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

Simon Gebremeskel, Alan Wong, Tina Davis, Emily C. Brock, John Leung, Julia Schanin, Bradford A. Youngblood

Allakos, Inc., Redwood City, CA

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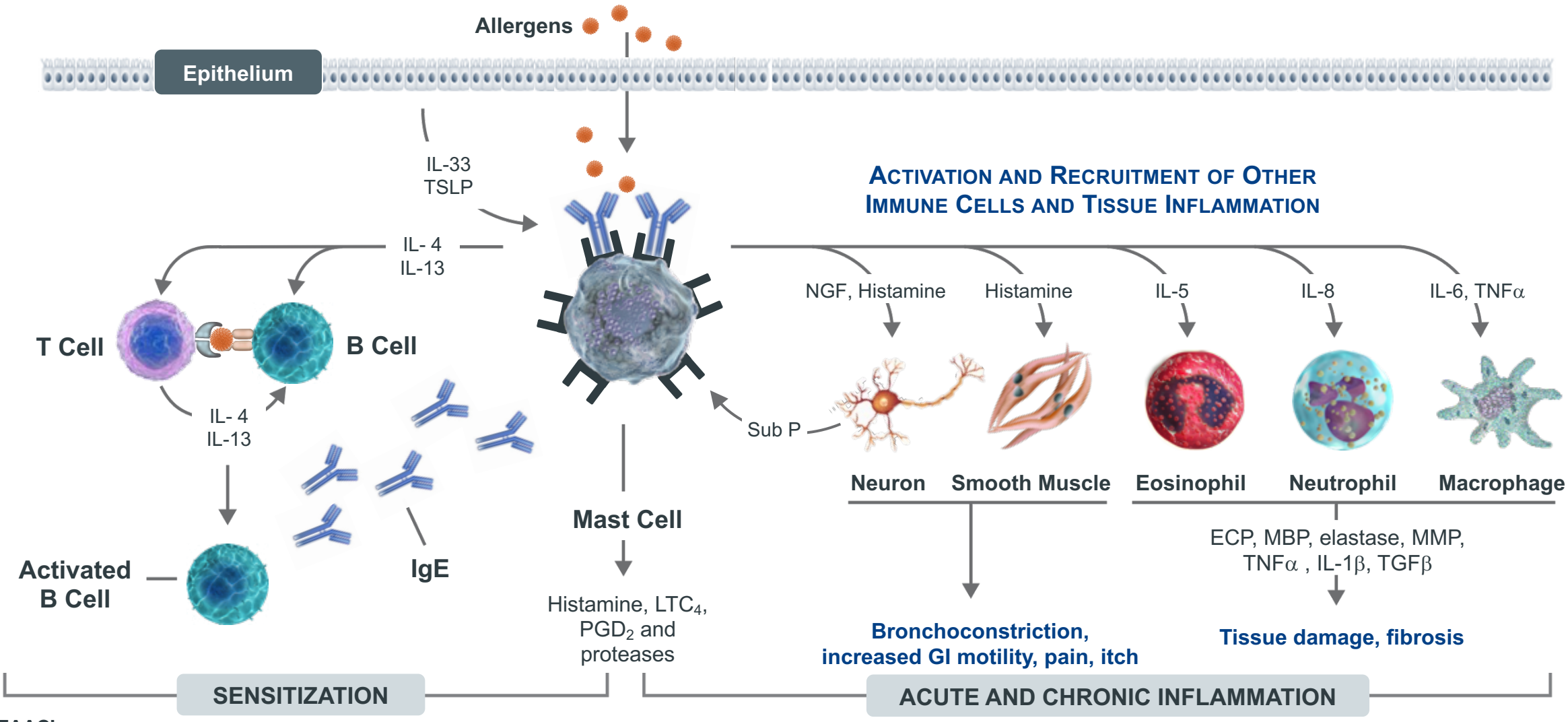
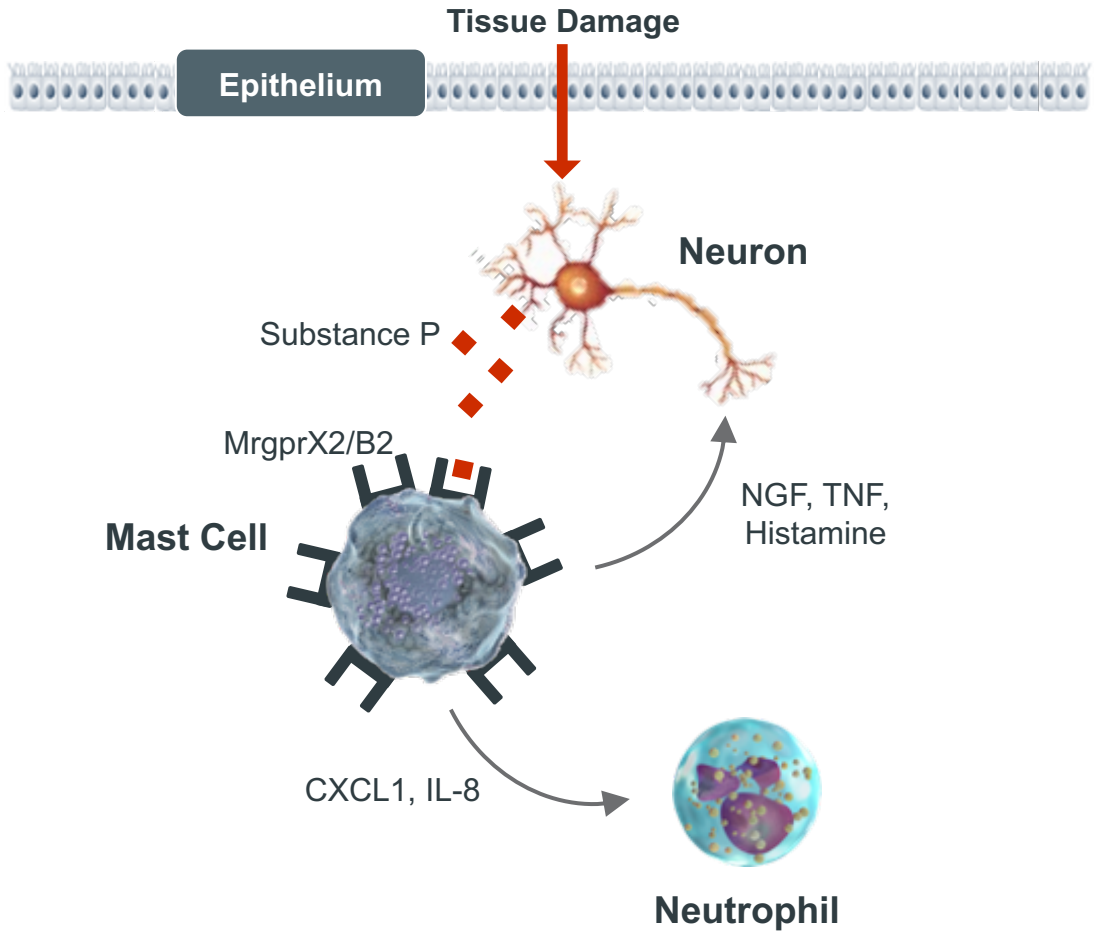
Disclosures

- 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



Substance P Drives Neurogenic Inflammation and Pain through Mast Cell Activation

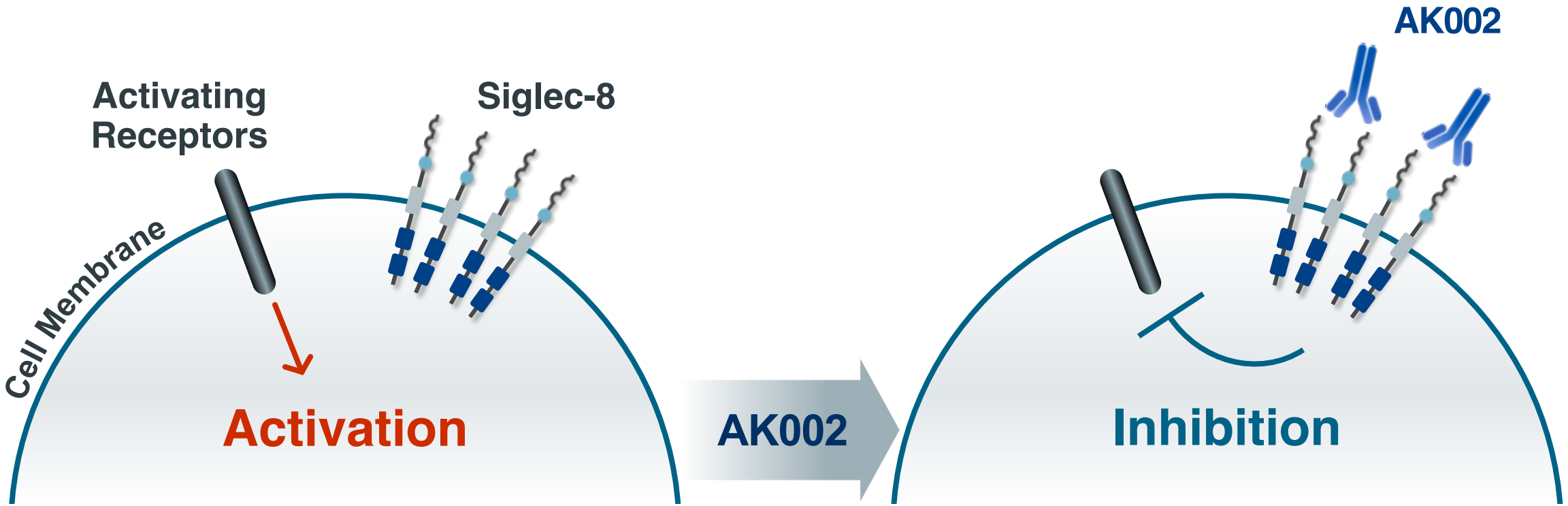


Adapted from Green et al. 2019. Neuron

- 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

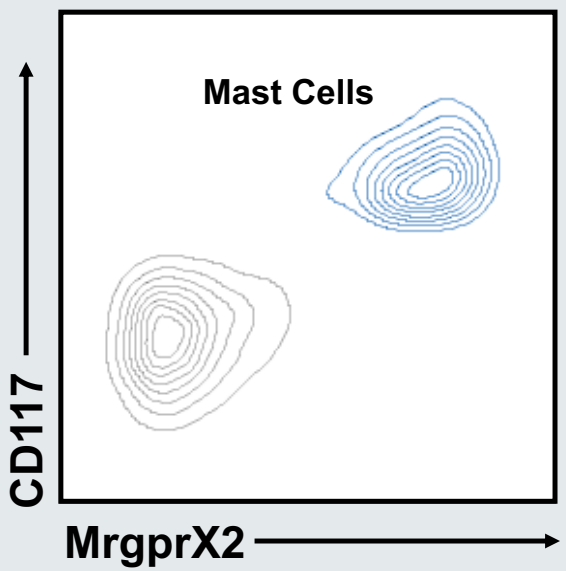
[1]Green, DP et al. Neuron (2019); [2]Varricchi, G et al Frontiers (2019); [3]Vena, GA et al. Clin Mol Allergy (2018); Sohn, W et al. Scand J Gastroenterol (2014)

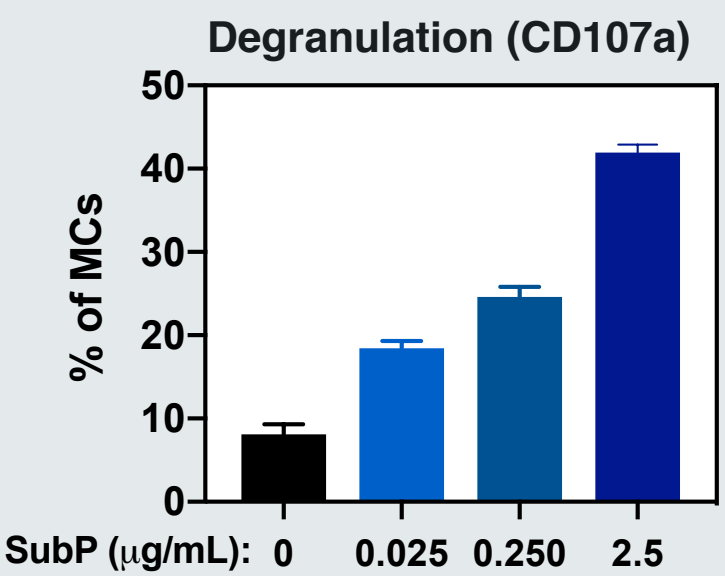
AK002 Broadly Inhibits Mast Cells and Depletes Eosinophils

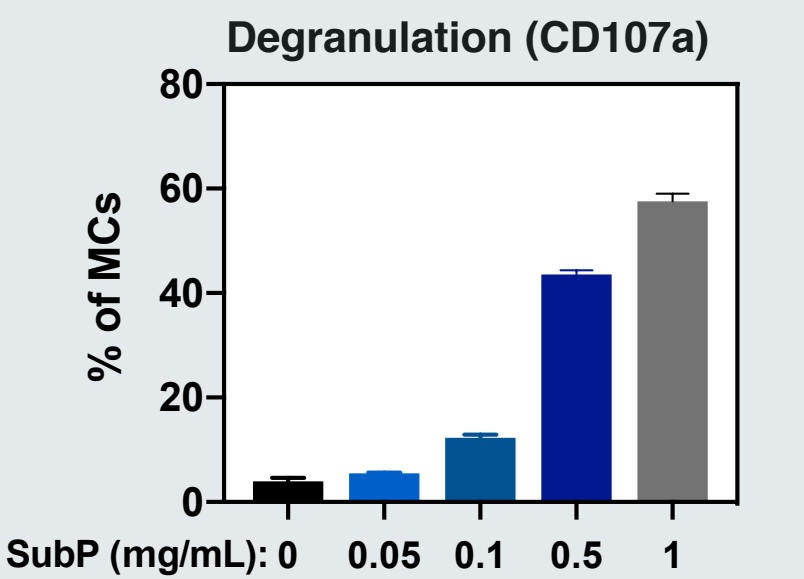


Youngblood, BA et al IAAI 2019

Substance P Selectively Activates Human and Mouse Mast Cells through MrgprX2/B2

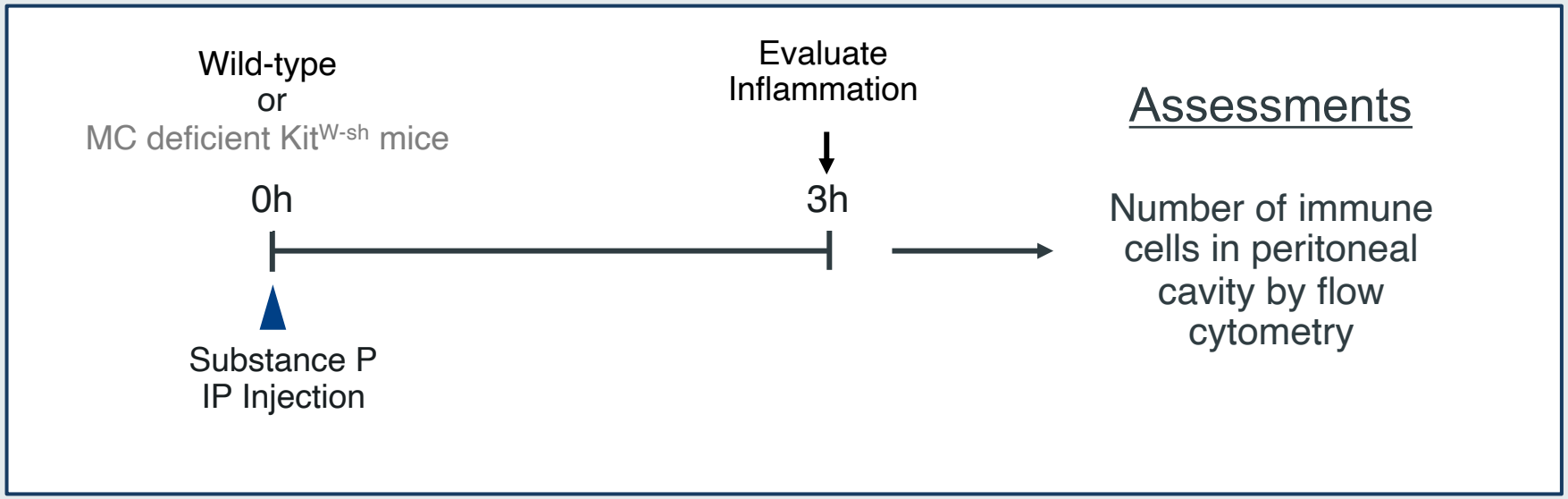






MrgprX2/B2 is selectively expressed on mast cells and stimulation with Substance P induces degranulation of human and mouse mast cells

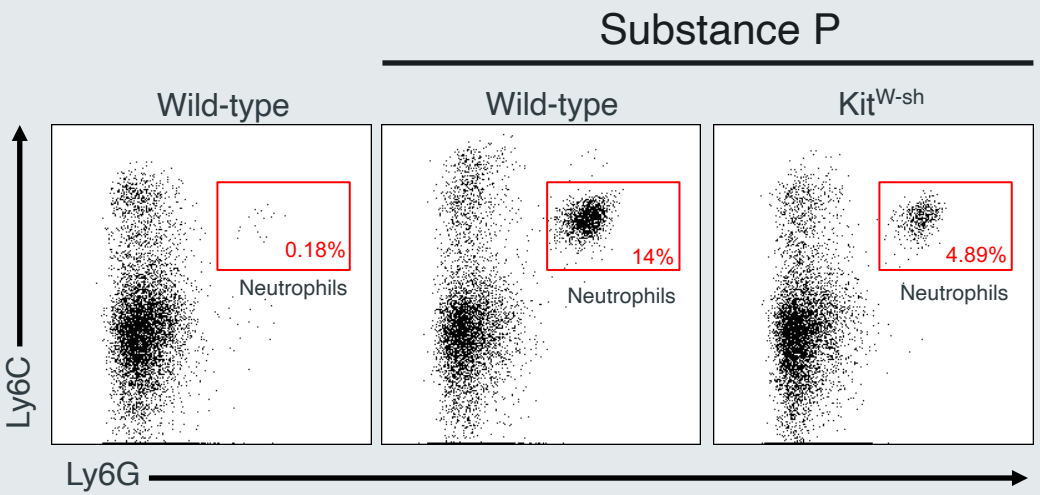
Mouse Model to Examine the Role of Mast Cells in Substance P-Induced Inflammation

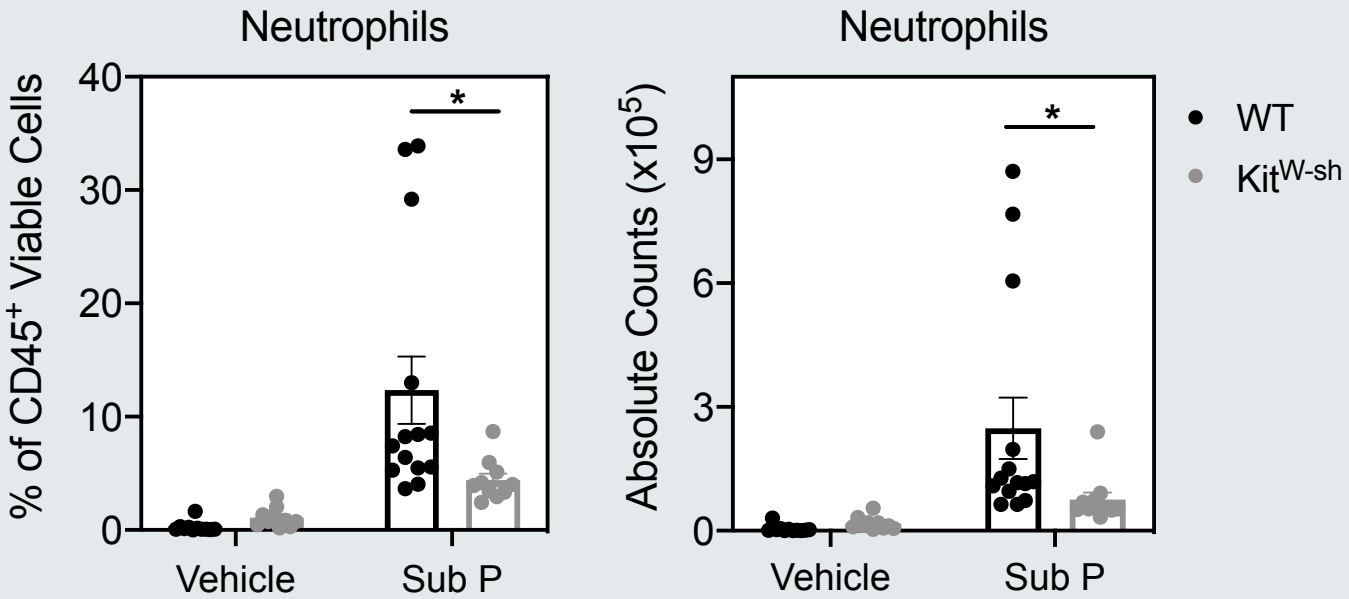


- Substance P and other MrgprB2 agonists have been shown to recruit neutrophils into local tissues, including the mouse footpad and peritoneal cavity[1,2]

[1]Green, DP et al. Neuron (2019); [2]Arifuzzaman, M et al Sci. Advances (2019)

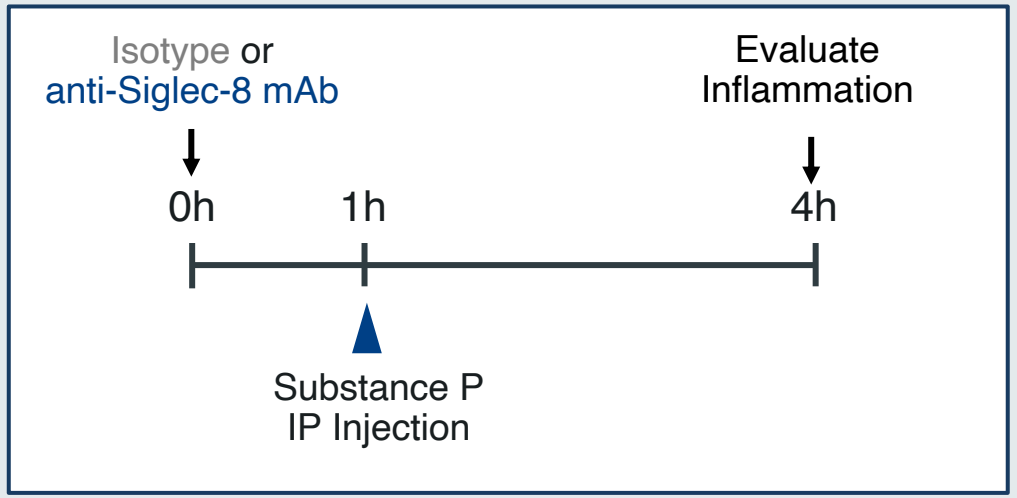
Mast Cells Play an Important Role in Substance P-Mediated Neutrophil Recruitment

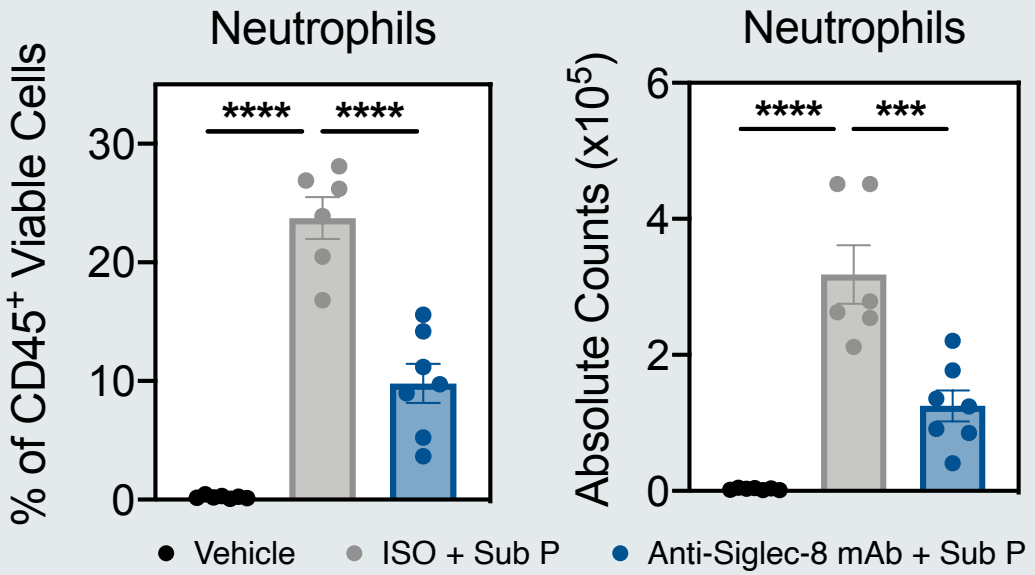




Substance P induces mast cell-dependent recruitment of neutrophils into the peritoneal cavity

Anti-Siglec-8 mAb Reduces Sub P-Mediated Neutrophil Infiltration

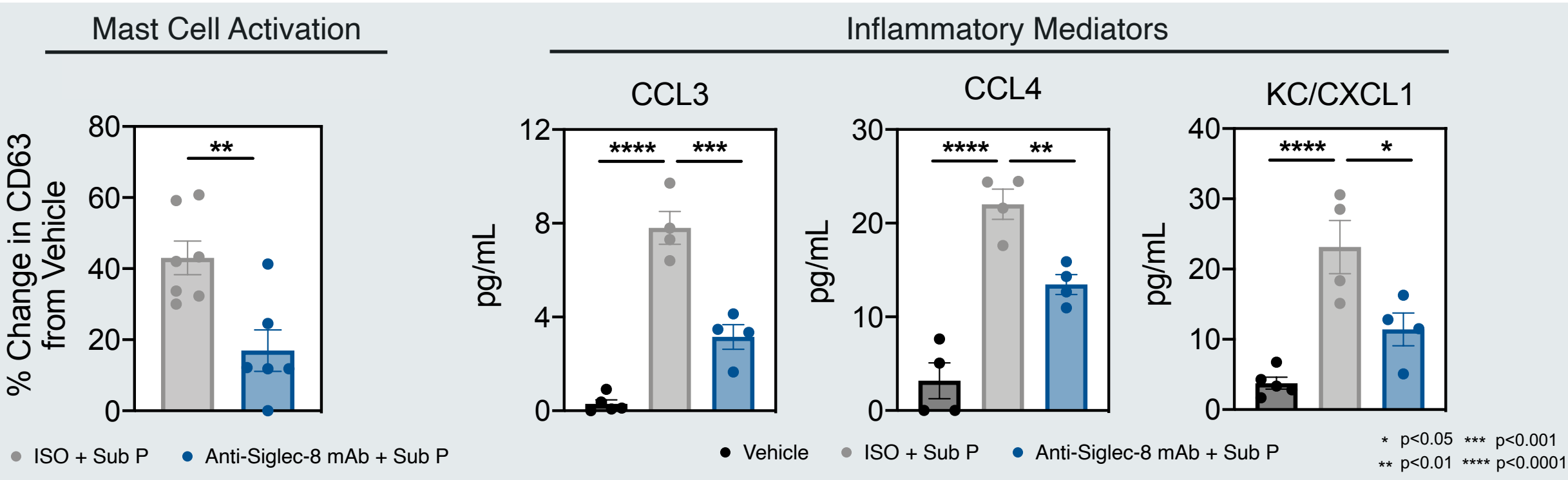




*** p<0.001 **** p<0.0001

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