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Title: Blockade of thymic stromal lymphopoietin receptor (TSLPR) reduces atopic inflammation in a cynomolgus monkey model of asthma

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Body: TSLP pathway blockade is a potential strategy for asthma treatment, as TSLP modulates cytokine production by mast cells and regulates the activation of dendritic cells (DCs), which prime the differentiation of naïve T cells into inflammatory Th2 cells. We thus tested the effects of TSLPR blockade on the development of allergic inflammation and bronchoconstriction in cynomolgus monkeys after Ascaris suum allergen challenge. Antibodies against human TSLPR were generated and confirmed to be cross-reactive to cynomolgus. Animals were dosed weekly with either vehicle (n=8) or TSLPR HuMAb (n=8) for 6 weeks and their responses to A.Suum challenge at baseline, week 2 and week 6 were assessed. TSLPR HuMab treated subjects showed reduced bronchoalveolar lavage (BAL) eosinophil counts (p=0.04), reduced lung resistance (RL) area under the curve (p=0.04), and reduced IL-13 cytokine levels in BAL fluid (p=0.03) in response to challenge at 6 weeks compared to control subjects. To understand the molecular changes underlying these differences, pre- and 8h post-challenge BAL samples from Mab-treated and control subjects were profiled using expression microarrays. Genes up-regulated by allergen challenge overlapped strongly with 11 genes up-regulated in DCs when stimulated by TSLP (TSLP-DC signature). At 6 weeks, treatment with TSLPR HuMAb reduced the overall number of differentially expressed genes and significantly reduced the induction of the TSLP-DC signature relative to control subjects (p = 0.05). These results demonstrate promising efficacy for TSLPR blockade in an allergen challenge model where TSLP activation of DCs may play a key role.