Title: **Specific immunoregulatory epitopes in the treatment of allergic disease**

Session: Biologics Track 3: New Directions in Immunotherapy

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Synthetic peptide immunoregulatory epitopes (SPIREs) are T cell epitopes derived from important allergens that are used for peptide immunotherapy in allergic diseases. The peptides are selected on the basis that they represent major T cell epitopes of the allergen and are too small to crosslink allergen-specific IgE on the surface of effector cells such as basophils and mast cells [(1)]. Administration of peptides at the appropriate dose and dose interval has been shown to induce enduring clinical tolerance to allergen which is associated with the induction of regulatory T cell function that may be mediated through the upregulation of IL-10 production. Recent data from two phase 2b clinical trials of a SPIRE preparation for cat allergy (clinical development name: Cat-PAD) demonstrated improved tolerance of allergen exposure in an Environmental Exposure Chamber (EEC) [(2)]. When compared to studies conducted in similar settings and using similar clinical outcomes (for example the Total Rhinoconjunctivitis Symptom Score; TRSS), therapy with Cat-PAD demonstrated clinical efficacy that was at least as good in the short term as existing pharmacotherapy or current allergen immunotherapy approaches (subcutaneous or sublingual allergen immunotherapy) [(3)]. Longer term efficacy appears to be better than any existing therapies. After four intradermal injections over a three month period, clinical efficacy was maintained for two years after the initiation of therapy [(4)]. In both trials, the adverse events profile was indistinguishable from placebo. Taken together these results suggest that peptide immunotherapy may be a safe and efficacious new approach to allergic diseases that will reduce treatment times, thereby enhancing compliance and ultimately expand the number of patients opting for disease-modifying therapy.

The immunological mechanisms of action of peptide immunotherapy remain partially understood. To date, our work has provided strong evidence that the immunosuppressive cytokine IL-10 is upregulated following peptide immunotherapy [(5-7)]. In a murine model of cat allergen-specific peptide immunotherapy, efficacy was dependent on the increased production of IL-10 by T cells [(7)]. Interestingly, IL-10-secreting T cells were most abundant in the lung, the target organ in this murine model of allergic airways disease. These results suggest that IL-10-secreting regulatory T cells may be specifically recruited to sites of allergen contact, thereby providing tissue-specific regulation of inflammatory responses. We have found evidence for the induction of a CD4+ population of T cells (in human studies) with regulatory/suppressive activity [(8)]. In early, higher dose, clinical studies we found evidence for reduction in allergen-driven proliferation and Th1/Th2 cytokine production in vitro [(5-6)]. More recently, in studies using lower cumulative doses of peptides, upregulation of IL-10 responses has been observed but without clear reductions in Th1/Th2 cytokines (unpublished data).

Taken together, our results suggest that peptide immunotherapy (in the absence of adjuvants) leads to meaningful improvements in clinical outcomes and has an improved safety profile compared to subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Efficacy appears to be associated with modification of the allergen-specific immune response with an increase in the

immunoregulatory cytokine IL-10. Further mechanistic studies are currently underway to improve our understanding of the precise cellular and molecular pathways that result in clinical efficacy.

References

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