Tregitopes improve murine asthma by promoting highly suppressive and antigen specific Tregs

Marieme Dembele1, Shao Tao1, Amir Massoud2, Victoria Zismanov1, Gabriel Kaufman1, Sandra Lelias3, Bruce Mazer, MD FAAAAI1, Anne De groot3; 1The McGill University Health Center, 2Harvard University, 3Epivax, Inc.

RATIONALE: Tregitopes (T Regulatory Epitopes) are immunoglobulin G-derived peptides known to promote tolerance by activating regulatory T cell (Treg) activity and expanding Tregs in-vitro and in-vivo.We hypothesized that Tregitopes abrogate OVA and ragweed-driven murine allergic airway disease by inducing highly suppressive T regulatory cells capable of modulating Teffector cells and promote tolerance in an antigen-specific manner.

METHODS: C57BL/6 mice were treated with hTregitope084-hTregitope289, hTregitope167-hTregitope289, IVIg (positive control) and vehicle control. In addition to assessing airway hyperresponsiveness (AHR) and peribronchial/perivascular inflammation by flexivent and H&E stain respectively, we measured changes in T cell phenotype and inflammatory response using flow cytometry. Cytokine profiles from lung homogenates were assessed by ELISA. We also evaluated antigen specificity by adoptive transfer of sorted Tregs from treated mice to syngeneic antigen-sensitized mice.

RESULTS: Co-treatment with allergen improved lung function and abrogated OVA-driven peribronchial/perivascular inflammation in the IVIg, hTregitope084-hTregitope289 and hTregitope167-hTregitope289 groups compared to the vehicle control group as quantified by histological scoring (1.5 6 .2887, 1.46.2449, 1.46.2449, 3.0 6 .5774). Neutrophilic and monocytic lung infiltration was reduced in response to Tregitope treatment in two AAD models (ragweed and OVA). We also observed reduced Th17, Th1 and Th2 cytokine expression and levels upon treatment. Compared to ragweed+vehicle-control-exposed Tregs, transferred ragweed+Tregitope-exposed Tregs abrogated lung inflammation when adoptively transferred in ragweed allergic mice, as portrayed by histological scoring (5.336.67, 2.336.33. 2.336.33), but did not do so in OVA allergic mice (5.676 0.33, 5.6760.33, 5.06 1.0).

CONCLUSIONS: Tregitopes can improve murine asthma by promoting the expansion of highly suppressive and antigen-specific Tregs.

AK002, an Anti-Siglec-8 Antibody, Suppresses Acute IL-33-induced Neutrophil Infiltration and Attenuates Tissue Damage in a Chronic Experimental COPD Model Through Mast Cell Inhibition

Julia Schanin1, Emily Brock, MA2, John Leung2, **Philip Hansbro3**, Brad Youngblood, PhD2; 1Allakos, Inc., 2Allakos, 3University of Newcastle.

RATIONALE: IL-33 stimulation of mast cells is believed to play a role in driving acute and chronic inflammation in many diseases including, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis (AD), and inflammatory bowel disease. Siglec-8 monoclonal antibodies (mAb) have been previously shown to inhibit multiple modes of mast cell activation, including by IgE, and selectively deplete eosinophils. However, the effect of an anti-Siglec-8 antibody has not been evaluated in IL-33-driven models of inflammation.
METHODS: Acute neutrophil recruitment was induced in Siglec-8-Transgenic (TG) mice by intraperitoneal injection of IL-33. Peritoneal lavage was collected and analyzed 3 hours later. Experimental COPD was induced by exposing TG mice to chronic cigarette smoke (CS) for 12 weeks followed by analysis of lung function and inflammation in bronchoalveolar lavage (BAL) fluid.
RESULTS: IL-33 administration induced the release of proinflammatory cytokines/chemokines and rapidly recruited neutrophils to the peritoneal cavity. Siglec-8 mAb treatment decreased the production of inflammatory mediators, such as IL-6 and MCP-1, and inhibited neutrophil infiltration. Therapeutic treatment with a Siglec-8 mAb also significantly suppressed CS-induced experimental COPD. Siglec-8 mAb treated groups displayed reduced neutrophil infiltration in BAL fluid and significantly improved lung function. Lastly, treatment with a Siglec-8 mAb decreased activation of mast cells in ex-vivo human lung tissue induced by IL-33 and TSLP.
CONCLUSIONS: Siglec-8 mAb treatment decreased acute and chronic inflammation by inhibiting IL-33 activation of mast cells. An anti-Siglec-8 approach may have the potential to treat diseases associated with eosinophil and mast cells, including those with elevated IL-33, such as COPD, asthma, or AD.