

AK002, an Anti-Siglec-8 Antibody, Suppresses Acute IL-33-induced Neutrophil Infiltration and Attenuates Tissue Damage in a Chronic Experimental COPD Model Through Mast Cell Inhibition

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RATIONALE: IL-33 stimulation of mast cells is believed to play a role in driving acute and chronic inflammation in many diseases including, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis (AD), and inflammatory bowel disease. Siglec-8 monoclonal antibodies (mAb) have been previously shown to inhibit multiple modes of mast cell activation, including by IgE, and selectively deplete eosinophils. However, the effect of an anti-Siglec-8 antibody has not been evaluated in IL-33-driven models of inflammation.

METHODS: Acute neutrophil recruitment was induced in Siglec-8-Transgenic (TG) mice by intraperitoneal injection of IL-33. Peritoneal lavage was collected and analyzed 3 hours later. Experimental COPD was induced by exposing TG mice to chronic cigarette smoke (CS) for 12 weeks followed by analysis of lung function and inflammation in bronchoalveolar lavage (BAL) fluid.

RESULTS: IL-33 administration induced the release of proinflammatory cytokines/chemokines and rapidly recruited neutrophils to the peritoneal cavity. Siglec-8 mAb treatment decreased the production of inflammatory mediators, such as IL-6 and MCP-1, and inhibited neutrophil infiltration. Therapeutic treatment with a Siglec-8 mAb also significantly suppressed CS-induced experimental COPD. Siglec-8 mAb treated groups displayed reduced neutrophil infiltration in BAL fluid and significantly improved lung function. Lastly, treatment with a Siglec-8 mAb decreased activation of mast cells in ex-vivo human lung tissue induced by IL-33 and TSLP.

CONCLUSIONS: Siglec-8 mAb treatment decreased acute and chronic inflammation by inhibiting IL-33 activation of mast cells. An anti-Siglec-8 approach may have the potential to treat diseases associated with eosinophil and mast cells, including those with elevated IL-33, such as COPD, asthma, or AD.