

## 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 elements of the autoimmune response. The ITN will address this challenge by focusing therapeutic efforts on strategically designed combinations of different targeted agents based on immune mechanistic rationale.

These therapeutic opportunities will emerge from understanding immune mechanisms at the intersection of (i) T1D pathogenesis and (ii) specific targeted intervention, using in-depth immune profiling of subjects in previous T1D trials, new mechanism-focused clinical studies, and collaboration with other consortia and research groups.

## Strategy

Objective	Method	Candidates	Approach
<b>Effector T cell depletion</b>	Assess safety, specificity, and efficacy of novel biologics derived from other disease applications	<ul style="list-style-type: none"> <li>&gt; Anti-CD38</li> <li>&gt; Anti-SLAMF7</li> <li>&gt; Anti-CXCR3</li> <li>&gt; LFA3-Ig</li> <li>&gt; ATG</li> </ul>	Collaborate with industry partners to accelerate mechanistic studies of these agents in autoimmune disease trials
<b>Effector T cell deviation</b>	Assess durability of T cell exhaustion induced by targeted therapy	<ul style="list-style-type: none"> <li>&gt; Teplizumab</li> <li>&gt; LFA3-Ig</li> <li>&gt; ATG</li> <li>&gt; PD1 agonist</li> </ul>	Validate exhaustion markers correlating with metabolic outcome
<b>Enhance regulatory T cells</b>	Assess antigen-specific regulation following immune intervention	<ul style="list-style-type: none"> <li>&gt; IL2 muteins</li> <li>&gt; Tocilizumab</li> </ul>	Implement monitoring tools in mechanism-based studies of autoimmune trials

Objective	Method	Candidates	Approach
<b>Consolidate remission</b>	Add regulatory strategies to effector depletion/deviation strategies	<ul style="list-style-type: none"> <li>&gt; Teplizumab + anti-IL7R</li> <li>&gt; LFA3-Ig + tocilizumab</li> <li>&gt; Teplizumab + tocilizumab</li> </ul>	Address regulatory and safety issues in staged trial design
<b>Explore alternative induction pathways</b>	Build upon transplant and cancer experience with pathway-specific targets	<ul style="list-style-type: none"> <li>&gt; Anti-CD40L</li> <li>&gt; PD1-agonist</li> </ul>	Design small proof-of-concept trials in islet transplantation or recent-onset T1D
<b>Explore tolerogenic antigen delivery</b>	Assess safety and immunologic activity of novel antigen-based therapeutics	<ul style="list-style-type: none"> <li>&gt; PLGA particles</li> <li>&gt; RBC particles</li> <li>&gt; Nanoparticles</li> <li>&gt; LSEC targeting</li> </ul>	Design small proof-of-concept trials in established T1D
<b>Build a biomarker profile of response</b>	Identify and validate immune phenotypes and genetic markers that correlate with c-peptide outcomes	<ul style="list-style-type: none"> <li>&gt; WB transcriptome</li> <li>&gt; Single-cell transcripts</li> <li>&gt; Multiparameter flow cytometry</li> <li>&gt; Epigenetic signatures</li> </ul>	Implement mechanistic studies and harmonize data analysis across T1D trials

## Implementation

The ITN will prioritize studies in recent-onset T1D that interrupt effector cell activity, utilizing agents that induce immunomodulation and regulation to achieve durable preservation of beta cell function. Priority will be given to combination therapies based on feasibility, mechanistic rationale, and those that are guided by a set of mechanistically oriented clinical studies. All trials will use optimized immune monitoring strategies, largely based on prior studies, to define phenotypes associated with successful outcome. “Antigen-plus” trials incorporating the therapeutic use of an antigen with immunomodulators, is a strategy we will continue to explore with the understanding that such a strategy will be dependent upon safety and commercial availability of therapeutic antigen.

The ITN will also explore novel trial designs to better understand the pharmacodynamics of immune modulators based on the analysis of prior trials suggesting that successful response to immunotherapy could be improved with more personalized dosing regimens. Such trials are best explored in small, mechanism-based clinical studies that utilize adaptive designs and are paired with state of the art immune monitoring and novel techniques to assess disease progression such as pancreatic imaging. Although these types of designs add complexity, they potentially accelerate early phase clinical research.

We will emphasize mechanistic 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 monitor regulatory T cell parameters 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. As we continue to incorporate new multidimensional molecular and cellular approaches, advanced bioinformatics strategies will be developed and incorporated into trial designs. The ITN will continue to support biomarker validation in the context of our clinical trials and will partner with other groups to systematically mine existing datasets to identify novel targets for immune modulation.

Through TrialShare and via strong collaborative partnerships with JDRF, Diabetes UK, and TrialNet, the ITN will share expertise in T1D mechanistic assays with other investigators and consortia, and collaborate on standardization and next-generation assay development, especially sample sparing approaches that are critical for our pediatric studies. 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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