Immune Tolerance Network

Strategic Plan: Type 1 Diabetes

Goals and Objectives

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General Principles

Therapeutic intervention in T1D must interrupt the autoimmune response against islet antigens, coupled with regulation of recurrent islet-specific immunity, in order to achieve preservation of beta cell function. Partial therapeutic responses have been achieved by immunomodulation using various biologic agents but these responses have only been achieved in a subset of patients and have generally not been durable, emphasizing the need to address multiple arms of the autoimmune response. The ITN will lead the therapeutic effort to combine different targeted agents directed against both adaptive and innate components of immunity. The ITN will also partner with other clinical trial efforts to optimize the mechanistic understanding of T1D intervention therapy of different types.

Strategy

The ITN will prioritize studies in recent-onset T1D that evaluate combinations of agents that induce immune immunomodulation (e.g., through deviation and regulation mechanisms) with agents that interrupt effector cell activity (e.g., through depletion or exhaustion mechanisms), to achieve durable preservation of beta cell function. Priority combination therapies will be selected based on feasibility, guided by a set of mechanistically oriented clinical studies. Antigen-specific immunomonitoring tools will be optimized to define a phenotype associated with successful outcome, and will be extended to prediabetic studies through partnership with TrialNet.

Clinical Objectives

The overall objective is to maintain C-peptide secretory capacity in recently diagnosed T1D subjects through the use of combination therapeutics in both small mechanism-based clinical studies (to better understand disease pathology) and fully powered clinical trials (using agents with validated mechanisms). We will consider trial concepts that propose therapeutic agents in the following categories:

- Effector cell depletion or deviation, followed by co-stimulatory blockade. Priority will be given to Treg-sparing strategies, and to the potential for adding antigen or agents that address metabolic intervention in a later stage
- Effector cell depletion or deviation, plus anti-cytokine agents to block re-emerging pathogenic profiles while preserving regulatory pathways
- Regulatory T cell enhancement or replacement, plus cytokines or agents designed to stabilize a regulatory profile
- Induction with anti-cytokine agents followed by co-stimulatory blockade, where the induction agent has previously been successful at inducing T1D remission (measured as stable C-peptide levels)
- Antigen or antigen nanoparticle plus anti-cytokines or agents designed to induce a regulatory profile
- Evaluation of the effects of immune therapies on beta cells, either in collaboration with other groups or by development of targeted assays

Priority will be given to therapeutic combinations that have shown efficacy in pre-clinical T1D models, and to therapies that use agents previously shown to have mechanisms of action consistent with the above conceptual frameworks.

Mechanistic Objectives

The overall objective is to establish assays that correlate immunological parameters with beneficial and/or deleterious clinical outcomes in ITN trials. We will prioritize assays that measure islet-specific T cell depletion and deviation in the clinical trial setting, and which provide a transcriptional immunologic profile that is indicative of a sustained C-peptide outcome. The ITN will lead and partner with efforts to monitor and maintain regulatory T cell function in the context of T1D intervention trials, and will compare T cell phenotypes and profiles in responder cohorts from multiple trials, partnering with other consortia and investigators. The ITN will continue to support biomarker validation in the context of our clinical trials. Specific mechanistic study objectives include:

- Development of a biomarker index for regulatory/effector T cell phenotypes that correlate with retention of C-peptide levels
- Monitoring autoreactive (islet-specific) T cell responses, linking repertoire and function
- Standardization of multiparameter flow assessment of T1D-associated signaling pathways in hematopoietic cells
- Evaluation of systems biology approaches to profile therapeutic response markers in peripheral blood
- Collaboration with other groups to support biomarker efforts (e.g., proinsulin, C-peptide ratios, methylated promoter assays, miRNA assays, etc.)

The ITN will share expertise in T1D mechanistic assays with other investigators and consortia, and collaborate on standardization and next-generation assay development. When other T1D trials are consistent with ITN scientific objectives, we will partner with mechanistic protocol development, and offer ITN assay capabilities and data management tools to other organizations.

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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For questions or information about partnering with the ITN, contact Philip Bernstein, Executive Director of Strategic Review and Planning at **pbernstein@immunetolerance.org**.