

# An Agonistic Monoclonal Antibody Against Siglec-6 Selectively Inhibits and Reduces Human Tissue Mast Cells

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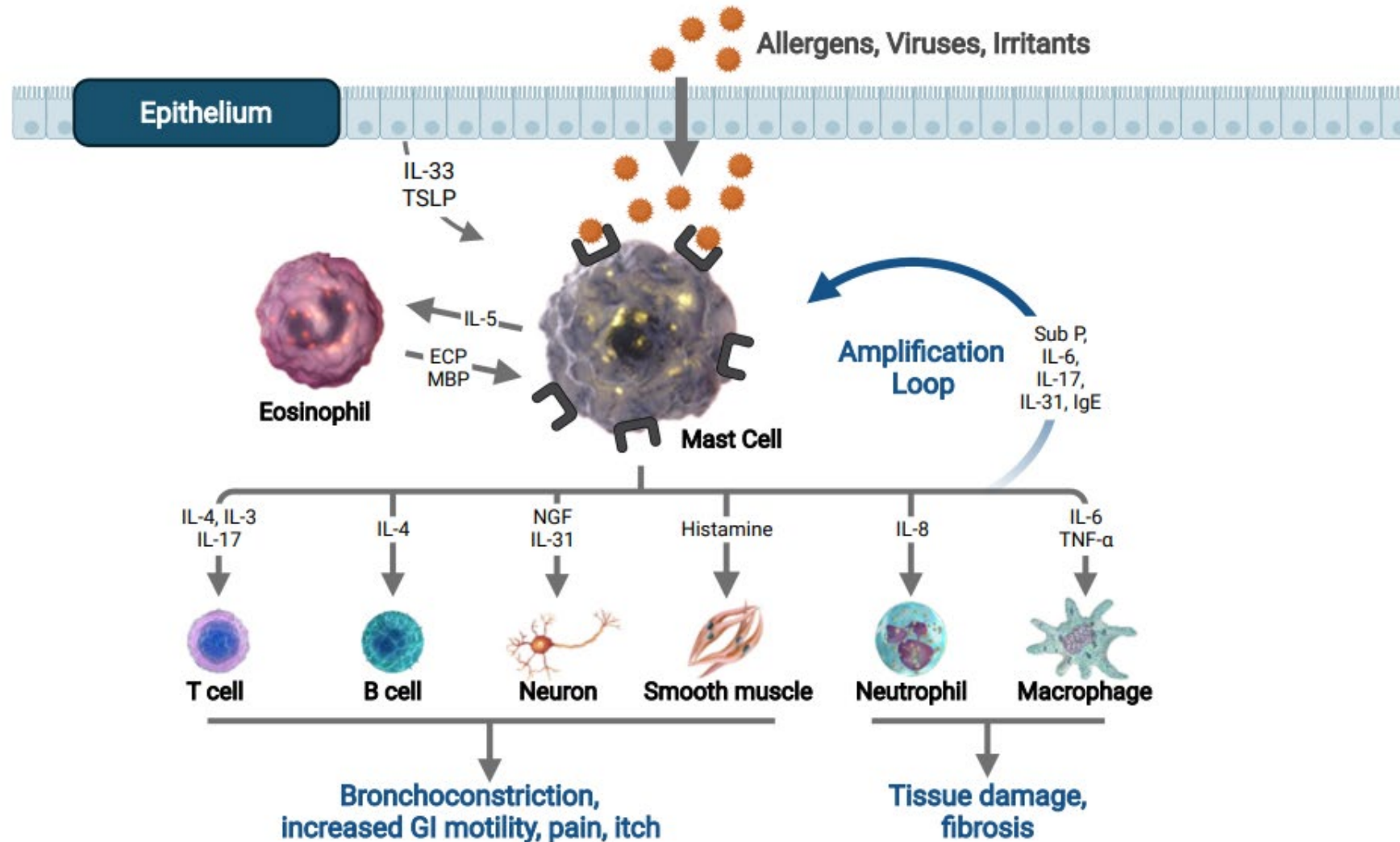
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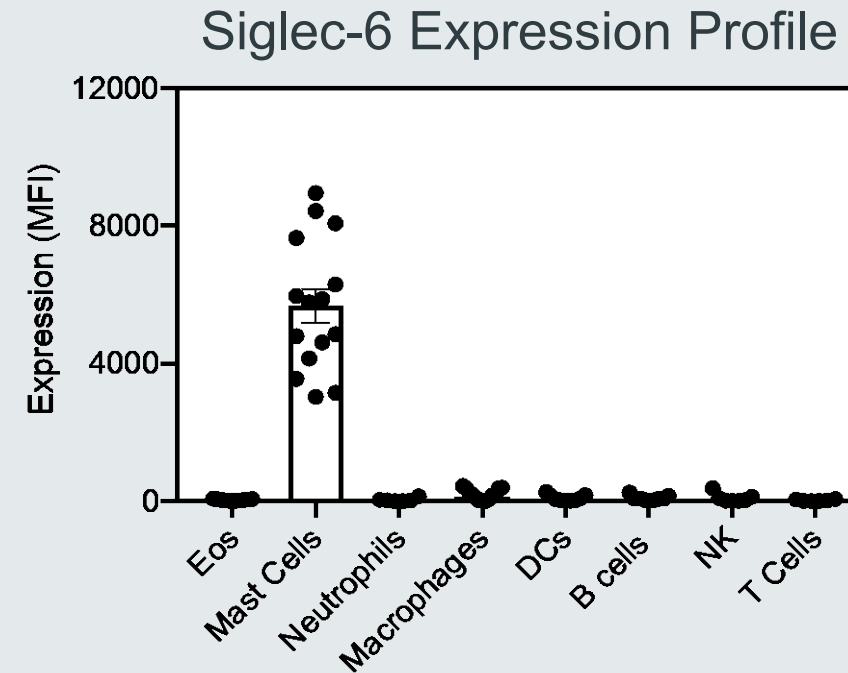
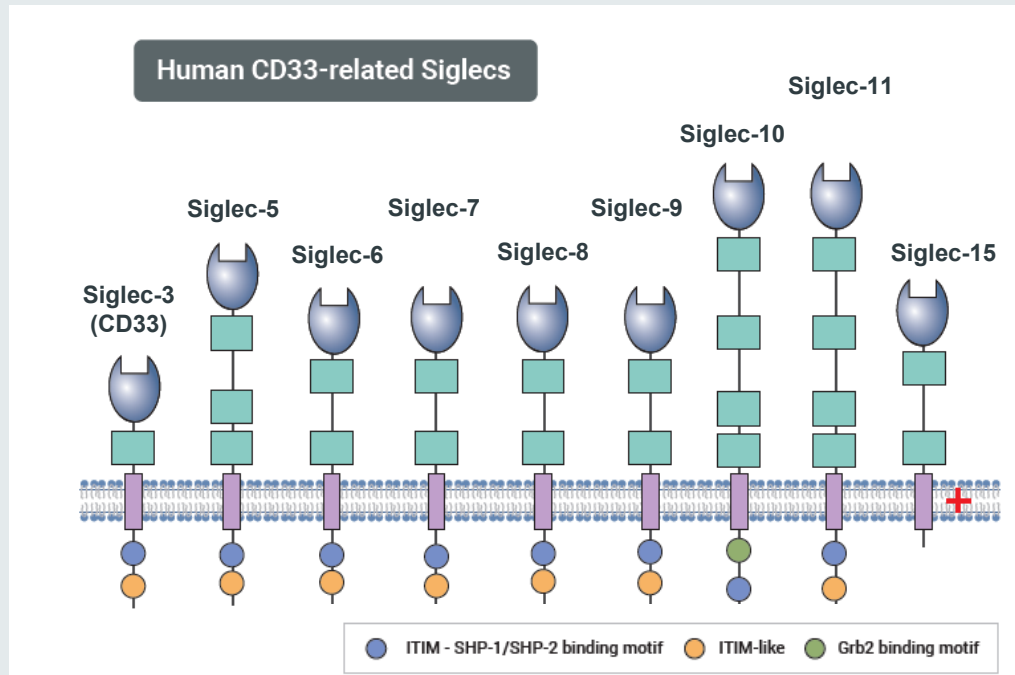
# Disclosures

- Employee of Allakos Inc.

# Mast Cells are Key Drivers of Acute and Chronic Inflammation

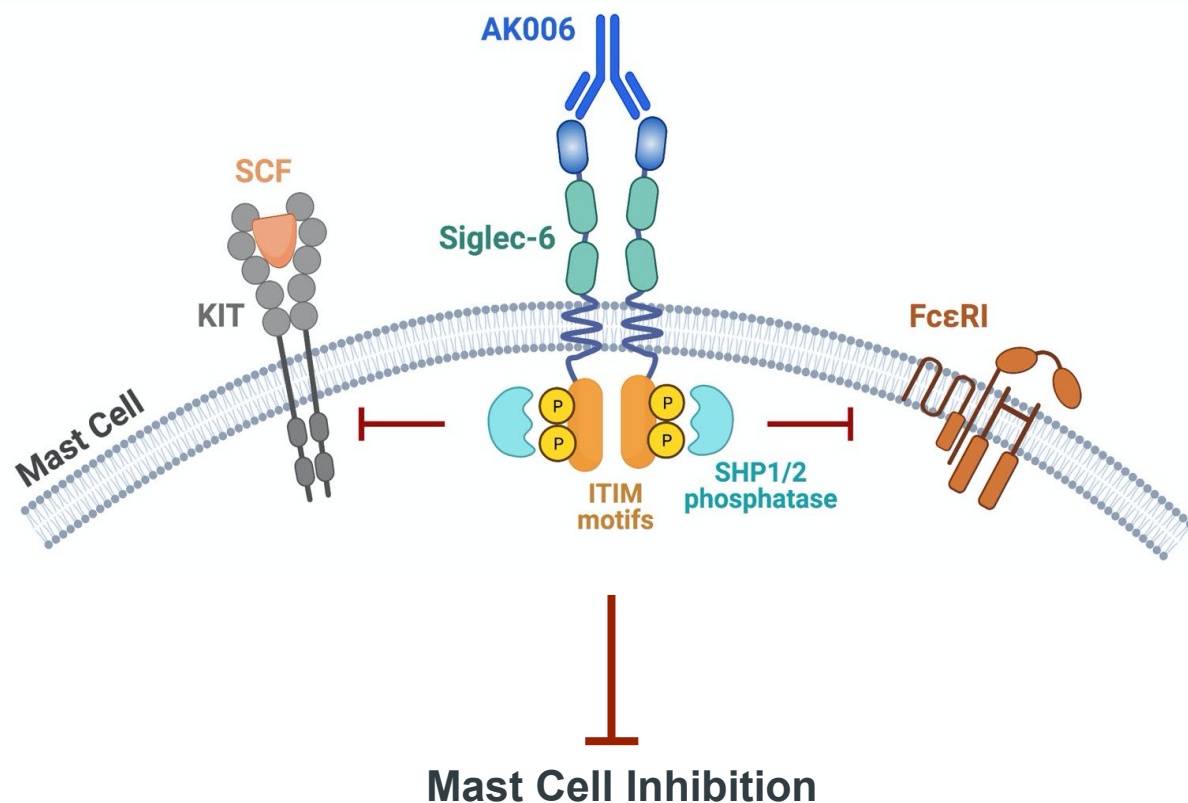


# Siglec-6 is Selectively Expressed on Human Tissue Mast Cells



These findings are consistent with previously published studies using single cell sequencing<sup>1</sup> and proteomic<sup>2</sup> approaches

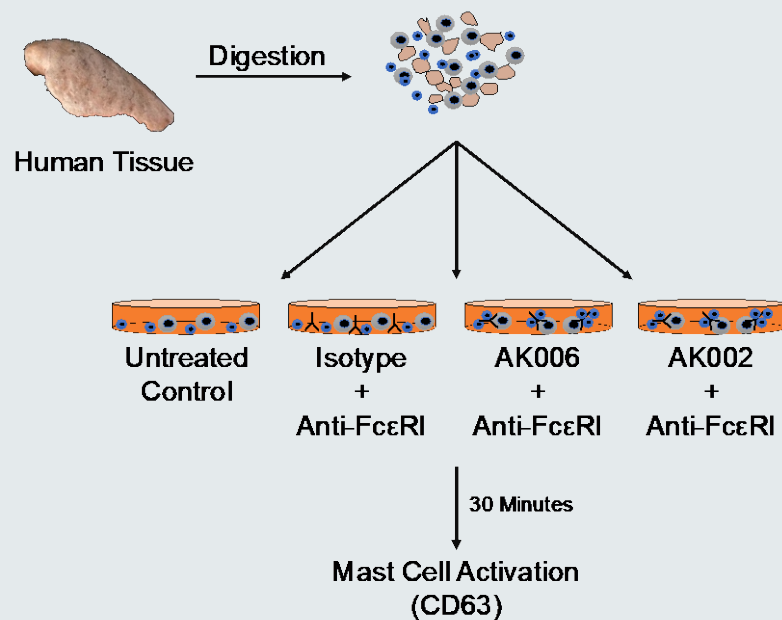
# AK006: Siglec-6 mAb that Selectively Targets Mast Cells



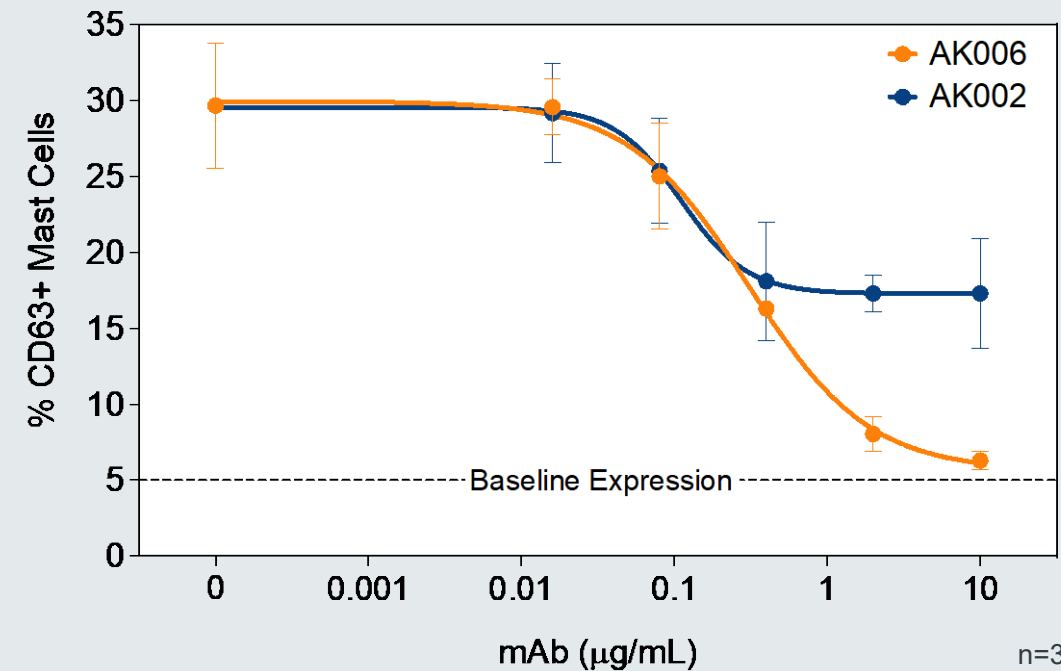
- AK006 is a humanized IgG1 agonistic Siglec-6 mAb that selectively targets mast cells
- High affinity mAb selected for potent Siglec-6 agonism
- Unique MOA that differentiates from other mast cell-targeting molecules
  - Broad mast cell inhibition via Siglec-6 ITIM agonism
  - Reduction of mast cells via Fc-dependent mechanism
- Opportunity to selectively and completely target mast cells in mast cell-driven diseases

# AK006 Inhibits Mast Cell Activation in Human Tissues

## Human Tissue Mast Cell Activation Assay



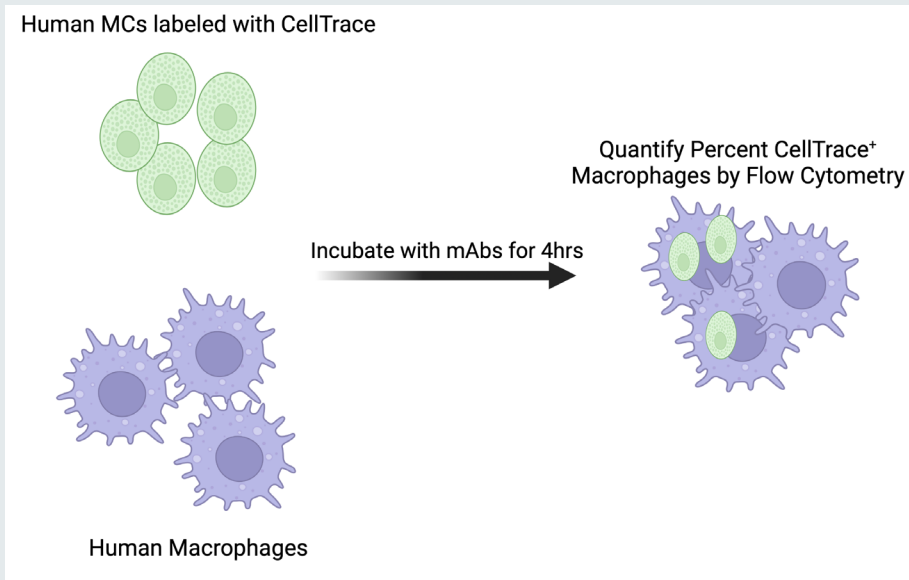
## IgE-Activated Human Tissue Mast Cells



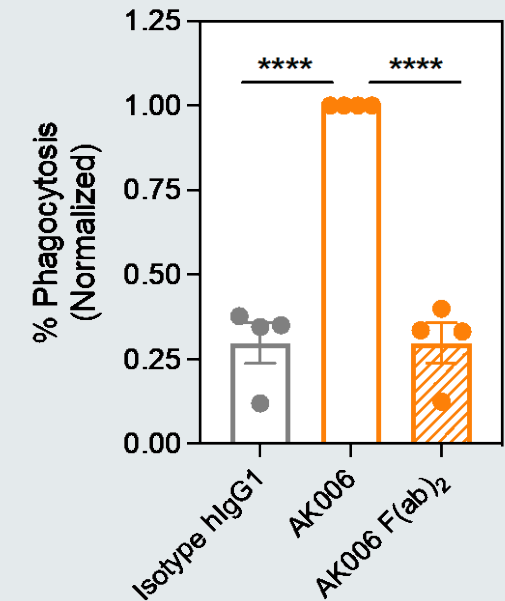
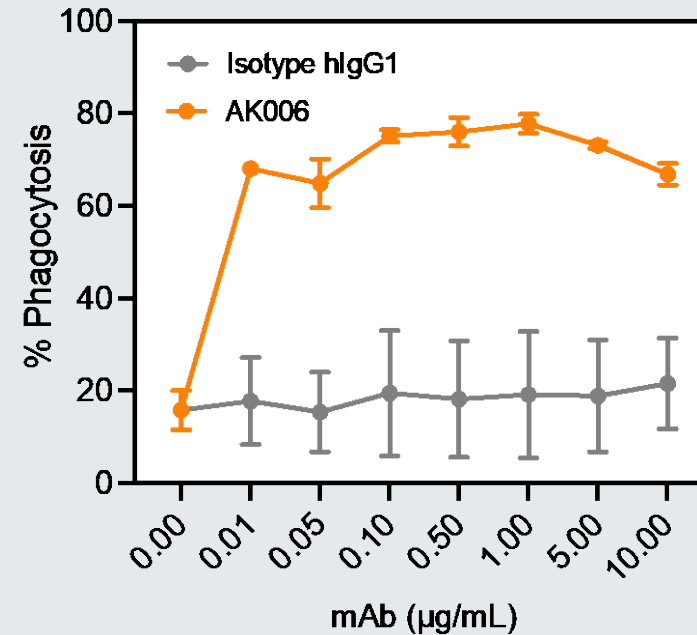
AK006 potently inhibits IgE-mediated mast cell activation

# AK006 Induces Antibody-Dependent Cellular Phagocytosis (ADCP) against MCs

## ADCP Assay Schematic



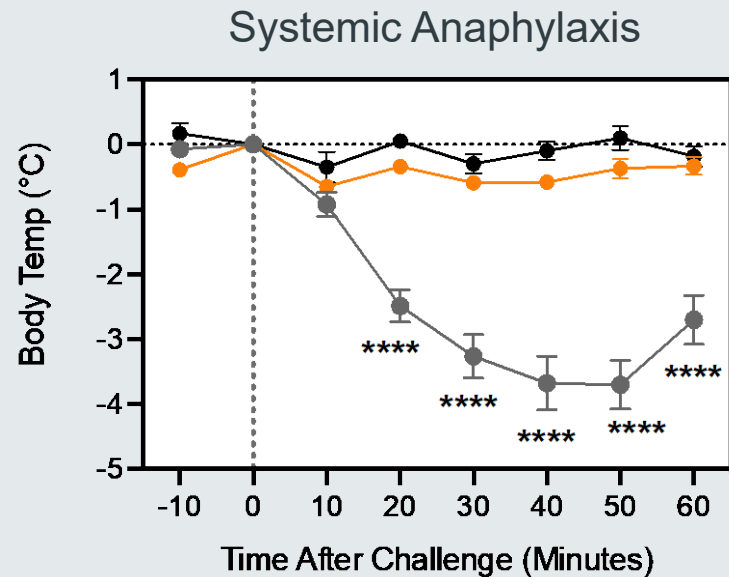
## ADCP Assay with Human MCs



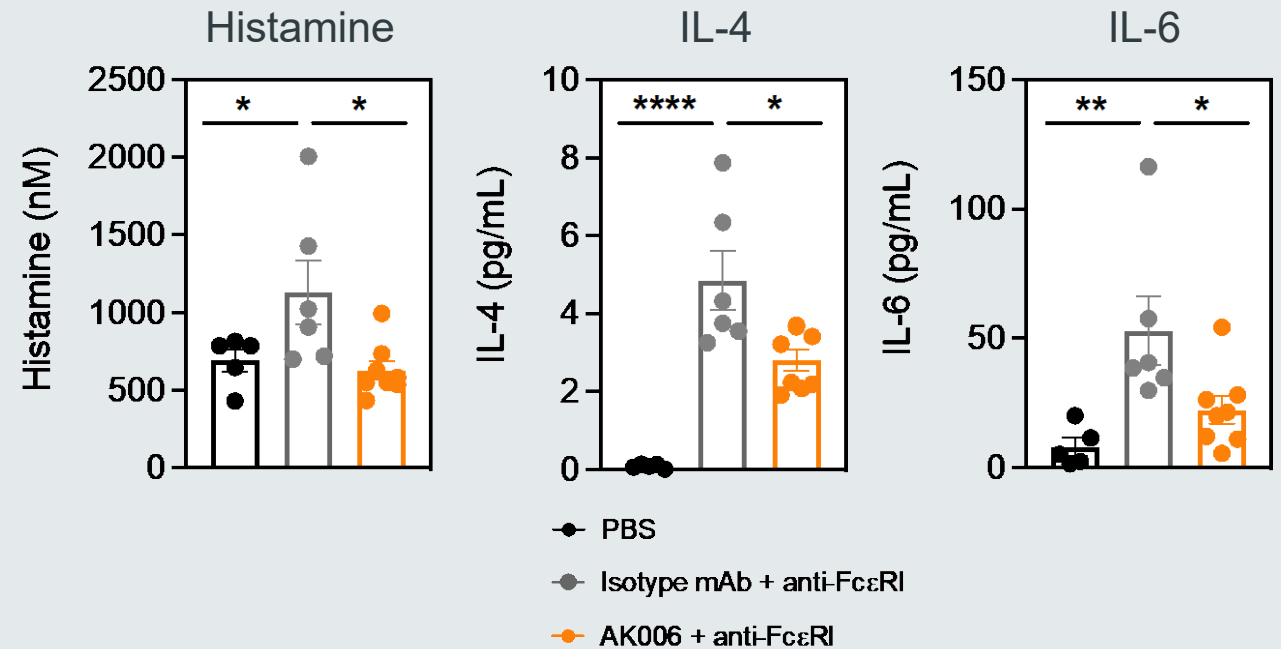
- Co-culturing human MCs with macrophages in the presence of AK006 induces phagocytosis of MCs that requires the Fc-portion of the antibody
- ADCP of human MCs represents a novel strategy to selectively reduce MCs via Siglec-6 targeting

# AK006 Completely Protects Against Systemic Anaphylaxis in Humanized Mice

## Humanized Mouse Model of Anaphylaxis



## Inflammatory Mediators

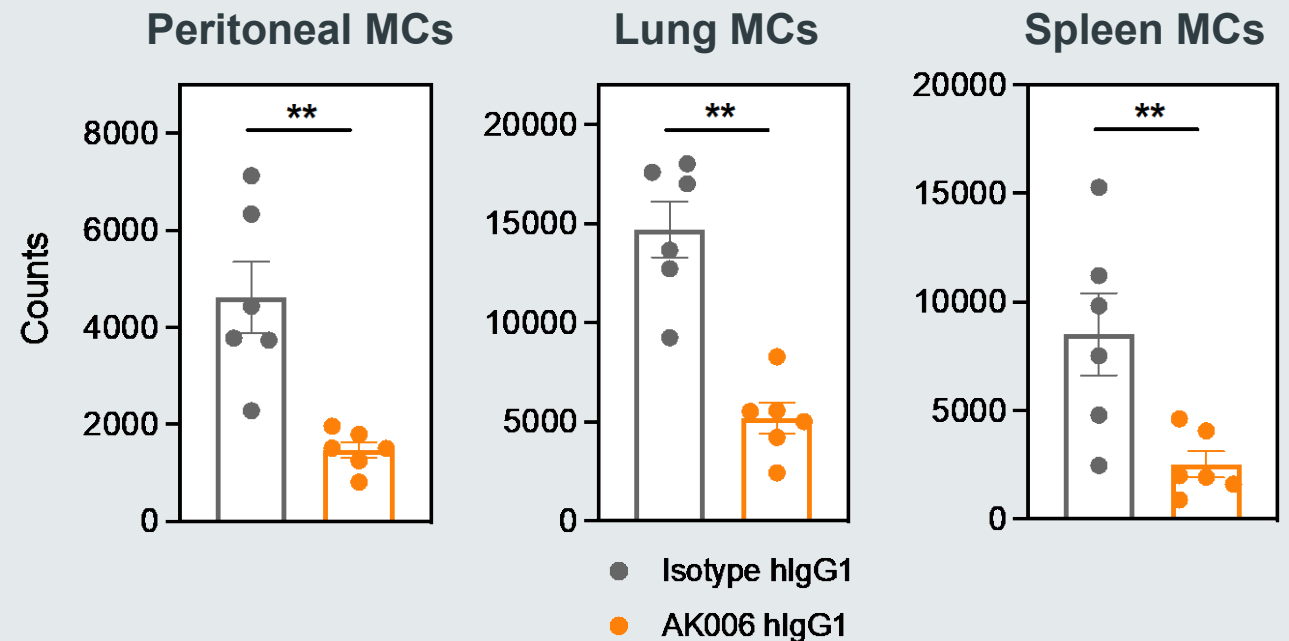
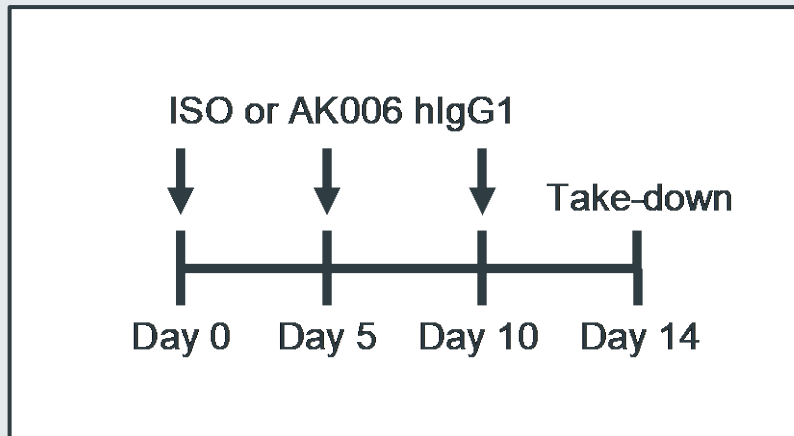




# AK006 Reduces Human MCs in Humanized Mice

## Two-Week Dosing Study in Humanized Mice

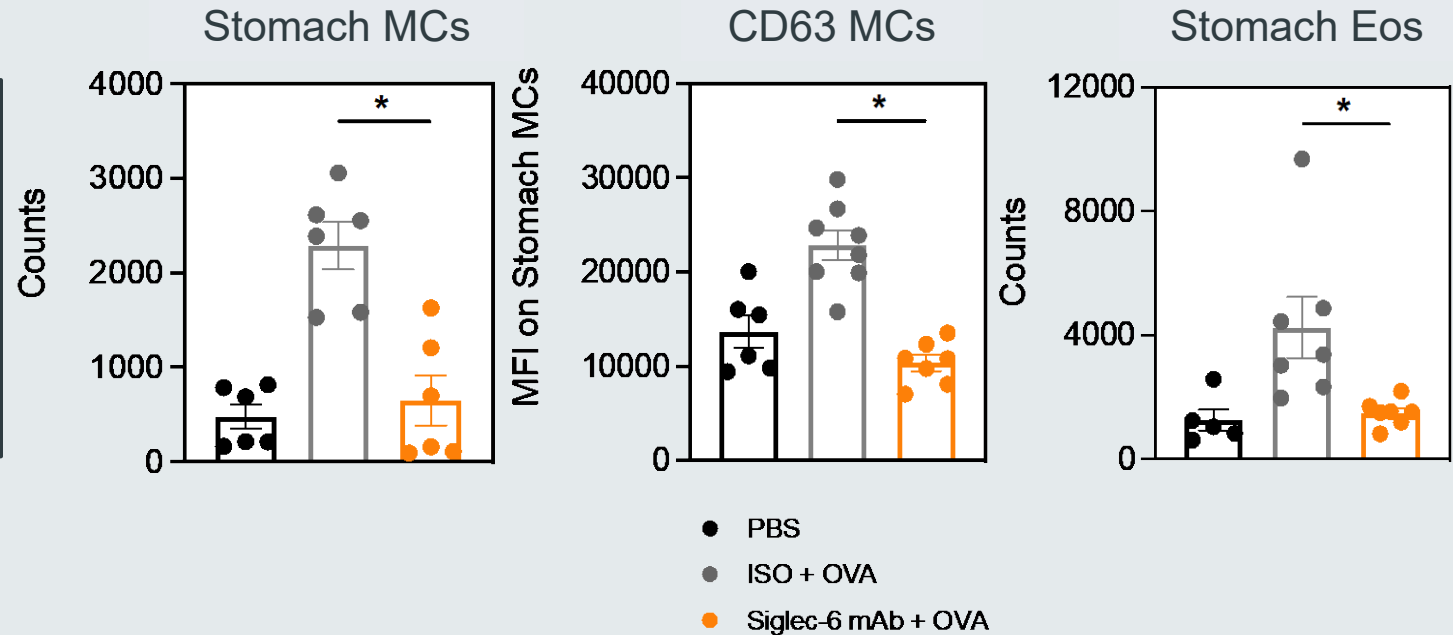
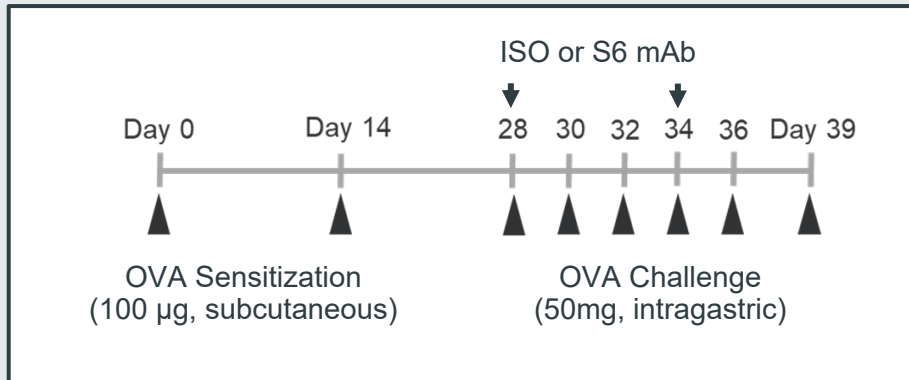
## Human Tissue MCs



- Humanized mice (NSG-SGM3) were dosed for two weeks with AK006 or an isotype control mAb
- Mice treated with AK006 displayed significantly reduced MCs across multiple tissues and was not seen in mice dosed with a f(ab')<sub>2</sub> fragment of AK006 (data not shown)

# Allergic Gastrointestinal Disease Model in Siglec-6 Transgenic Mice

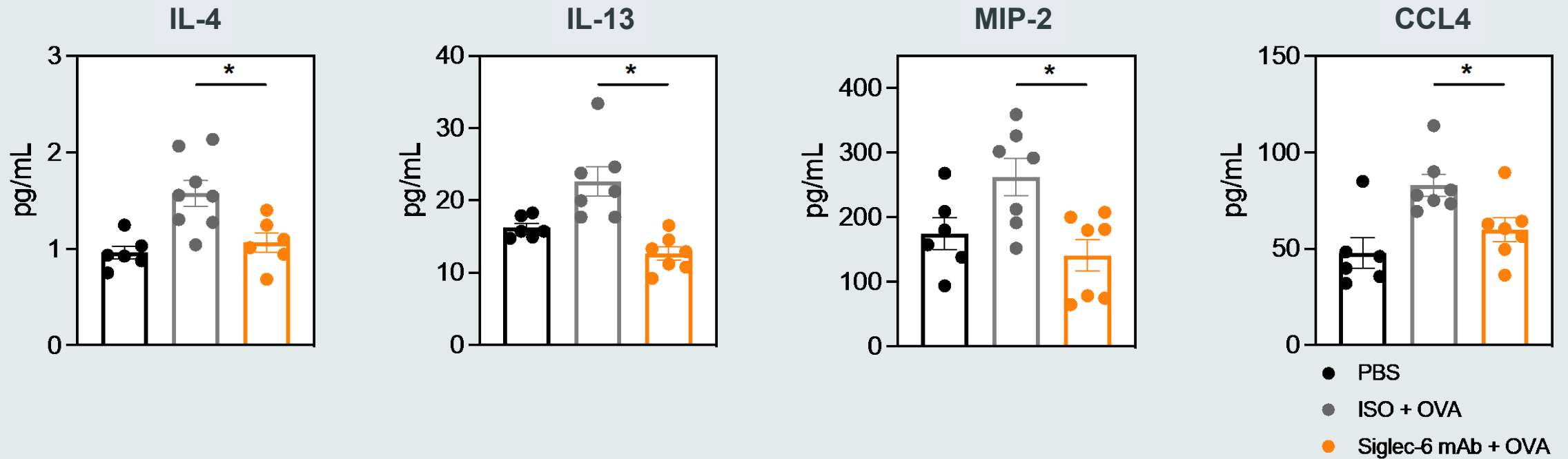
## Model of OVA-Induced Allergic GI Disease



- OVA-sensitized and challenged mice showed increased MC infiltration, activation, and eosinophilia in the stomach
- Mice treated with a Siglec-6 mAb demonstrated inhibition of OVA-induced inflammation

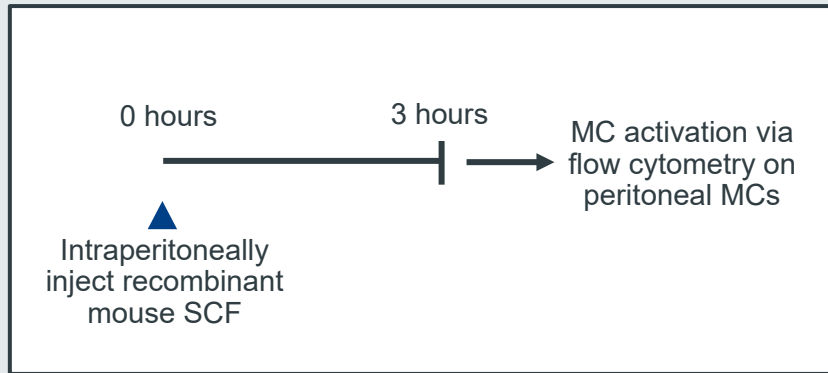
# AK006 Reduces Cytokines and Chemokines in Allergic GI Model

## Cytokines and Chemokines in Serum

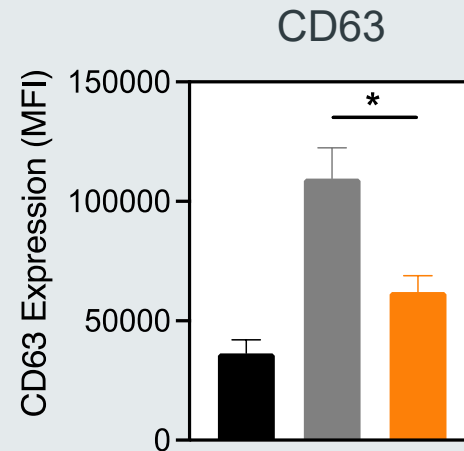


# AK006 Inhibits KIT-mediated Mast Cell Activation in Siglec-6 Transgenic Mice

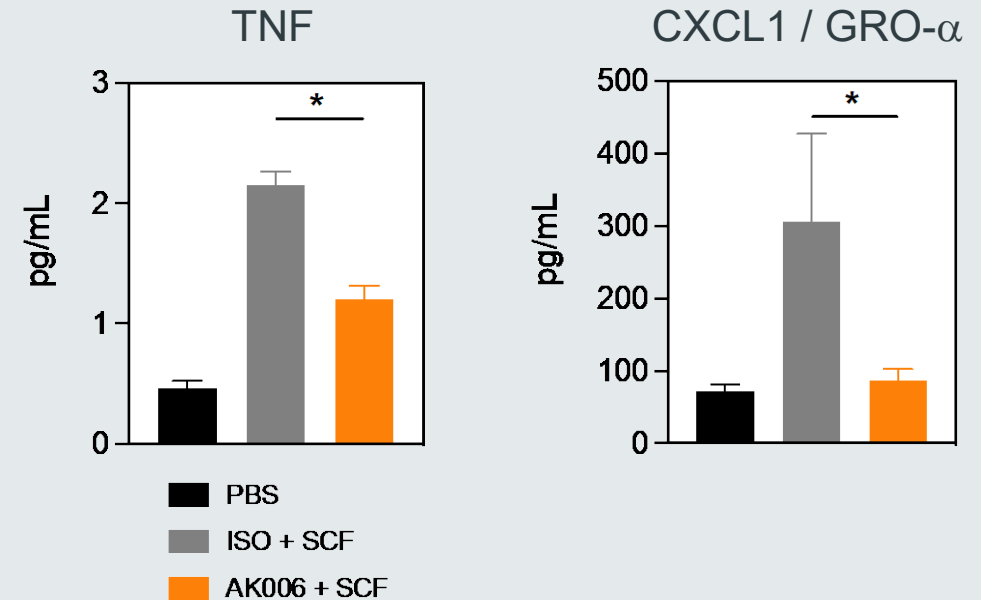
## Model of SCF-mediated MC Activation



## Mast Cell Activation



## Cytokines and Chemokines



SCF, stem cell factor; \*  $p < 0.01$ ; n=7-8 mice/group

- Treatment with AK006 reduced SCF-induced MC activation and mediator production

# Summary

- **AK006 is a humanized IgG1 agonistic Siglec-6 mAb that selectively targets mast cells**
- **Unique MOA that differentiates from other mast cell-targeting molecules**
  - Inhibition of both IgE-dependent and independent mast cell activation
  - Reduces mast cell numbers in tissue
- **First-in-human study planned 1H 2023**

# Acknowledgements

## Allakos Research Team



## Scientific Advisory Board

- Bruce Bochner
- Bob Schleimer

## University of Mass Medical School

- Mike Brehm