Seminar:  **Mechanisms and Biomarkers Related to Sublingual and Subcutaneous Immunotherapy**

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Allergen immunotherapy is allergen-specific, allergen dose- and time-dependent and is associated with long-term clinical and immunological tolerance that persists for years after discontinuation. Injection allergen immunotherapy for seasonal pollinosis is associated with the amelioration of seasonal symptoms, bronchial hyperresponsiveness and a reduced requirement for rescue medication. Clinical responsiveness to allergen immunotherapy has been shown to exceed the duration of treatment by several years, a clear advantage over the use of anti-IgE or anti-allergic drugs.

The suppression of the late-phase allergic responses in the skin, nose and the lung has been reported following treatment. Several studies have reported inhibition of the early and the late response following an intradermal allergen challenge.

Successful allergen immunotherapy (conventional subcutaneous and sublingual) is accompanied by the suppression of numbers of T-helper 2 (Th2) effector cells, eosinophils, basophils, c-kit+ mast cells and neutrophils infiltration in target organs, induction of IL-10 and/or TGF-β+ Treg cells and increases in ‘protective’ non-inflammatory blocking antibodies, particularly IgG4 and IgA2 subclasses with inhibitory activity. These events are accompanied by a reduction and/or a redirection of underlying antigen-specific Th2-type T cell-driven hypersensitivity to the allergen(s) used for therapy. This suppression occurs within weeks or months as a consequence of the appearance of a population of regulatory T cells that exert their effects by mechanisms involving cell–cell contact, but also by the release of cytokines such as IL-10 (increases IgG4) and TGFβ (increases specific IgA). The more delayed-in-time appearance of antigen-specific T-helper 1 responses and alternative mechanisms such as Th2 cell anergy and/or apoptosis may also be involved. The mechanisms of sublingual immunotherapy are similar to those following a subcutaneous administration of allergen, whereas it is likely that additional events following antigen presentation in the sublingual mucosa and regional lymph nodes are involved.

Cellular (cell surface and intracellular flow cytometry, EliSpot, tetramer, basophil activation) and serology assays (immune reactive IgG4, IgE-facilitated allergen binding) have been used successfully to investigate and monitor immunologic changes and induction of immunologic tolerance following immunotherapy.

In this seminar, we will discuss novel mechanisms of immunotherapy and relevant immunologic techniques listed above for investigating immunological changes and induction of immunologic tolerance following immunotherapy.