A Siglec-8 Antibody Reduces Substance P-induced Inflammation by Inhibiting MRGPR-mediated Mast Cell Activation

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Disclosures

• Authors are employees of Allakos, Inc.

• AK002 is an investigational drug in clinical development as is not FDA or EMA approved
Mast Cells Are Key Drivers of Inflammatory Disease

**SENSITIZATION**
- Allergens
- Epithelium
- IL-33, TSLP
- IL-4, IL-13
- T Cell
- B Cell
- Activated B Cell
- IgE

**ACTIVATION AND RECRUITMENT OF OTHER IMMUNE CELLS AND TISSUE INFLAMMATION**
- Neuron
- Smooth Muscle
- Eosinophil
- Neutrophil
- Macrophage
- Histamine, LTC₄, PGD₂, and proteases
- Histamine
- NGF, Histamine
- IL-5
- IL-8
- IL-6, TNFα
- ECP, MBP, elastase, MMP, TNFα, IL-1β, TGFβ

**ACUTE AND CHRONIC INFLAMMATION**
- Bronchoconstriction, increased GI motility, pain, itch
- Tissue damage, fibrosis
Substance P Drives Neurogenic Inflammation and Pain through Mast Cell Activation

- Substance P is a neuropeptide that activates mast cells through the MrgprX2/B2 receptor, leading to cytokine release, pain, itch, and recruitment of immune cells\(^1,2\)

- Multiple diseases have been shown to be associated with Substance P-mediated mast cell activation, including chronic urticaria, psoriasis, and atopic dermatitis\(^2,3\)

- Elevated Substance P levels as well as increased mast cell numbers and activation have also been reported in the mucosa of patients with gastrointestinal disorders\(^4\)

- Based on numerous studies implicating Substance P/MrgprX2-mediated mast cell activation in the pathogenesis of multiple diseases there is a significant need to identify potential therapies that can modulate this pathway

Adapted from Green et al. 2019. Neuron

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AK002 Broadly Inhibits Mast Cells and Depletes Eosinophils

Activating Receptors

Siglec-8

Cell Membrane

Activation

Mast cell
Eosinophil

Inflammatory response

Inhibition

Mast cell
Eosinophil

ADCC/Apoptosis

AK002

Youngblood, BA et al IAAI 2019
Substance P Selectively Activates Human and Mouse Mast Cells through MrgprX2/B2

MrgprX2/B2 is selectively expressed on mast cells and stimulation with Substance P induces degranulation of human and mouse mast cells.
Mouse Model to Examine the Role of Mast Cells in Substance P-Induced Inflammation

- Substance P and other MrgprB2 agonists have been shown to recruit neutrophils into local tissues, including the mouse footpad and peritoneal cavity\(^1,2\)

\(^1\)Green, DP et al. Neuron (2019); \(^2\)Arifuzzaman, M et al. Sci. Advances (2019)
Mast Cells Play an Important Role in Substance P-Mediated Neutrophil Recruitment

Substance P induces mast cell-dependent recruitment of neutrophils into the peritoneal cavity
Anti-Siglec-8 mAb treatment significantly reduces Substance P-mediated neutrophil recruitment into the peritoneal cavity.
Anti-Siglec-8 mAb Inhibits Substance P-Mediated Inflammation and Mast Cell Activation

Anti-Siglec-8 mAb decreases Substance P-induced chemokine production and mast cell activation, indicative of direct mast cell inhibition.
Conclusions

- Studies using mast cell deficient mice show reduced Substance P-mediated inflammation, implicating mast cells as key effector cells in Substance P-mediated inflammation.

- Treatment with an anti-Siglec-8 mAb significantly inhibits Substance P-mediated mast cell degranulation, chemokine production, and neutrophil infiltration.

- Targeting mast cells with an anti-Siglec-8 mAb may have the potential to treat diseases associated with Substance P/MrgprX2-mediated mast cell activation, such as irritable bowel syndrome, functional dyspepsia, atopic dermatitis, and chronic urticaria.