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 presentations that involve 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.

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. The ITN's approach to tolerance in autoimmune diseases attempts to address these challenges through a coordinated program of clinical studies aimed at establishing a mechanistic proof-of-principle in diseases where a self-antigen has been identified and/or where the target organ is accessible for serial sampling and mechanistic study.

Given the complex nature of these diseases, our approach will be increasingly focused on specific mechanisms that build upon results from past and ongoing trials by investigating combinations of therapeutics that target more than one pathogenic pathway. 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).

Strategy

The ITN will prioritize studies in a few selected autoimmune diseases, building on previous experience (e.g., systemic lupus erythematosus, ANCA-associated vasculitis, psoriasis, multiple sclerosis), prioritizing diseases with a relevant antigen (whether self or microbial in origin) that can be targeted and monitored (e.g., pemphigus, MS, ANCA-associated vasculitis), and/or diseases with accessible tissue (e.g., psoriasis, inflammatory bowel disease, pemphigus, scleroderma). Priority will be given to studies that evaluate combinations of agents that induce immune deviation and/or regulation, produce effector cell depletion or exhaustion, to achieve durable clinical remission of disease. For antigen induced tolerance to be effective, combination therapies may also include an anti-inflammatory drug to create the appropriate environment for sustained suppression of autoimmunity.

Clinical Objectives

Trials will be prioritized in the following categories:

- Effector cell depletion or deviation, followed by co-stimulatory blockade – priority will be given to Treg-sparing strategies
- 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 ameliorating disease
- 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

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.

- Development of gene expression profiles integrated with epigenetic analysis of pathogenic and regulatory T cell subsets, to define molecular profiles of active autoimmunity versus successful tolerance induction
- Validation of biomarkers that correlate with clinical remission and guide successful discontinuation of immunosuppression
- Validation of B cell assays that quantitatively measure pathogenic autoreactivity
- Measurement of self-antigen reactive T-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 the target tissue

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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