Immune Tolerance Network

Strategic Plan: Allergy

Goals and Objectives

immunetolerance.org

General Principles

Current desensitization therapy is not sufficiently durable, so alternate allergen formulations, routes of administration, and more specific immunotherapy strategies are needed to induce tolerance. The ITN will focus 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 continue to prioritize "allergen-plus" concepts in which immunomodulators directed against immune targets critical to disease pathogenesis are combined with specific allergen immunotherapy.

Strategy

The ITN will continue to prioritize studies on one perennial allergen (cat dander), one season allergen (grass pollen), and one food allergen (peanut), while expanding our portfolio to take advantage of opportunities to collaborate with other groups (e.g. using house dust mite or cockroach allergens). Allergen plus strategies continue to be our main focus as novel immunomodulators – including adjuvants and drugs targeting specific immunological modulators implicated in allergic responses – become available allowing us to test depletion, deviation, and other immunologic pathways as mechanisms of allergen-specific tolerance. As new forms of allergens (e.g. peptides) become available, we will consider using these in our "allergen plus" trials. Alternate routes of allergen immunotherapy are also being considered as new allergen formulations are becoming available. Clinical trials, whether large-scale trials or smaller mechanistic studies, will be designed to test specific mechanisms of tolerance allowing investigators to build upon the results in order to develop a road-map to tolerance. The ITN will continue to prioritize early intervention studies and to build upon insights from prior prevention studies (e.g. LEAP) to develop new biomarkers, including genetic and epigenetic, that will inform new therapeutic approaches. In the context of the above scientific focus, the ITN will strive to incorporate advanced clinical trial designs such as "umbrella" and "basket" designs, as well as adaptive trial designs into the portfolio. We will continue to explore surrogate endpoints that will allow us to shorten the duration of our tolerance trials.

Clinical Objectives

To achieve durable nonresponsiveness to allergen exposure through both small mechanistic-based clinical studies and randomized, controlled trials focusing on clinical outcomes.

Specific therapeutic concepts to be tested include:

- Anti-cytokine plus allergen
- T cell depletion plus allergen
- Immune deviation strategies
- Treg-inducing strategies
- Modified allergens/allergen fragments
- Alternative routes of allergen administration
- Early allergen exposure
- The role of the microbiome in inducing tolerance

Mechanistic Objectives

Specific mechanistic concepts will be tested in all allergy studies, so that clinical outcomes can be related to immunologic events such as deviation, expansion of regulatory T and/or B cells, effector T cell deletion, exhaustion or anergy, or development of protective antibodies. These studies will be designed to help create a portfolio of mechanistic endpoints that correlate with desensitization and tolerance. Other specific mechanistic objectives include:

- Development of assays for B cells (Bregs), dendritic cells, and epigenetic markers
- Establishing and maintaining the capacity to conduct a panel of standardized assays to be used in all ITN allergy trials, and made available through collaboration to other investigator and consortia
- Evaluation of genetic and epigenetic biomarkers of disease pathogenesis in clinical trial outcomes
- Understanding the role of the microbiome in the development and resolution of allergic disease
- Incorporating immunologic evaluations of target organs (e.g. biopsies, brushings) and bone marrow, in addition to peripheral blood cells
- Partnering with other organizations on natural history of allergy studies for the conduct of mechanistic research on immune tolerance and 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.

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