

## General Principles

Current desensitization therapy is not sufficiently durable, so alternate allergen formulations, routes of administration, and more specific immunotherapy strategies are needed. The ITN will collaborate with all groups of allergy investigators to fill these gaps, focusing on providing cutting-edge assays that evaluate changes to the adaptive immune response to allergens in the context of experimental therapy. ITN clinical studies will pioneer the concept of “allergen-plus,” in which novel immunomodulators and immune targets are assessed in combination with specific allergen immunotherapy.

## Strategy

The ITN will prioritize studies on one perennial allergen (cat dander), one season allergen (grass pollen), and one food allergen (peanut). Alternate routes of allergen desensitization will be considered. Allergen will be combined with novel immunomodulators—both adjuvants and specific immunological targets implicated in allergic responses—to invoke depletion and deviation mechanisms of tolerance. Study designs, both large scale clinical trials as well as smaller mechanistic studies, will take into consideration and take advantage of the heterogeneity of clinical phenotypes in the study design. The ITN will also lead efforts to combine data across trials—including partnering with other consortia and investigators—to fill gaps in biomarker validation in response to SIT, particularly with respect to the allergen-specific T cell response.

## Clinical Objectives

To achieve durable nonresponsiveness to allergen exposure through both small mechanistic-based clinical studies and controlled clinical trials, specific therapeutic concepts to be tested include:

- Anti-cytokine plus allergen (e.g., anti-TSLP plus; CATNIP)
- T cell depletion plus allergen (e.g., anti-CRTH2 plus)
- Immune deviation strategies (e.g., GLA adjuvant plus)
- Treg-inducing strategies
- Modified allergens/allergen fragments (e.g., peptides, recombinant proteins, nanoparticles)
- Alternative routes of administration (e.g., epicutaneous, intradermal, intralymphatic)

## Mechanistic Objectives

Specific mechanistic concepts should be incorporated in all allergy studies, relating clinical outcome to immune deviation, regulatory T and/or B cells, effector T cell deletion or anergy, and protective antibody responses. These studies should aim at creating a portfolio of surrogate mechanistic endpoints that correlate with desensitization and tolerance. Other specific mechanistic objectives include:

- Development of assays for B cells (B-regs), dendritic cells and epigenetic markers
- Establishment of a panel of standardized assays that will be utilized in all ITN allergy trials, and made available through collaboration to other investigator and consortia-initiated studies – this panel will incorporate novel allergen-specific T cell phenotyping and induced cytokine and basophil profiles, together with traditional laboratory correlates of allergic responses
- Focus on the target organ (e.g., biopsies, brushings) and bone marrow, in addition to peripheral blood cells
- Partnerships with other organizations on natural history of allergy studies for biomarker validation

**The Immune Tolerance Network (ITN)** is a collaborative network for clinical research focused on the development of therapeutic approaches for asthma and allergy, autoimmune diseases, type 1 diabetes and solid organ transplantation that lead to immune tolerance. These tolerogenic approaches aim to reprogram the immune system so that disease-causing immune responses are stopped while maintaining the immune system's ability to combat pathogen infection. The Network develops, funds and conducts mechanistic, laboratory-based studies in conjunction with clinical trials through collaborations with academic, governmental and industry researchers.

The ITN is funded by a grant awarded to the Benaroya Research Institute at Virginia Mason, the University of California San Francisco and the Massachusetts General Hospital from the National Institute of Allergy and Infectious Disease of the National Institutes of Health.

For questions or information about partnering with the ITN, contact Philip Bernstein, Executive Director of Strategic Review and Planning at [pbernstein@immunetolerance.org](mailto:pbernstein@immunetolerance.org).