

General Principles

While transplantation provides life-saving therapy for individuals with end-stage organ failure, long-term outcomes are suboptimal. This is in large part due to inadequate efficacy of immunosuppressive regimens, medication toxicities, and immune compromise. Our core clinical hypothesis is that the ability to safely and reliably induce robust and durable tolerance will improve graft and patient outcomes after transplantation by optimizing long-term allograft function without incurring the toxicities associated with current regimens of generalized and lifelong immunosuppression.

While progress has been made, to date, tolerance across MHC barriers has been achieved in limited numbers of patients. Studies by the ITN and other groups, in both induced and spontaneous tolerance, have shown roles for deletion and regulation as mechanisms of tolerance, and have pointed to T cell exhaustion and transitional B cells as potential biomarkers. The ITN will conduct studies that seek to extend these findings, improve the safety of tolerance protocols, broaden their applicability to more patients, and refine the use of biomarkers to guide drug withdrawal. Study populations may include:

- De novo transplant candidates or recipients
- Patients with functioning transplants
- Highly sensitized transplant candidates

The central mechanistic premise underpinning the ITN transplant tolerance strategy is that the induction and maintenance of transplant tolerance, as is the case for self-tolerance, will require the engagement of multiple immunologic mechanisms. In the T cell compartment these include:

- Clonal deletion to achieve a low precursor frequency of high-avidity donor-reactive T cells (naive and memory)
- Checkpoint control (e.g. CTLA-4, PD-1 dependent mechanisms)
- Specific regulation to control residual lower-avidity donor-reactive T cells

In the case of deleterious specific humoral immunity, targets may include: memory B cells, plasma cells, regulatory B cells, and/or follicular helper T cells.

Strategy

Based on accumulated experience, our current working hypothesis is that multi-modal regimens that target more than one immunologic pathway will be required to provide broadly applicable transplant tolerance. Drawing from the multi-phase drug development paradigm, the ITN will employ a “road to tolerance” strategic framework for multi-step evaluation of concepts and components that may ultimately be combined in a multi-modal tolerance regimen.

The ITN will conduct interventional studies that explore selected individual immunologic mechanisms, such as deletion, exhaustion/senescence, and regulation as components of a roadmap to tolerance. Consideration of trial evaluation and potential next steps on the roadmap will guide prioritization. We will continue to emphasize studies that build upon our experience in liver and kidney while exploring emerging opportunities in other organ transplantation, including islet and vascular composite allograft.

The ITN seeks to partner with other research consortia and industry, and is open to concept proposals from the scientific community in the pursuit of the ITN clinical and mechanistic objectives.

Clinical Objectives

We will use our guiding principles and strategy to develop a roadmap for the design and conduct of trials to achieve robust and durable tolerance to an allograft, i.e., clinical, laboratory, and histological evidence of normal and/or stable allograft function, in the absence of generalized immunosuppression with concurrent immunocompetence to non-donor antigens.

Our approach is to test therapeutic interventions that target individual immunologic pathways at both clinical and mechanistic levels to determine which combination therapies will allow robust and durable transplantation tolerance. The ITN recognizes that an initial pilot study may not permit full drug withdrawal (although an immunologic alteration; i.e. deletion, regulation, etc., would be achieved and measurable), but would provide strong rationale to allow for full drug withdrawal when combined with an additional intervention in a follow-up study.

Mechanistic Objectives

ITN is committed to the development of robust and reproducible mechanistic assays as well as baseline and longitudinal biomarkers to guide:

- Candidate selection and stratification (e.g. permissive, resistant, high risk)
 - Regimen composition and/or intensity
 - Immunotherapeutic management
 - Identification of new targets
 - Design of new regimens
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In addition to global assessment of immunologic/inflammatory state (e.g. peripheral blood flow cytometry, transcriptome, metagenome, and proteome), we will explore integrated analysis and predictive modeling of high-throughput, high-dimensional single cell data (flow, transcript, repertoire, and epigenetics) that has shown promise in adjacent fields (e.g. autoimmunity, bone marrow transplantation, and cancer). Finally, we are committed to developing, evaluating, and standardizing assays to assess the strength and character of donor-specific T and B cell immunity within the ITN and in partnership with consortia and investigators from the community. New opportunities to track allospecific T cell responses, using cellular activation markers and TCR sequencing for detection of oligoclonal expansions, will form the framework for ITN's efforts to develop translational tools. Ideally, these assays will be useful as surrogate endpoints for monitoring the pathway to tolerance.

Examples of interventions could include (but are not limited to)

Initial induction steps could include

- Testing newly available therapeutic reagents that target specific cellular populations or mechanisms with good preclinical rationale for allospecific cell depletion
- Co-stimulatory blockade, especially in the presence of donor-specific tissue antigen
- Novel therapeutic approaches to induce B cell tolerance in patients who are donor-sensitized to induce (or prevent) de-sensitization

Second regulatory steps could include

- Exploring the potency and efficacy of different cell preparations (donor-specific anergic T cells, regulatory macrophages, regulatory dendritic cells, and others)
- Using combinations of pharmacologic and cellular approaches to promote regulation

Additional steps towards tolerance could include

- Post-transplant conditioning; i.e., designing tolerance induction protocols compatible with deceased donor organ transplantation
- Examining the role of innate immunity and inflammation in transplant tolerance cell therapies (Treg, donor cells [or antigens], targeting costimulation, co-inhibition, and cytokines)

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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