



# Type 1 Diabetes 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:

1. **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.
2. **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

ITN is interested in “tolerance” related trials for prevention of diabetes and loss of C-peptide secretion after diabetes onset as well as innovative assays of the autoimmune process. A large body of evidence indicates that risk of type 1A (immune mediated) diabetes is predictable in man and preventable in animal models. A number of the therapies that prevent type 1 diabetes in animal models relates to therapies that would fit under the umbrella of “tolerance induction”. Though autoantibody tests related to type 1 diabetes are well developed and standardized in multiple international workshops, it has proven more difficult to develop and confirm assays for T cell autoimmunity, in particular assays that can distinguish a patient developing or with new onset type 1A diabetes from control individuals. Thus current trials of therapies usually utilize preservation of C-peptide at disease onset or progression to diabetes as their primary endpoints, while it is recognized that disease relevant T Cell assays are a priority. To date ITN trials in new onset patients utilizing an insulin B chain peptide (phase I) and a monoclonal to CD3 have been approved. ITN is also extensively supporting studies of islet transplantation where both transplant rejection and autoimmunity are important factors and is helping with the development of a GAD “vaccine”. The ITN provides a series of cores with direct relevance to type 1 diabetes including tetramer core (J Nepom) with studies of GAD reactive T cells, ELISPOT core, autoantibody core (e.g. assays for GAD65, ICA512, and insulin autoantibodies), microarray core, etc.

It is planned that ITN will often collaborate with organizations such as TrialNet, the newly established North American network for prevention trials. It is assumed that trials for the

prevention of type 1 diabetes in at risk populations (e.g. first degree relatives) will by necessity have a primary focus in TrialNet. For trials of new onset patients collaborative studies will be most efficient and as study designs are created by TrialNet and IDS (see Carla Greenbaum, IDS web site) standardized protocols will be encouraged where possible. As trials are reviewed for ITN a number of obvious questions are usually discussed and attention to these questions in the Concept Proposal is advised:

1. Efficacy data in animal model of type 1 diabetes or relevant human data.
2. If the NOD mouse is the animal model studied, efficacy data at later stages of the disease process is appreciated (e.g. 12-16 weeks, new onset, blocking islet transplant destruction).
3. Efficacy data with dose response information and utilization of the agents the way they are proposed in man (e.g. in adjuvant, combination of agents).
4. Safety data as per FDA requirements and any information concerning safety in man.
5. Agent availability
6. Rationale for dose or schedule considered.
7. Rationale that the study is evaluating tolerance induction and not simply an immunosuppressive drug given long-term.
8. Good scientific rationale and evidence of some effect in man (e.g. induction of T cell or suppression of T cell response/ availability of surrogate markers to speed dose finding studies).
9. Phase I and II, and early phase III trials considered.
10. Design of clinical trials with standardized entry and endpoint criteria to foster comparison with other trials.
11. Utilization of core laboratories of ITN and interesting mechanistic studies.

It is not assumed that all of the above is available and there is the potential for help in developing certain critical information to allow trial development, and the ITN strives to be a collaborative iterative process helping to test new therapies.

## 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:

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