

# What's on the Horizon for the Targeted Treatment of Type 2-low Asthma?



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An impressive amount of progress has been made in identifying the molecular pathways that mediate type 2-high asthma, which has culminated in the introduction into clinical practice of neutralizing antibodies that specifically target IgE, type 2 cytokines (IL-4, IL-5, IL-13), and the airway epithelial cell-derived cytokine, thymic stromal lymphopoietin (TSLP). These biologic therapies reduce asthma exacerbations, allow reductions in corticosteroid requirements, and improve lung function when administered to patients with type 2-high asthma. Patients with asthma who have low blood eosinophil counts and low exhaled levels of nitric oxide (FENO) and disease that is not clinically allergen-driven are classified as having type 2-low disease. Patients with type 2-low asthma tend to be less responsive to corticosteroids and are characterized by neutrophilic airway inflammation or as being pauci-granulocytic (with neither neutrophilic nor eosinophilic airway inflammation). The molecular pathways that mediate type 2-low asthma are less well-defined than for type 2-

high asthma. Tezepelumab, a neutralizing antibody directed against TSLP, which currently is available for clinical use, is a biologic agent that reduces exacerbations in patients with severe asthmatics with either type-2 high or type 2-low disease, which includes individuals with blood eosinophil counts < 150 cells/mL or FENO levels < 25 parts per billion.<sup>1</sup> Potential mechanisms by which TSLP neutralization may be beneficial for the treatment of patients with type 2-low asthma includes effects on neutrophils, mast cells, smooth muscle cells, and fibroblasts. Although the ability of TSLP neutralization to reduce asthma exacerbations in patients with type 2-low asthma is an important advance, additional therapeutic strategies are needed. So, what is on the horizon for the targeted treatment of patients with type 2-low asthma? As shown in [Figure 1](#), therapeutic interventions that target pathways that involve IL-33, mast cells, and IL-6 have either already been evaluated or are currently under evaluation in clinical trials.

IL-33 is another airway epithelial cell-derived cytokine that may contribute to the pathogenesis of type 2-low asthma. IL-33 resides within the nuclei of airway epithelial cells and can be released upon cellular damage, for example because of viral infection. Mast cells express ST2, which is a component of the IL-33 receptor, and an IL-33-stimulated mast cell signature recently has been associated with severe neutrophilic asthma.<sup>2</sup> Consistent with this, conditioned media from IL-33-stimulated human mast cells has been shown to mediate the chemotaxis of human neutrophils.<sup>3</sup> Collectively, these findings suggest that an IL-33/mast cell/neutrophil axis might be active in a subgroup of patients with type 2-low asthma. A phase 2 clinical trial of astegolimab, a neutralizing antibody directed against ST2, recently has been reported to reduce asthma exacerbations in both an overall population of patients with severe asthma, as well as in a subgroup of patients with blood eosinophil counts < 300 cells/mL.<sup>4</sup> Additional studies will be needed to establish whether therapeutic strategies that target ST2 or IL-33 are effective for the treatment of type 2-low asthma.

Therapeutic strategies directly targeting mast cells are also being developed for patients with type 2-low asthma. Stem cell factor binds to its receptor, KIT, on mast cells to mediate multiple important functions that include differentiation, activation, chemotaxis, and

**ABBREVIATIONS:** FENO = fractional exhaled nitric oxide; PrecISE = Precision Interventions for Severe and/or Exacerbation; TSLP = thymic stromal lymphopoietin

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| Pathway                                  | Mediator         | Receptor             | Biomarker                 | Targeted Treatment    |
|------------------------------------------|------------------|----------------------|---------------------------|-----------------------|
| Airway Epithelial Cell-derived Cytokines | TSLP<br>IL-33    | TSLP Receptor<br>ST2 | FeNO<br>Blood Eosinophils | anti-TSLP<br>anti-ST2 |
| Mast Cells                               | Stem Cell Factor | KIT                  | Blood Eosinophils         | Imatinib              |
| Systemic Inflammation                    | IL-6             | IL-6 Receptor        | Plasma IL-6               | anti-IL-6             |

Figure 1 – Targeted treatments for patients with type 2-low asthma that either have been evaluated or are currently under evaluation in clinical trials. Created with [BioRender.com](https://BioRender.com).

survival.<sup>5</sup> Imatinib is a small molecule that binds the ATP-binding site of KIT and thereby inhibits its tyrosine kinase activity. A randomized, double-blind, placebo-controlled, 24-week, phase 2 trial has evaluated imatinib in patients with severe refractory asthma.<sup>6</sup> This study found that imatinib reduced mast cell activation and airway responsiveness to methacholine and improved FEV<sub>1</sub>. This study also showed that imatinib was most effective in patients with asthmatics with more neutrophilic and less eosinophilic inflammation, which suggested a role for mast cells in the pathogenesis of type 2-low asthma. The concept of utilizing imatinib to target mast cells is being investigated currently in a phase 2, proof-of-concept clinical trial, as part of the Precision Interventions for Severe and/or Exacerbation-prone (PrecISE) Asthma Network, where the intervention will be administered to patients with type 2-low asthma who have blood eosinophil counts < 300 cells/mL.<sup>5</sup> End points for PrecISE clinical trials include asthma exacerbations, asthma symptoms, and lung function. This study will provide additional data regarding the effectiveness of the targeting of mast cells as a treatment approach for type 2-low asthma.

IL-6-mediated systemic inflammation has also been identified as a pathway that may be active in a subset

of patients with type 2-low asthma. A cross-sectional analysis of patients with asthma at the University of California San Francisco and in the Severe Asthma Research Program (SARP) found that patients with high plasma levels of IL-6 had worse lung function and more frequent exacerbations.<sup>7</sup> Patients with IL-6-high asthma are characterized by obesity, metabolic dysfunction as indicated by hypertension and diabetes mellitus, and systemic inflammation with increased plasma levels of C-reactive protein.<sup>7</sup> Based on these findings, an “outside in” mechanism was proposed in which systemic IL-6-mediated inflammation that is caused by obesity may be a causal factor that drives increased asthma severity and an exacerbation-prone asthma phenotype.<sup>7-9</sup> These studies have served as the basis for including a trial using clazakizumab, a humanized anti-IL-6 neutralizing antibody, as one of the studies in the PrecISE Asthma Network.<sup>5</sup> Clazakizumab will be targeted to patients with asthmatics with high plasma IL-6 levels to assess whether IL-6 inhibition improves disease control. An analysis of 695 patients who participated in the Severe Asthma Research Program found that 24% of patients with type 2-low asthmatics, with blood eosinophil counts < 300 cells/mL and FENO < 25 parts per billion, had high plasma levels of IL-6.<sup>10</sup> Therefore, if shown to be effective, a subgroup of patients with type

2-low asthma and high plasma IL-6 levels potentially may benefit from treatment with neutralizing antibodies that target the IL-6 pathway.

Because the pathobiology of type 2-low asthma is heterogeneous, additional pathways will likely be identified that have a causal role in mediating disease. This will allow specific biomarkers to be defined that can select patients with asthma in whom the pathway is active so that targeted treatments can be administered to those patients who are most likely to respond. So, watch this space as novel treatment approaches continue to be developed to improve the lives of patients with type 2-low asthma.

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