Antolimab (AK002), an Anti-Siglec-8 Antibody, Inhibits IL-33-mediated Mast Cell Activation and Neutrophilic Inflammation

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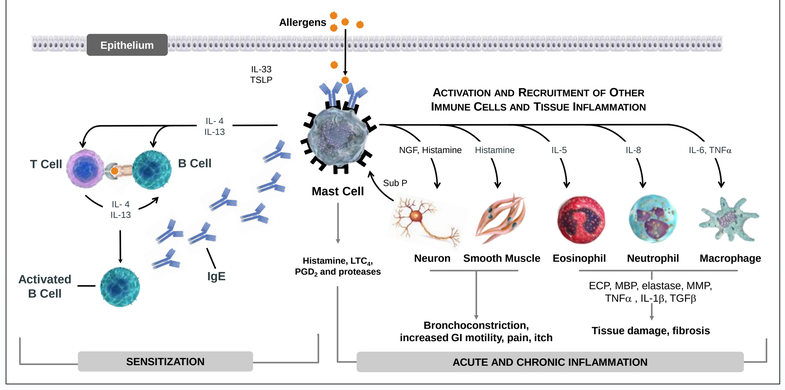
BACKGROUND

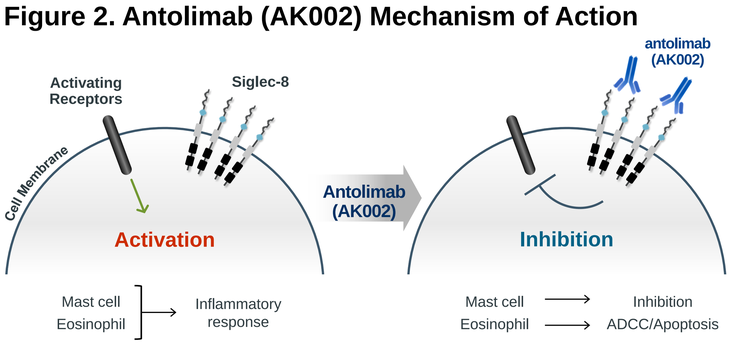
- IL-33 stimulation of mast cells is believed to enhance IgE-mediated degranulation and promote allergic inflammation
- Siglec-8 targeting monoclonal antibodies (mAb) have previously been shown to inhibit IgE-mediated mast cell activation and deplete eosinophils
- However, the effect of a Siglec-8 mAb has not been evaluated in IL-33-driven models of inflammation

Figure 1. Mast Cells and Eosinophils are Key Drivers of Acute and Chronic Inflammation



- Siglec-8 is an inhibitory receptor selectively expressed on human eosinophils and mast cells, and therefore represents a novel target for the treatment of debilitating allergic, inflammatory, and proliferative diseases such as termed eosinophilic gastrointestinal disorders (EGIDs), allergic conjunctivitis (AC), and chronic urticaria (CU)
- Antolimab (AK002) is a novel, humanized, non-fucosylated IgG1 monoclonal antibody to Siglec-8
- Engagement of Siglec-8 receptor by antolimab triggers:
  - Antibody dependent cell mediated cytotoxicity (ADCC) against eosinophils (blood)
  - Inhibition of mast cells and apoptosis of tissue eosinophils (tissue)
- Here we evaluate the effect of antolimab (AK002) in IL-33-driven models of inflammation

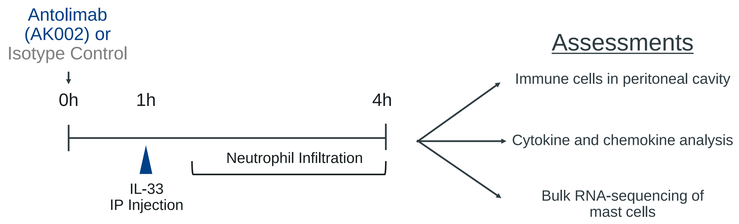
Figure 2. Antolimab (AK002) Mechanism of Action



METHODS

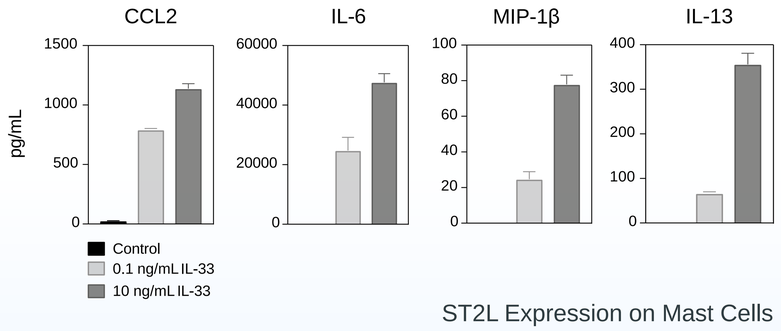
- Acute neutrophil infiltration was induced in by intraperitoneal injection of IL-33 in mice
- Immune cells in the peritoneum were analyzed by flow cytometry
- Mast cells were isolated by FACS and subjected to RNA-seq analysis

Figure 3. Mouse Model of IL-33-Induced Neutrophil Infiltration[1]



RESULTS

Figure 4. IL-33 Directly Induces Cytokine Production from Peritoneal Mast Cells in vitro



- Mast cells are the only ST2 (IL-33 receptor) expressing cells in the peritoneal cavity
- IL-33 directly activates mast cells and induces cytokine and chemokine production in vitro

ST2L Expression on Mast Cells

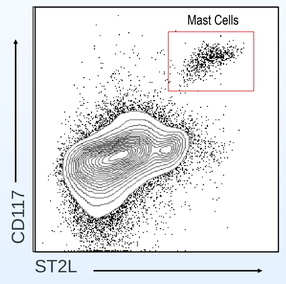
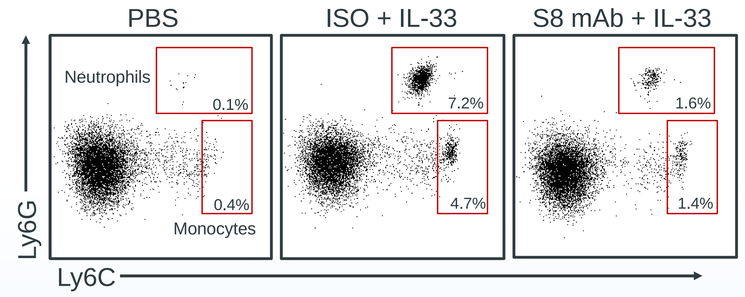


Figure 5. Antolimab (AK002) Reduces IL-33-driven Neutrophil Infiltration



- Intraperitoneal injection of IL-33 induces a rapid influx of neutrophils into the peritoneal cavity
- Treatment with antolimab (AK002) significantly reduces IL-33-driven neutrophil infiltration in the peritoneal cavity

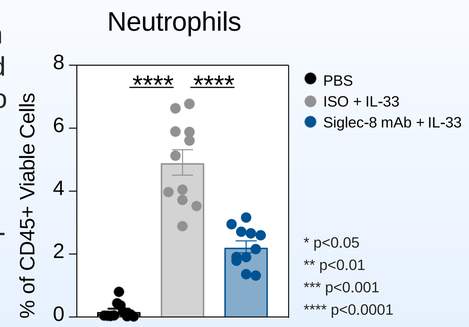
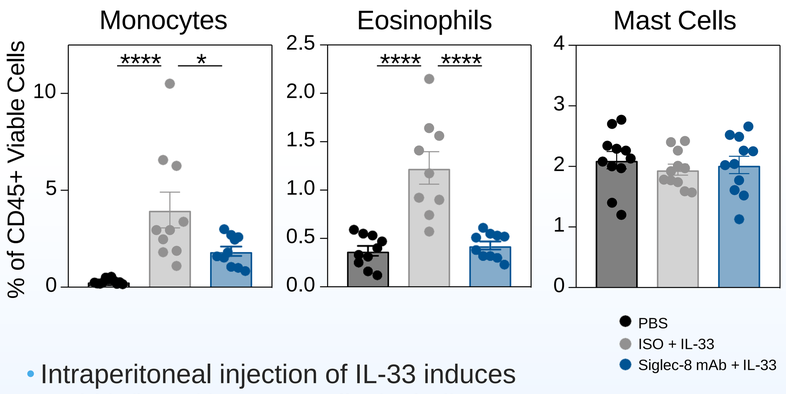


Figure 6. Antolimab (AK002) Decreases Monocyte and Eosinophil Infiltration Induced by IL-33



- Intraperitoneal injection of IL-33 induces rapid influx of immune cells, including neutrophils, monocytes, and eosinophils
- Treatment with antolimab (AK002) significantly reduces IL-33-driven immune cell infiltration, suggestive of MC inhibition

Figure 7. Antolimab (AK002) Decreases IL-33-induced Cytokine and Chemokines

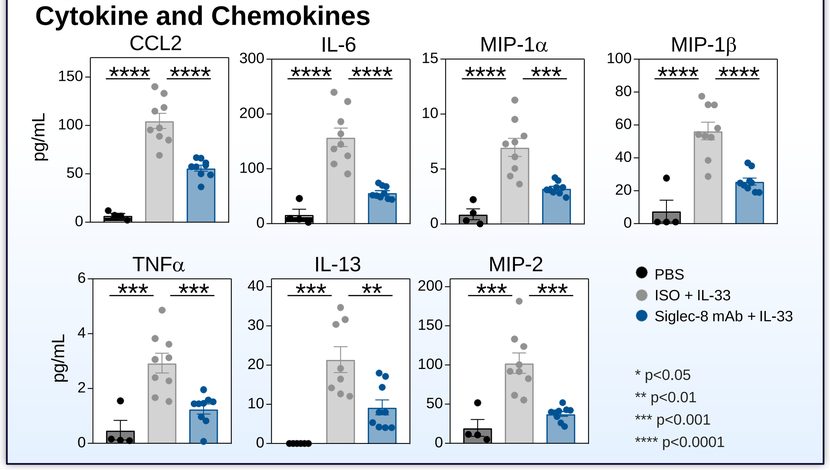
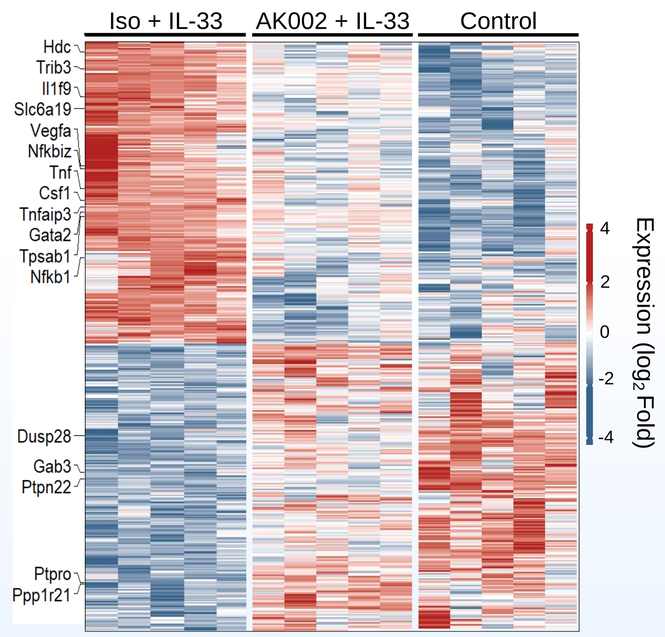
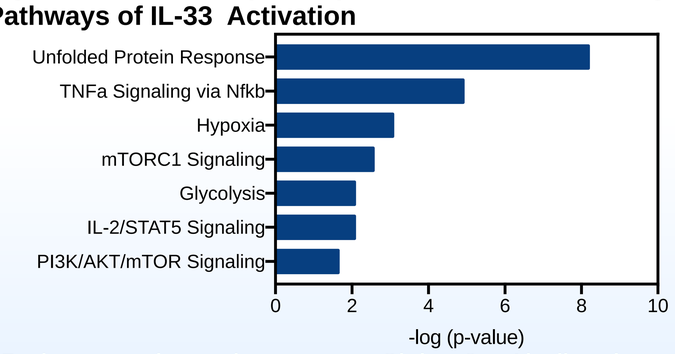


Figure 8: Antolimab (AK002) Globally Inhibits IL-33 Activated Mast Cells



- Antolimab (AK002) treatment substantially modulates the IL-33-activated mast cell transcriptome
- Antolimab (AK002)-treated IL-33 activated mast cells resemble mast cells from control mice compared to isotype-treated IL-33 activated mast cells

Figure 9: Antolimab (AK002) Inhibits Downstream Signaling Pathways of IL-33 Activation



- Pathway analyses demonstrate Siglec-8 mAb directly modulates downstream pathways of IL-33 activation

CONCLUSIONS/DISCUSSION

- Treatment with antolimab (AK002) decreased acute neutrophilic inflammation by inhibiting IL-33 activation of mast cells
- Targeting Siglec-8 may have the potential to treat diseases associated with mast cells and eosinophils, including those where IL-33 can exacerbate immune responses, such as atopic dermatitis, asthma, and food allergy

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Reference: 1) Model adapted from: Enoksson, M., et al. Blood 2013.