MRGPRX2 Mediates Mast Cell Activation and Neurogenic Inflammation in Lesional Biopsies from Patients with Atopic Dermatitis

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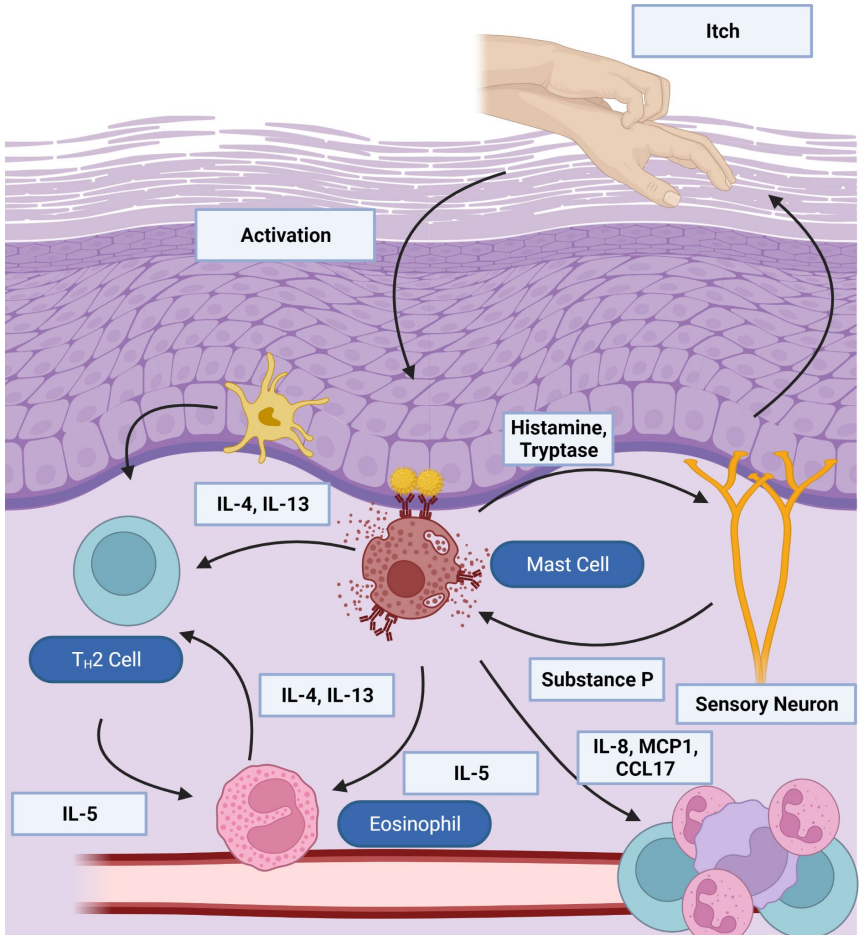
Disclosures

- Lirentelimab is an investigational drug candidate and is not FDA/EMA approved
- This study was funded by Allakos Inc.

Mast Cells Drive Itch and Neurogenic Inflammation in Skin

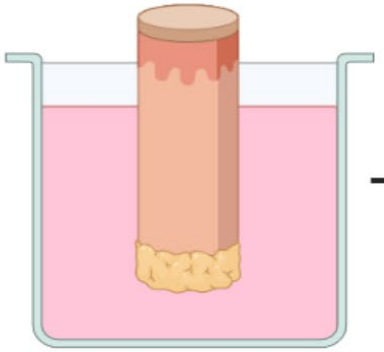


- Mast cells are elevated in atopic dermatitis (AD) tissue and are poised to be key drivers of itch
- Crosstalk between mast cells and sensory neurons contribute to itch via MRGPRX2
- The role of MRGPRX2 in contributing to AD pathogenesis has not been well studied

SOURCE: Allakos Data on File.

Evaluation of Local Inflammation in Fresh Skin Biopsies via Ex Vivo Immunological Assays

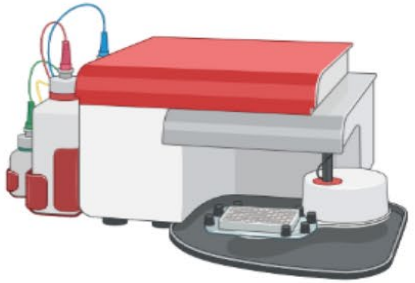
Ex vivo Culture:
Intact Skin Biopsy
5 hours

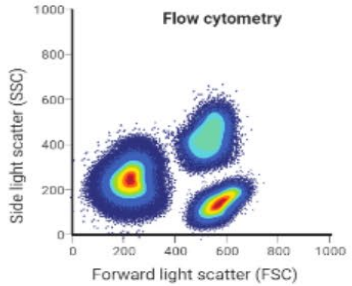


5 hour intact skin biopsy incubation

Supernatants:
ELISA and MSD

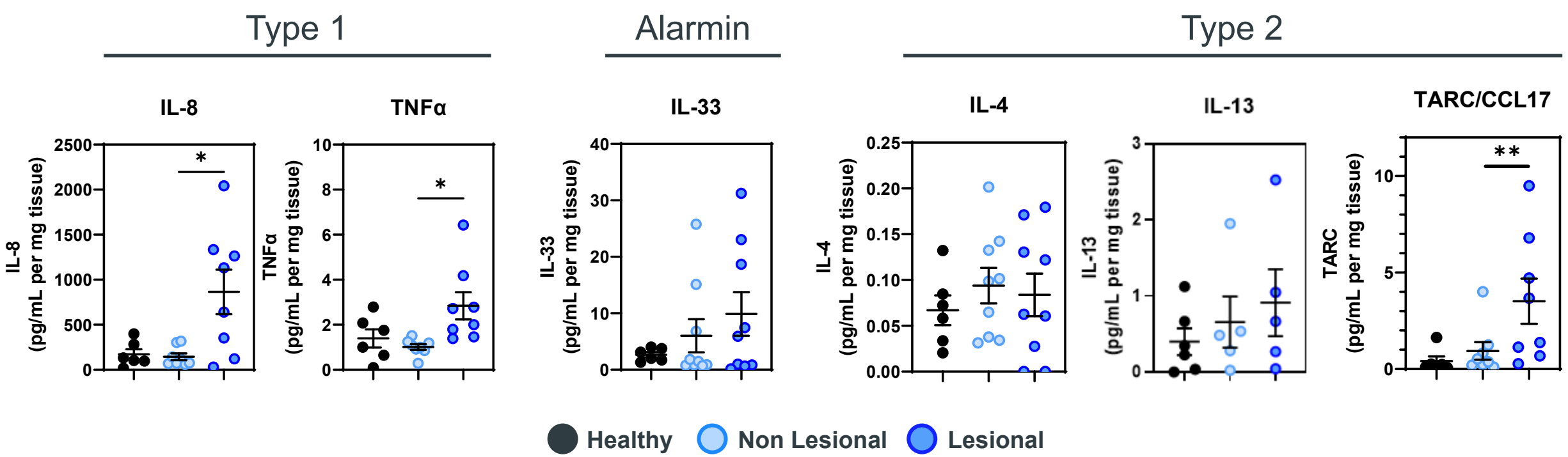
Biopsy Single Cell Suspesions:
Flow Cytometry





SOURCE: Allakos Data on File.

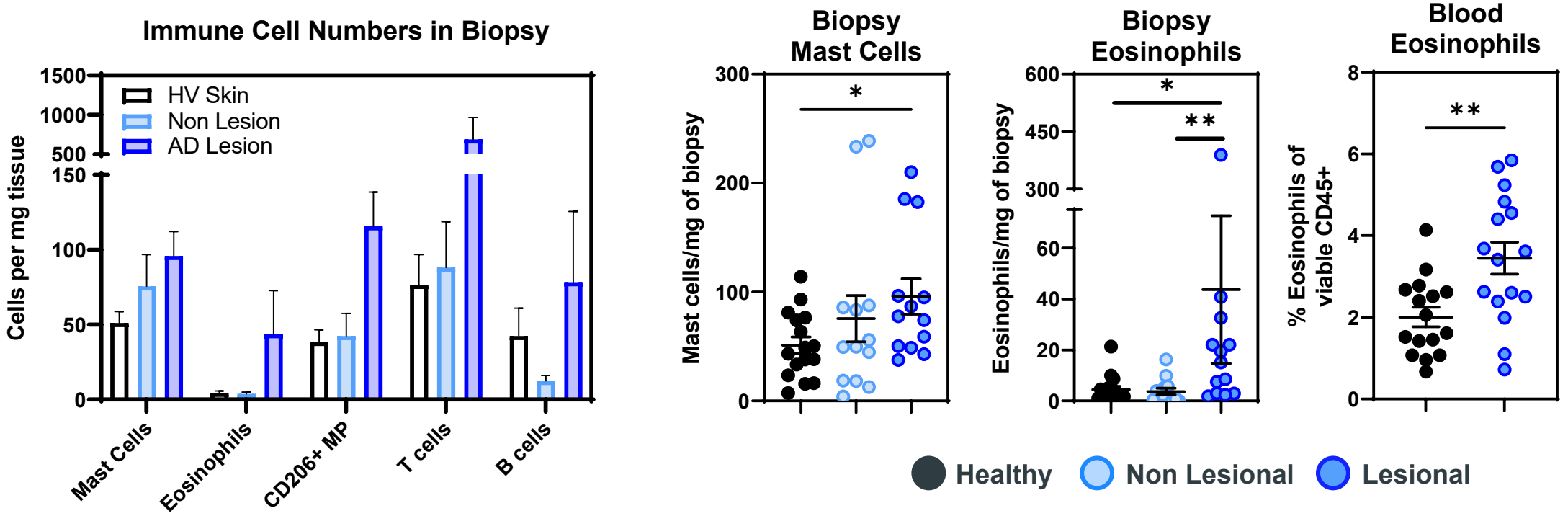
AD Skin Lesions Display Mixed Inflammatory Profile



AD skin biopsies show evidence of both Th1 and Th2 inflammation

SOURCE: Allakos Data on File.

Mast Cells and Eosinophils are Elevated in AD Lesions

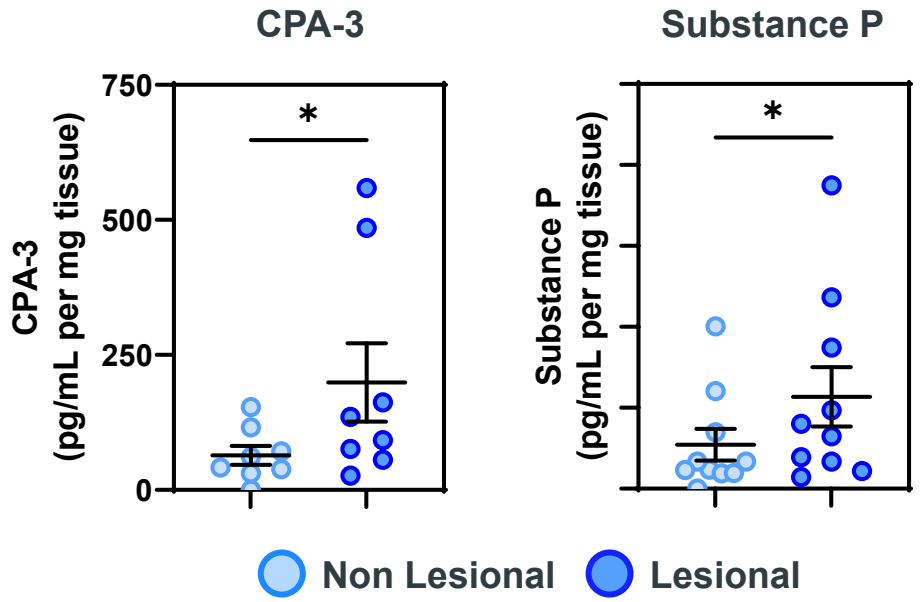


MCs and eosinophils may play a role in AD pathogenesis

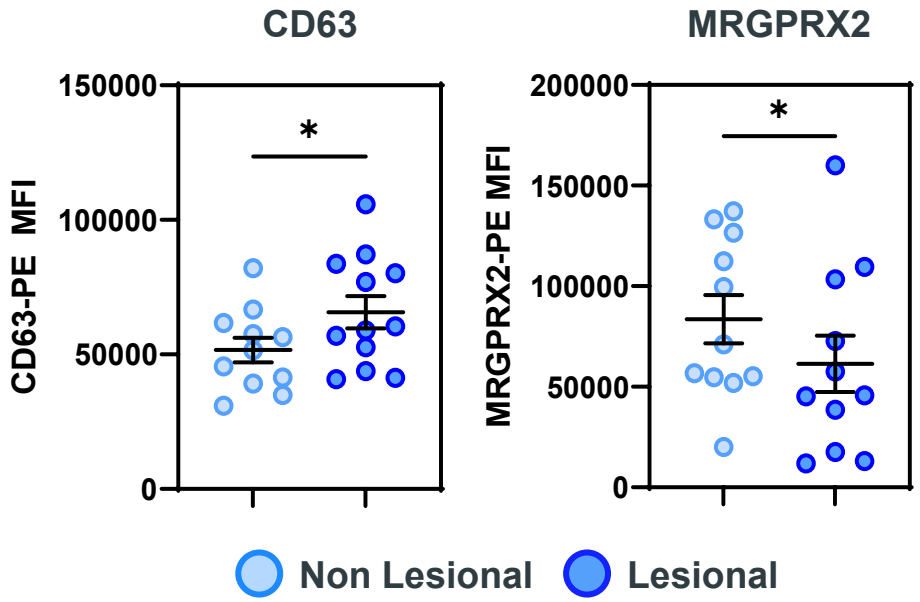
SOURCE: Allakos Data on File.

MRGPRX2-Substance P Axis is Active in AD Lesional Skin

Ex Vivo Biopsy Culture Supernatants



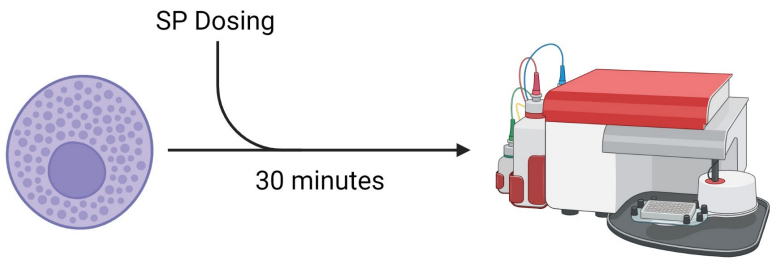
Surface Markers on Mast Cells

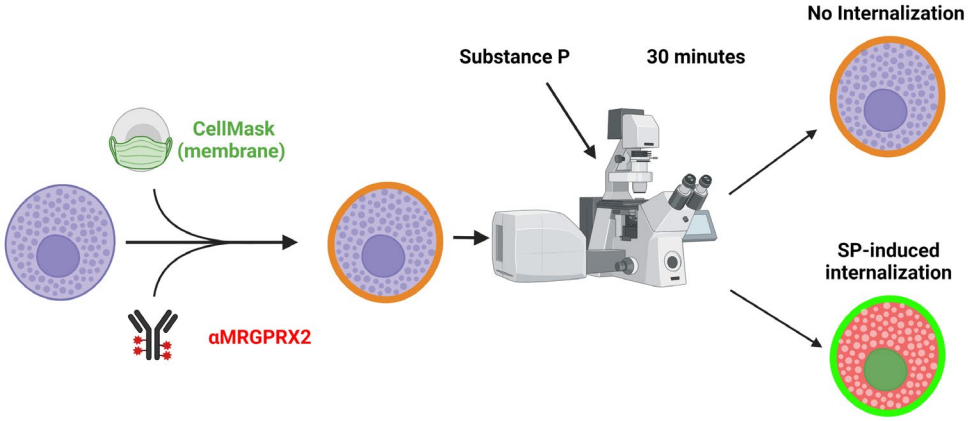


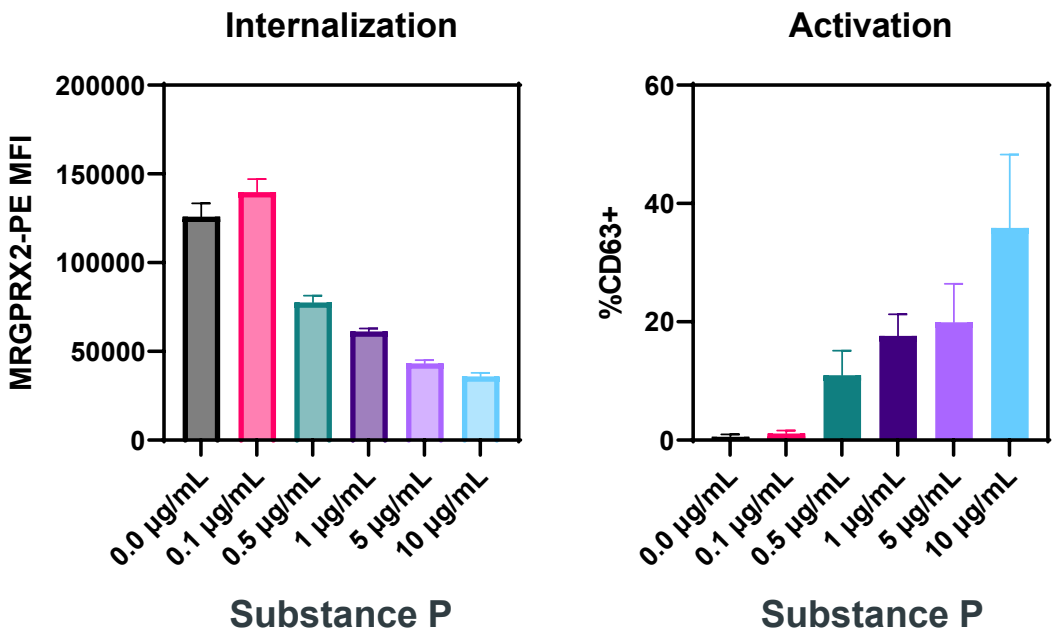
MRGPRX2-mediated MC activation is found in AD skin

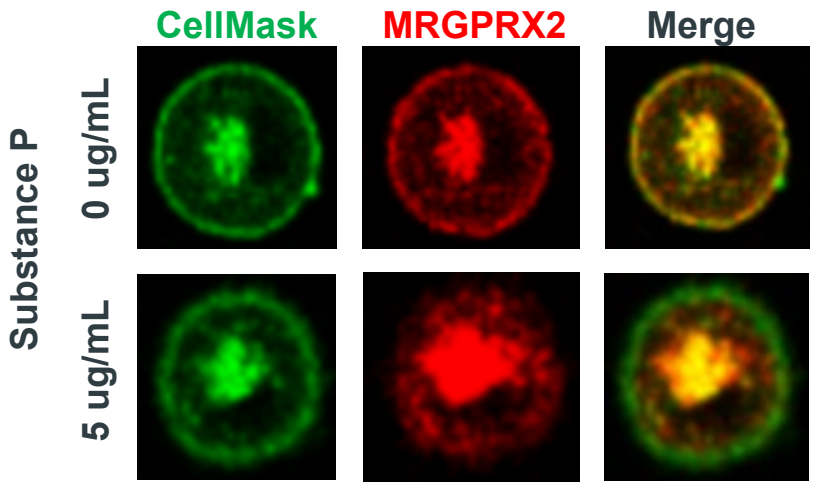
SOURCE: Allakos Data on File.

Substance P-mediated MC Activation Induces MRGPRX2 Internalization







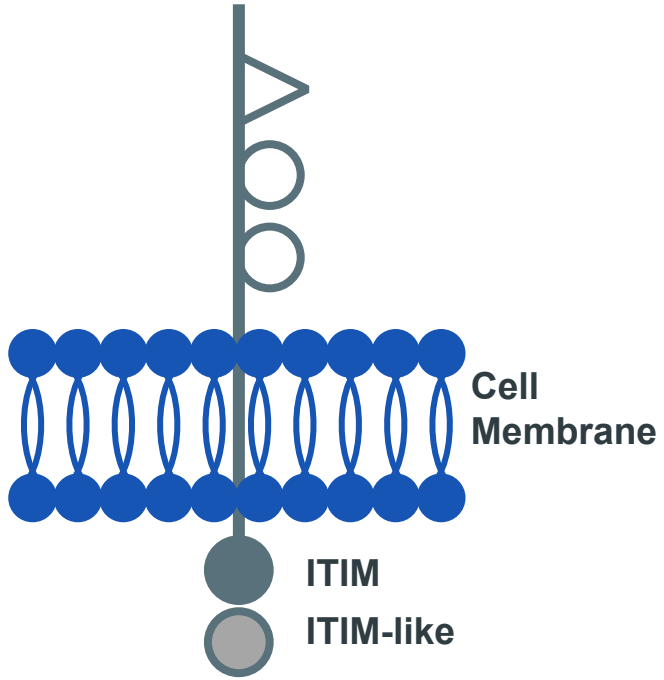


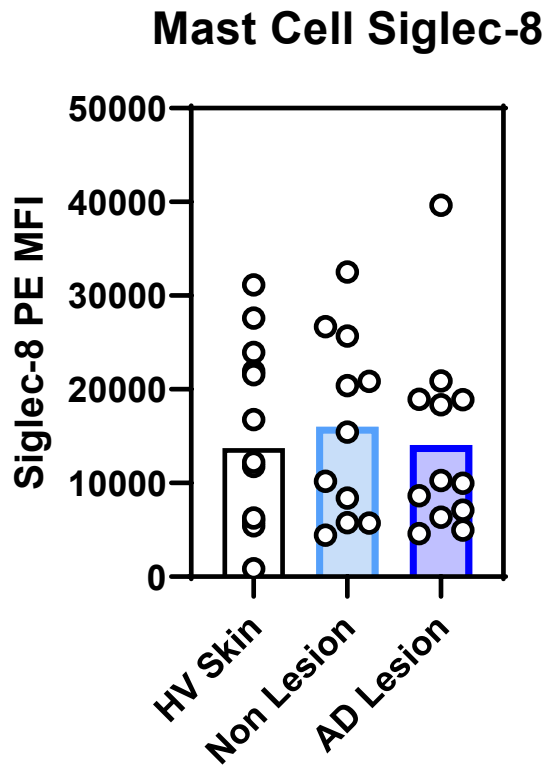
SOURCE: Allakos Data on File.

Sialic Acid-binding Immunoglobulin-like Lectin (Siglec)-8 is an Inhibitory Cell Surface Receptor on Mast Cells

Siglec-8

- Siglec-8 is a cell surface receptor of the CD33-related subfamily of Siglecs only found in humans
- Selectively expressed on eosinophils and mast cells
- Upon antibody engagement, Siglec-8 induces eosinophil depletion and mast cell inhibition



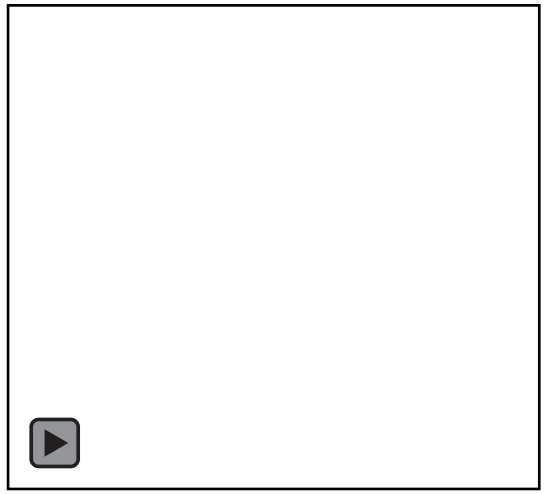


SOURCE: Adapted from O'Reilly and Paulson. Siglecs as targets for therapy in immune-cell-mediated disease. *Trends in Pharmacological Sciences.* Vol.30 No.5. 2009.

Siglec-8 mAb Inhibits Substance P-mediated Activation of MCs

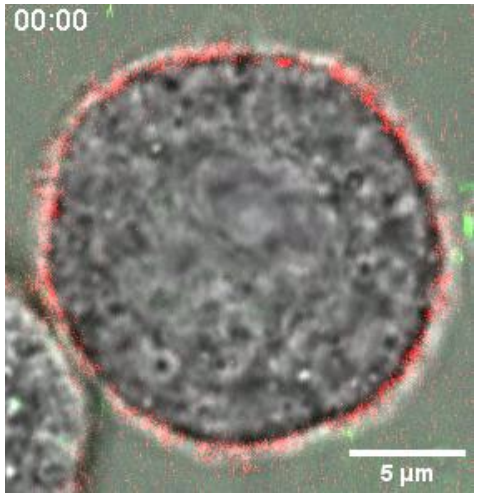
Human Mast Cells

Isotype



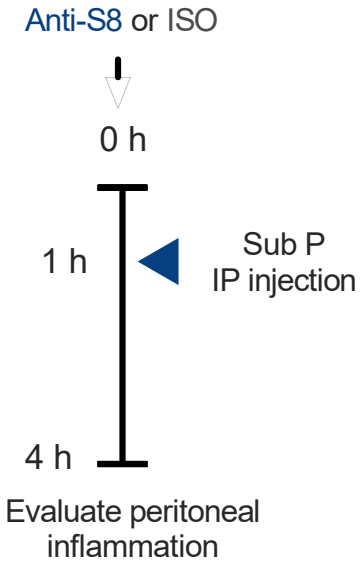
Avidin (exocytosed granules)

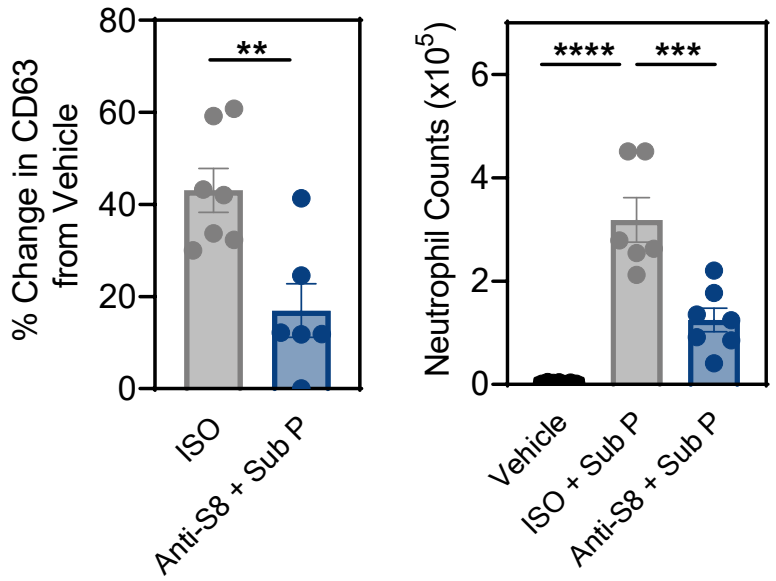
Anti-Siglec-8



Siglec-8

Siglec-8 Transgenic Mice





Siglec-8 represents a novel target to inhibit MRGPRX2-mediated MC activation

SOURCE: Allakos Data on File.

Summary

- Mast cells are elevated and activated in lesional skin of patients with AD
- Activation is in part driven through the MRGPRX2 axis
  - Levels of substance P are elevated in biopsy supernatants
  - MRGPRX2 surface levels are reduced on mast cells in lesional skin
- MRGPRX2 is internalized upon ligand engagement
- Targeting the inhibitory receptor Siglec-8 on mast cells represents an attractive approach to reduce MRGPRX2-mediated MC activation