



Allergy & Asthma Research Proposals

and the Immune Tolerance Network

Introduction

The Immune Tolerance Network (ITN) accepts proposals for novel clinical trials of tolerance therapies in allergy and asthma through its year round, two-stage proposal review system. New applications for research begin as “Concept Proposals,” which are short summaries that provide ITN reviewers with the opportunity to assess the proposal based primarily upon the quality and feasibility of the idea, rather than the logistics of the proposal.

In general, new Concept Proposals are generated from two sources:

- i) **Independent Investigators** – Investigators in the academic or business sectors are encouraged to bring their ideas for new clinical protocols of tolerance therapies in allergy and asthma to the ITN through new Concept Proposal submissions. The majority of new clinical trials adopted by the ITN begin as Concept Proposals from independent investigators.
- ii) **ITN Subgroup Directives** - Immune Tolerance Network members or the ITN Allergy and Asthma Subgroup may also develop ideas for new Concept Proposals. These proposals may follow the normal application review cycle, or may be offered to the academic and/or business sectors as RFPs or as collaborative ventures with the ITN.

Immune Tolerance Trials in Allergy and Asthma

Although the fundamental biological bases of tolerance differ little across many of the diseases studied by the ITN, certain special considerations must be taken into account that reflect the clinical circumstances of each individual disease. Therefore, in the case of allergy and asthma, “tolerance” may be operationally defined as:

a therapy that leads to an altered immune response that results in less morbidity/mortality but is not dependent upon the continued use of that treatment regimen, (i.e. the treatment can be stopped but the immune changes and improved health status will continue).

Examples of potential tolerance induction in asthma/allergy: IgE plus anti-IgE; rush immunotherapy; high dose allergen tolerance; sIL-4R or IL-4RA plus rush immunotherapy; cat peptide therapy; or use of chimeric IgG-allergens to induce tolerance.

It is a generally accepted principle within the ITN that immunotherapy for allergic asthma and allergic rhinitis induces a modified immune response to allergen that falls under the rubric of tolerance. New ways to achieve this outcome by using interventions along with immunotherapy are appropriate for the ITN to consider. New approaches to immunotherapy are also appropriate for the ITN. Examples are given below. “Rush immunotherapy” is strongly suggested in any protocol using immunotherapy because of time constraints and the ability to validate changes in a rigorous and a timely fashion. At the same time, the ITN recognizes that there are no convincing data that “rush immunotherapy” induces tolerance. Examples are given below.

- ◆ Treatment that improves current immunotherapy: Test potential tolerance intervention treatment plus Rush immunotherapy vs. Rush immunotherapy.
- ◆ New forms of therapy (e.g. peptides, CpG): Test potential tolerance intervention treatment alone vs. placebo vs. possibly some standard form of therapy, e.g. pre-seasonal, rush etc.

Special Considerations for Allergy and Asthma Proposals

Applicants should note that the ITN proposal review system differs from traditional study section review in that a much higher degree of interactivity takes place between applicants and the ITN - the ITN's mission is to develop the most effective and scientifically profitable studies as possible. Therefore, investigators are strongly encouraged to contact members of the ITN Asthma and Allergy Subgroup prior to submitting their final Concept Proposal. The Subgroup can provide potential investigators with valuable feedback that can maximize the chances of a successful proposal.

DRUG ACQUISITION

It is an unfortunately common occurrence that, while a specific therapy or drug may have sufficient and compelling published data to warrant further clinical investigation, actual acquisition of the agent in question can be difficult. The ITN recognizes that drug acquisition can be a major difficulty in developing innovative tolerance directed trials and offers assistance to investigators to overcome this impediment. The ITN has developed a specific subcommittee to assist with drug acquisition through pharmaceutical industry or through ITN purchase or production. Investigators wishing to request assistance in this respect should contact the ITN Director of Scientific Review.

ENDPOINTS

In proposing studies in Allergy and Asthma, investigators should keep in mind that measurements of clinical and tolerance endpoints should be made before, during and after the primary "exposure(s)" and as related to subsequent exposures (seasonal or purposely challenged). What is listed below is not meant to be required in any one study but is an effort to provide a wide-ranging view of appropriate assays to provide guidance for tolerance studies in asthma and allergy:

Examples of Clinical endpoints:

- Clinical symptoms scores, medication use, etc (cite Hopkins studies)
- Quality of life scores (cite Juniper reference)
- Measurements of function (acoustic rhinometry, spirometry for asthma, Peak Flow monitoring, methacholine challenge)
- Clinical response to specific challenge (nasal, ocular, pulmonary, skin)

Examples of Tolerance endpoints

- Antibody response to allergen or peptide to include IgE, IgG, IgG4
- Antigen/allergen responsiveness in vivo (can be measured in a variety of ways, e.g. proliferation, cytokine production, arrays on cells before, during and after therapy)
 - Count antigen reactive cells in blood – tetramers for antigen specific cells, recognizing that tetramers are not generally available for allergens at present.
 - Skin test challenge pre and post (immediate and late phase responses) biopsy with immune histology
- Blood Cell response in vitro following therapy (specific allergen, eg. Amb A1, whole allergen e.g short ragweed. Measure of the following: Elispot; proliferation; cytokine production (Q-PCR); array on unstimulated cells plus stimulated cells. Assess arrays on fresh cells and on stimulated cells.
- Nasal Lavage (+/-scrape/biopsy) pre, during and post therapy
 - Antigen specific IgE, IgG, IgG4
 - Cells for cytokine production (Q-PCR), fluid for cytokine protein
- Nasal challenge (pre and post) (immediate and late phase responses)
 - Symptom score
 - Acoustic rhinometry
 - Antigen specific IgE, IgG, IgG4
 - Cells for cytokine production (Q-PCR), fluid for cytokine protein

- Inhalational antigen challenge (pre and post) (immediate and late phase)
 - Induced sputum, BAL, mucosal biopsy (pre and post)
 - Antigen specific IgE, IgG, IgG4
 - Cells for cytokine production (Q-PCR), fluid for cytokine protein
- Skin test challenge pre and post (immediate and late phase responses)
 - Biopsy with immune histology

PROTOCOL DEVELOPMENT

Once a clinical trial proposal has been fully approved by the ITN steering committee (through Full Application review), protocol development will proceed with participation from the Investigator(s), the ITN Allergy and Asthma Subgroup and the ITN's Clinical Trials Group. The Subgroup will assist in the process by providing expert scientific and medical expertise when necessary. The ITN Clinical Trials Group provides wide-ranging services that include statistical, regulatory, logistical, administrative and other clinical trial development, implementation and management functions.

PERFORMANCE OF TRIAL

This may involve the development of a number of sites depending on the enrollment needs of the study.

Questions:

If you are interested in submitting a concept proposal for a study in Allergy or Asthma to the Immune Tolerance Network and have questions regarding the process, please contact:

Dr. Anita Corman Weinblatt
Director of Scientific Review
aweinblatt@immunetolerance.org
Phone: 240.497.0006