Immune Tolerance Network

Strategic Plan: Autoimmunity

Goals and Objectives

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General Principles

The autoimmune therapeutic area represents a broad category of human disease that involves a variety of organ targets and thus presents a significant challenge with respect to the development of therapies designed to re-establish self-tolerance. These syndromes include conditions in which autoimmunity is clearly implicated as causal, in light of identification of autoantibodies to relevant autoantigens; diseases suspected to be autoimmune because of the presence of autoantibodies, although the autoreactive response has not been proven to be pathogenic and could be a consequence or marker of tissue damage; and other diseases often considered to be "autoimmune," such as psoriasis or inflammatory bowel disease, characterized by organ-targeted inflammation but without evidence of a stimulating autoantigen. In the latter, the term autoinflammatory has been applied as opposed to autoimmunity.

Given the complex nature of these diseases, our approach will increasingly focus on specific mechanisms that build upon results from past trials, ultimately leading to the investigation of combinations of therapeutics that target more than one pathogenic pathway. Ultimately, successful approaches will allow deliberate withdrawal of immunosuppression with the possible exception of maintenance, low-dose, anti-inflammatory medication that sustains immune quiescence of the target organ(s).

The ITN is committed to working with other consortia, industry, and independent investigators in the development of our clinical and mechanistic objectives.

Strategy

The ITN will prioritize studies in a few selected autoimmune diseases, building on previous experience and diseases in which a relevant antigen that can be targeted and monitored, especially in diseases with accessible tissue. While we will continue to be proactive in areas where we have experience, we will also consider new diseases that present compelling opportunities.

Our goal is to conduct trials that evaluate combinations of agents that induce immune deviation and/or regulation while producing effector cell depletion or exhaustion, to achieve durable clinical remission of disease. To achieve this goal, the ITN will develop combination therapies as mechanistic-based studies in which the first agent in a sequential therapy is chosen to test a specific immune strategy (e.g. deletion, regulation, deviation) and a second agent is subsequently added that targets a complementary pathway, especially during immune reconstitution. In this way, we are defining tolerance as a multi-step pathway where each step is assessed independently as to achieving a pre-defined mechanistic effect, and where each step is a necessary part of a combination that has good rationale for tolerance. The ITN recognizes that a single (first) agent may not have clinical efficacy, although an immunologic alteration (i.e. deletion, regulation, etc.) would be achieved and measurable. It would, however, result in a therapeutic effect when combined with the second agent.

Clinical Objectives

Priority will be given to trials that target multiple pathogenic mechanisms such as those that treat disease activity (e.g. deletion) and others that induce and maintain disease quiescence (e.g. regulation). These could include therapeutics that target pathogenic lymphocytes, cytokines, chemokines, and regulatory cells; antigen-specific approaches where available will be prioritized. To this end, trials in the following categories will be developed, particularly in combination (sequential) approaches. While sequential therapy trials are our primary objective, pilot studies will be implemented to facilitate development in a step-wise manner:

Induction

- Effector cell depletion or deviation, followed by co-stimulatory blockade while preserving regulatory pathways
- Effector cell depletion or deviation, plus anti-cytokine agents to block re-emerging pathogenic profiles while preserving regulatory pathways
- Blocking pathogenic cytokines, followed by co-stimulatory blockade, in which the induction agent has either been previously been successful at ameliorating disease or has a demonstrated tolerogenic immunological effect

Regulation

- Regulatory T cell enhancement or replacement with agents designed to stabilize a regulatory profile
- Regulatory B cell enhancement or replacement with agents designed to stabilize a regulatory profile

Novel antigen-specific approaches

- tolerogenic vaccines
- nanoparticles, etc.

Development of **effective novel approaches to autoimmune diseases** that currently lack effective treatment

Successful implementation of **combination approaches to systemic autoimmune diseases**, such as SLE, that lead to durable remission of organ-threatening manifestations, especially lupus nephritis.

Mechanistic Objectives

Because different tissue antigens are targeted in different diseases, and some conditions target a diverse array of autoantigens, it is challenging to develop biomarkers of tolerance in autoimmune disease. The ITN attempts to address these challenges through a coordinated program of clinical trials that are aimed at establishing a mechanistic proof-of-principle in diseases such that an immunologic effect can be correlated with a change in disease status or a surrogate response.

The overall objective is to define molecular predictors and correlates of durable clinical remission and the development of new biomarkers of immune tolerance and regulation that will reliably guide clinical decisions to taper immunosuppressive medications.

The following will be prioritized:

- Development of gene expression profiles integrated with epigenetic analysis of immune cell subsets associated with disease compared to those associated with durable remission, to define molecular profiles of active autoimmunity versus successful tolerance induction
- Discovery and validation of biomarkers that correlate with treatment and clinical remission and guide successful discontinuation of immunosuppression
- Assays designed to assess disease heterogeneity to better inform patient stratification when testing specific mechanisms of tolerance
- Assessment of immunocompetence in the context of withdrawal from immunotherapy
- Enumeration and molecular profiling of autoreactive T and B cells
- Longitudinal analysis of accessible target organs using histological and gene expression analysis techniques, to define a molecular profile of organ-specific tolerance
- Development of single cell analyses in cryopreserved target tissue
- Novel assessments of the human microbiome will be incorporated into our assessment of patient therapies

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****,*
Director of Strategic Review and Planning, at ***pbernstein@immunetolerance.org****.*

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