Lirentelimab (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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BACKGROUND

- IL-33 stimulation of mast cells is believed to play a role in driving allergic and non-allergic inflammation in many diseases including asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis (AD), and inflammatory bowel disease (IBD) (Figure 1)
- Siglec-8 monoclonal antibodies (mAb) previously have been shown to inhibit mast cell activation and selectively deplete eosinophils in atopic diseases
- However, the effect of an anti-Siglec-8 antibody has not been evaluated in non-allergic models of inflammation

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

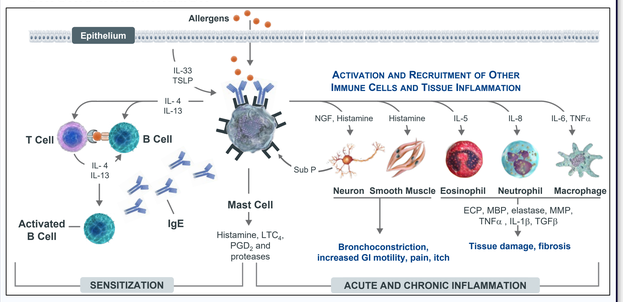
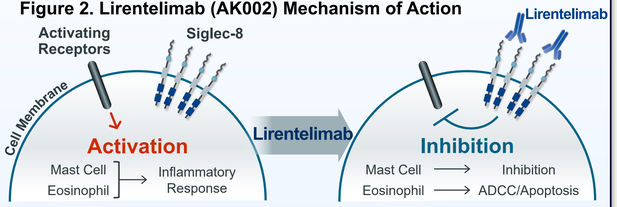


Figure 2. Lirentelimab (AK002) Mechanism of Action

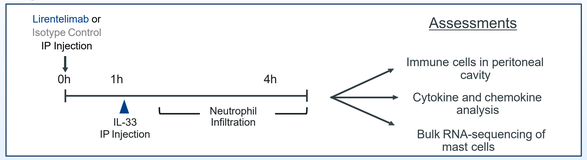


- Siglec-8 is an inhibitory receptor selectively expressed on human eosinophils and mast cells, and therefore represents a novel target for the treatment of allergic, inflammatory, and proliferative diseases
- Lirentelimab is a novel, humanized, non-fucosylated IgG1 monoclonal antibody to Siglec-8
- Engagement of Siglec-8 receptor by lirentelimab triggers:
  - Antibody dependent cell mediated cytotoxicity (ADCC) against blood eosinophils and apoptosis of tissue eosinophils
  - Inhibition of mast cells
- Here we evaluate the inhibitory activity of lirentelimab in acute and chronic non-allergic disease models

METHODS

- Acute MC-dependent neutrophil recruitment was induced in Siglec-8-Transgenic (TG) mice by intraperitoneal injection of IL-33[1] (Figure 3)
- Peritoneal lavage was collected and analyzed 3 hours later
- Experimental COPD[2] was induced by exposing TG mice to chronic cigarette smoke (CS) for 12 weeks followed by analysis of lung function and inflammation. Mice were dosed therapeutically on week 8 with lirentelimab or isotype control mAb

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



RESULTS

Figure 4. Lirentelimab Reduces IL-33-driven Non-allergic Inflammation

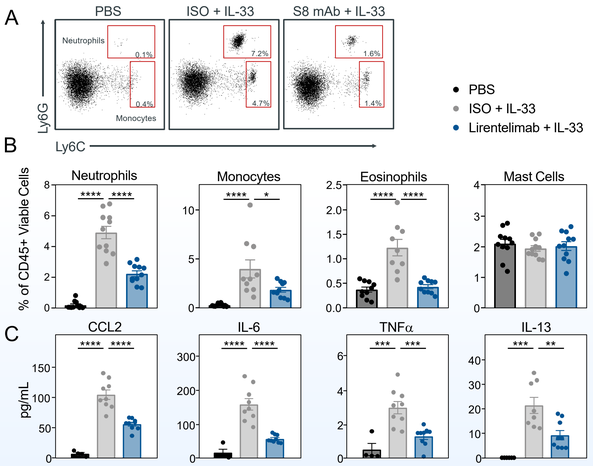


Figure 4: (A) Representative dot plots of neutrophils and monocytes. (B) Frequencies of peritoneal neutrophils, monocytes, eosinophils, and mast cells and (C) cytokine and chemokine levels in PBS-control mice (black) or IL-33-treated mice dosed with an isotype control (gray) or Siglec-8 mAb (blue).
Graphs are plotted as individual mice; * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001

- Lirentelimab significantly reduces mast cell mediated IL-33-driven inflammation, suggestive of mast cell inhibition

Figure 5. Lirentelimab Globally Inhibits IL-33 Activated Mast Cells

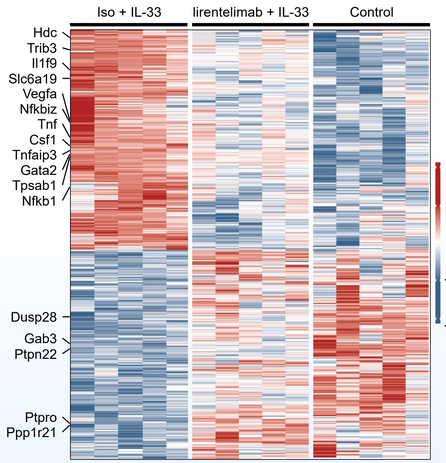


Figure 5: Heatmap of the top differentially expressed genes in peritoneal mast cells that were FACS-sorted after treatment with IL-33 + isotype mAb (left), IL-33+ lirentelimab (middle), or PBS-control (right) and subjected to RNA-sequencing. Genes displayed in the heatmap were the top 445 genes that were significantly modulated by IL-33 and normalized by lirentelimab treatment. Each column represents transcriptome data from individual mice (n=5/group)

- IL-33 directly activates mast cells and lirentelimab treatment substantially modulates the mast cell transcriptome
- These data suggest that lirentelimab reduces IL-33-driven non-allergic inflammation by inhibiting mast cells

Figure 6. Lirentelimab Inhibits Downstream Signaling Pathways of IL-33 Activation

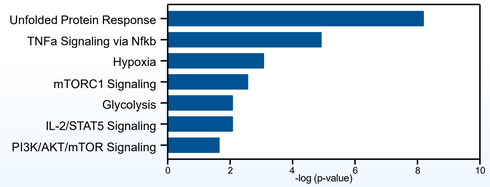


Figure 6: Hallmark gene enrichment analysis of genes upregulated with IL-33 treatment and downregulated with lirentelimab as shown above.

- These data support that lirentelimab inhibits critical signaling pathways required for IL-33 activation

Figure 7. Lirentelimab Reduces Chronic Inflammation and Improves Lung Function in Cigarette-Smoke-Induced Experimental COPD

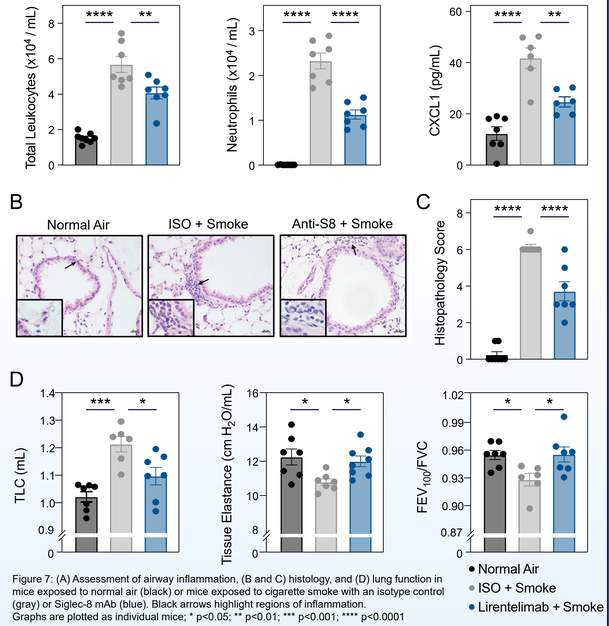


Figure 7: (A) Assessment of airway inflammation, (B and C) histology, and (D) lung function in mice exposed to normal air (black) or mice exposed to cigarette smoke with an isotype control (gray) or Siglec-8 mAb (blue). Black arrows highlight regions of inflammation.
Graphs are plotted as individual mice; * p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001

- Therapeutic dosing with lirentelimab significantly decreases chronic inflammation and protected against lung function decline in a non-allergic model of cigarette smoke-induced experimental COPD

CONCLUSIONS

- In addition to the demonstrated anti-inflammatory activity in allergic diseases, lirentelimab, an anti-Siglec-8 mAb, also reduces non-allergic inflammation by inhibiting non-IgE-mediated mast cell activation
- These data support the clinical evaluation of anti-Siglec-8 mAbs, such as lirentelimab as a therapeutic approach in both allergic and non-allergic diseases, such as type 2 low asthma, COPD, and IBD

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Reference: 1) Model adapted from: Enoksson M, et al. Blood. 2013. 2) Beckett E, et al. JACI. 2013.