airway responses and suggest that blocking TSLP in asthma may modulate multiple aspects of disease progression and prevent exacerbations. MedImmune is currently investigating the effects of tezepelumab in a Phase II asthma development program in collaboration with Amgen.

Emerging science: MedImmune has a key interest in understanding epithelial biology and identifying ways to modulate epithelial function. Indeed, we have reported a number of critical observations regarding the crosstalk between epithelial cytokines and ILC function. Specifically, IL-33 has been implicated through genetic and functional studies to play a role in inflammatory diseases, including asthma. Multiple mechanisms have evolved to regulate the activity of IL-33 and its receptor, ST2, including proteolytic processing

and neutralization of soluble ST2. We have shown that *in vivo* regulation of this cytokine is also tightly controlled by oxidation, which is associated with a conformational change rapidly eliminating ST2-dependent activity[7]. IL-33 activation is predominantly associated with T_H2 immunity via the induction of IL-13 from ILC2s and T_H2 cells. However, we have demonstrated a novel role for this cytokine in COPD, whereby cigarette smoke exposure is associated with a striking redistribution of ST2 expression, the consequence of which alters the response to IL-33 towards an exaggerated T_H1-skewed effect[8]. Thus, IL-33 can significantly enhance both T_H1 and T_H2-like inflammatory responses in disease.

In-house studies have confirmed that epithelial cytokines are tightly linked with ILC2 function and recently discovered that the remarkable plasticity in these cells permits a rapid and robust inflammatory response in T_H1 and/or T_H2 immunity[9,10]. Here we found that the pro-inflammatory cytokine IL-1 is a critical upstream regulator of ILC2 function and plasticity, where IL-12 is a key switch determining the outcome; ILC2 activation or ILC2-ILC1 conversion[9]. This phenotypic switch has biological relevance for COPD since cigarette smoke exposure and/or infection can trigger ILC1 conversion and, importantly, the increased frequency of ILC1s in patients with COPD correlate with disease severity and susceptibility to exacerbations[10]. Thus, functional plasticity in ILC2s exacerbates anti-viral immunity and may have adverse consequences in respiratory diseases like COPD. Additional research is ongoing to characterize the extent of ILC plasticity and whether manipulating these pathways may offer therapeutic approaches in disease.

MedImmune's commitment to these and other scientific innovations exploit our capabilities in biologics, immunotherapies, protein engineering technologies and devices. With a strong focus on translational science and personalized healthcare capabilities, strengthened by collaborations with world-renowned scientists and academic institutions, as well as partnerships with like-minded science-led companies, our current pipeline will provide multiple options for therapeutic intervention, with significant potential for disease modification across the spectrum of respiratory, inflammation and autoimmunity; oncology; and cardiovascular and metabolic diseases.

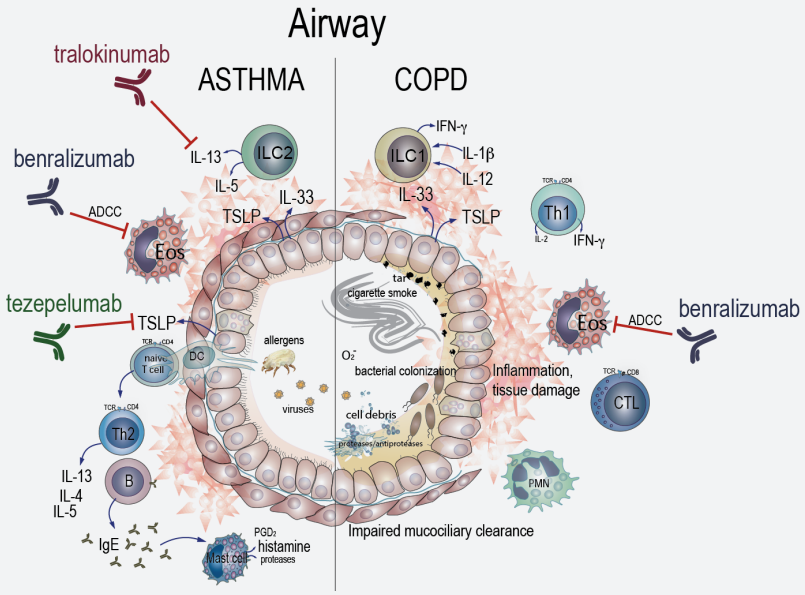

Figure 1 | Pathophysiological Processes associated with Asthma and COPD. Allergens, pathogens, cigarette smoke, toxins, and other particulate matter accumulate in the airway lumen and result in the activation and injury of airway epithelial cells. Epithelial cells release various mediators, including the innate cytokines IL-33, IL-25 and TSLP, which initiate or amplify airway inflammation. These cytokines combine with other stimuli to activate and recruit a variety of innate immune cells in the lung (e.g., eosinophils, mast cells, dendritic cells, macrophages, innate lymphoid cells, basophils and polymorphonuclear cells), a process which consequently triggers adaptive immune responses and the production of mediators that amplify inflammation in many different ways. These mediators include reactive oxygen species (O_2^-, H_2O_2), cytokines (IL-1, IL-2, IL-4, IL-5, IL-12, IL-13, interferon-γ, GM-CSF, TNFα), proteases, chemokines, prostaglandins, immunoglobulins and histamine. Together, these cells and their mediators drive inflammation and tissue damage, airway hyperresponsiveness and constriction, mucus hypersecretion and epithelial hyperplasia, airway remodeling and emphysema and impaired mucociliary clearance, all of which are associated with clinical sequelae of asthma and COPD. The three monoclonal antibodies that have been discussed and demonstrated to have clinical efficacy in asthma or COPD are indicated, the red T-shaped symbols indicate the molecular target of the respective antibody and its antagonistic activity against the target, except for Benralizumab which is an ADCC-enhanced antibody resulting in eosinophil and basophil depletion.

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ABBREVIATIONS

ADCC (antibody-dependent cell-mediated cytotoxicity), B (B cell), CD (cluster of differentiation protein), COPD (chronic obstructive pulmonary disease), CTL, (cytotoxic T lymphocyte), DC (dendritic cell), IFN (interferon), IgE (immunoglobulin E), IL (interleukin), ILC (innate lymphoid cell), O_2^- (superoxide), PGD_2 (prostaglandin D_2), PMN (polymorphonuclear cell), TCR (Tcell receptor), Th (T helper cell), TSLP (thymic stromal lymphopoietin).