**Atopic Dermatitis Skin Biopsies Have High Numbers of Activated Mast Cells that Are Inhibited by Lirentelimab (AK002) After Stimulation Ex Vivo**

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**BACKGROUND**

- Loss of epithelial barrier integrity is a critical step in the development of atopic dermatitis (AD) whereby the alarmin cytokines IL-33 and TSLP activate inflammatory cells such as mast cells (MCs). While MCs have been shown to be elevated in AD, there is need for further characterization of their pathogenic role.

- Siglec-8 is an inhibitory receptor expressed on mast cells and eosinophils and represents a new potential therapeutic target for AD given the pathogenic role of MCs.

**METHODS**

- Single-cell suspensions were prepared by enzymatic & mechanical digestion of fresh biopsies from patients clinically diagnosed with AD (n=6) or disease control tissue (n=10).

**RESULTS**

- Multi-color flow cytometry was performed to quantify immune cells and evaluate the activation state of eosinophils & mast cells as shown in Figure 4.

- Mast cells were FACS-sorted from AD biopsies or non-diseased skin tissues followed by overnight incubation with or without PMA/Ionomycin.

- Cell-free supernatants were collected the following day and cytokines were quantified using meso scale discovery (MSD) system.

- The following cytokines were analyzed: IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-18, IL-33, GM-CSF, INFγ, TNFα, CCL2, CCL3, CCL4, and VEGF.

**CONCLUSIONS**

- Human skin mast cells express the inhibitory receptor Siglec-8, and activation of mast cells via FcεRI is inhibited with lirentelimab.

- Mast cells are elevated in number and are basally activated in AD biopsies with high levels of surface-bound IgE.

- Lirentelimab inhibits IL-33/TSLP-mediated mast cell activation in AD skin biopsies, suggesting lirentelimab can broadly inhibit multiple modes of mast cell stimulation including, IgE, IL-33, and TSLP.

- Mast cells appear to be important in AD, and targeting mast cells via Siglec-8 with lirentelimab may represent a novel therapeutic approach to the treatment of AD and other allergic diseases.