

## General Principles

The ability to safely and reliably induce robust and durable tolerance should 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. Tolerance across MHC barriers has been achieved in limited numbers of patients using bone marrow transplantation and chimerism. 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.

## Strategy

The ITN will prioritize interventional studies that explore selected strategies for safely and reliably inducing robust and durable transplantation tolerance via a combination of deletion of alloreactive cells and promotion of antigen-specific regulatory cells. We will prioritize those studies that build upon our experience in liver and kidney transplantation. The accompanying mechanistic portfolio will focus on elucidating the potency, specificity, and adaptability of various approaches to transplantation tolerance that are being tested, as well as identifying biomarkers that predict or diagnose tolerance. The ITN will actively and strategically partner with other research consortia to better understand the pre-clinical pipeline and expand our clinical and our mechanistic reach.

## Clinical Objectives

Our primary goal is 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 will build upon established clinical observations and well-supported mechanistic hypotheses, prioritizing clinical trials of liver and kidney transplantation.

### Underlying Hypotheses and Concepts:

- Identification of stable, spontaneously tolerant renal transplant patients will allow us to identify biomarkers of tolerance which, when coupled with markers of rejection, will increase the safety and success of future trials of immunosuppression withdrawal in transplant recipients
- Although transient (14 days) mixed chimerism resulted in sustained normal renal allograft function in the absence of immunosuppression, late allograft biopsy findings were abnormal, suggesting that more sustained mixed, or full, chimerism may be necessary to achieve tolerance
- Sustained systemic antigen delivery utilizing novel approaches to antigen presentation in the context of immunodepletion will lead to renal allograft tolerance
- Immunosuppression withdrawal for adult and pediatric liver transplant recipients can elucidate mechanisms by which tolerance is established and/or maintained and thereby guide the design of novel tolerance induction therapies

#### Underlying Hypotheses and Concepts (continued):

- Administration of sufficient regulatory T cells to achieve a favorable ratio of T regulatory cells to T effector cells will favor the development of tolerance
- Renal allograft tolerance is associated with a B cell gene/FACS signature characterized by increased transitional B cells
- Liver allograft tolerance is associated with immune exhaustion/senescence of antigen reactive T cells
- Tolerance is associated with at least partial deletion of donor reactive T cells
- Non-deleted donor reactive cells are controlled by Tregs in tolerant patients
- Tolerance is associated with loss of indirect alloresponses

Priority will be given to those clinical studies that are designed to explore these mechanistic hypotheses, including:

- Post-transplant tolerance conditioning; i.e., designing tolerance induction protocols compatible with deceased donor organ transplantation
- Examination of the effects of differing conditioning protocols on the variability of surviving HSCs in combined HSC-solid organ transplant protocols
- Combinations of pharmacologic and cellular approaches to promote regulation, e.g., low-dose IL-2 (or IL-2R agonists) plus antigen-specific Tregs
- Exploration of the potency and efficacy of different cell preparations (donor-specific anergic T cells, regulatory macrophages, regulatory dendritic cells, and others) in combination with depletion and/or “tolerogenic” immunosuppression regimens to induce tolerance
- Examination of the role of innate immunity and inflammation in transplant tolerance
- Partnerships with other organizations for the development of tolerance trials in other (than liver and kidney) organs and tissues
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- Partnering with other organizations for the development of tolerance trials in other (than liver and kidney) organs and tissues

## Mechanistic Objectives

Specific mechanistic study concepts include:

- Derivation of mechanistic surrogates for tolerance endpoints that can support innovative trial designs and facilitate efficient trial execution (may cross disease boundaries)
- Delineation of peripheral blood or allograft tissue biomarkers predictive or diagnostic of allograft tolerance and/or absence of tolerance – these biomarkers may also serve to guide new therapeutic approaches
- Harmonization of sample collection across trials to allow for better biomarker validation
- Development of robust assays to identify donor-specific hyporesponsiveness or regulation
- Development of assays to identify and track donor-reactive T cells

**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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