

## IMMUNE TOLERANCE

The successful induction of immune tolerance is a major therapeutic goal for the treatment of many immune-mediated diseases, including autoimmune disorders such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis; asthma and allergic diseases; and to preventing rejection of transplanted solid organs, tissues, and cells.

Tolerance-induction approaches seek to selectively block harmful immune responses. For example, in transplantation, donor-specific immune tolerance—a selective blockade of immune responses directed against the graft—would enable long-term graft survival without the complications and risks of infection, malignancy, and atherosclerosis associated with systemic immunosuppressive therapy. In asthma and allergic diseases, the goal of tolerance research is to develop methods to block allergic immune responses to allergens, such as cockroach and house dust mite, that cause or exacerbate these diseases. In autoimmune diseases, tolerance-induction approaches seek to block those immune responses that cause the body to mistakenly attack its own organs, tissues, or cells. Two decades of intensive basic research in immunology have provided a solid foundation of knowledge and understanding that will enable the application of promising tolerance-induction strategies to the treatment of human disease.

NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) supports basic research to elucidate mechanisms responsible for immune tolerance, translational research to facilitate the application of immune-tolerance approaches to human diseases, and clinical research to evaluate novel therapeutic

approaches to induce and maintain immune tolerance. New approaches are being investigated to accomplish the following:

- Improve understanding of the molecular mechanisms responsible for the induction and maintenance of immune tolerance;
- Replace or improve suboptimal treatment protocols for immune-mediated diseases;
- Discover methods to prevent or reverse immune-mediated disorders for which no effective therapies are currently available;
- Create an efficient research infrastructure for the development and rapid testing of tolerogenic agents in human immune-mediated diseases; and
- Clarify mechanisms by which tolerogenic agents suppress disease.

With co-sponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International, NIAID supports the Immune Tolerance Network (ITN). ITN is an international consortium of more than 80 investigators in the United States, Canada, and Europe, dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and to preventing rejection of transplanted organs, tissues, and cells. The goal of these therapies is to “re-educate” the immune system to eliminate injurious immune responses and graft rejection while preserving protective responses to infectious agents. ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The ITN has 18

approved clinical protocols, a variety of state-of-the-art core facilities, and several additional studies of the immune mechanisms that lead to development, maintenance, or loss of clinical tolerance. Currently, ITN supports seven clinical trials in solid organ and islet transplantation and two cohort studies to understand the immune mechanisms involved in the acquisition of spontaneous tolerance to organ grafts.

ITN is currently involved in the following areas of clinical research:

- Allergy
- Asthma
- Diabetes
- Islet cell, kidney, and liver transplantation
- Bone marrow transplantation
- Multiple sclerosis (MS)
- Psoriatic arthritis
- Systemic lupus erythematosus

Examples of active ITN clinical research studies include the following:

- A phase II placebo-controlled trial will evaluate the safety and efficacy of a treatment for ragweed allergy that involves omalizumab, an anti-IgE antibody, and immunotherapy. A follow-up study will examine whether persistent immunologic and clinical tolerance has been achieved.
- A phase I trial will analyze and monitor the safety of human insulin B chain peptide in subjects with type 1 diabetes.
- A phase I study will assess the safety of one dose of CTLA4-IgG4m, an immunosuppressive biologic, in patients with relapsing-remitting MS. This open-

label, dose-escalation safety study will include 24 subjects enrolled over a period of approximately 18 months.

- A phase II trial will assess the safety, tolerability, and immunogenicity of a subcutaneously administered chemical conjugate of *Amb a 1* (the major allergen of ragweed pollen) and immunostimulatory oligonucleotide sequences of (unmethylated) DNA in ragweed-allergic adults. This Dynavax product is a DNA vaccine.
- A phase II trial, multicenter study will evaluate the lipid-lowering drug atorvastatin in patients at high risk of developing MS.

As clinical therapies for inducing tolerance move forward, it is essential to develop “tolerance assays”—tests and procedures to monitor patient response and their ability to maintain a tolerogenic state. ITN has established a set of core laboratories to develop diagnostic assays for the induction, maintenance, and loss of tolerance. These core facilities include microarray analyses of gene expression, bioinformatics approaches to develop analytic tools for clinical and scientific data sets from the ITN-sponsored trials, enzyme-linked immunospot (ELISPOT) assay analyses of protein expression, and cellular assays for T cell reactivity.

Examples of current ITN mechanistic assays include the following:

- Development of antigen-specific assays for donor-specific tolerance in renal transplant recipients;
- Cytokine production in children with preclinical and clinical type 1 diabetes; and

- Identification and mechanistic investigations of tolerant kidney transplant patients.

More information on ITN's mission and research is available at [www.immunetolerance.org](http://www.immunetolerance.org).

In collaboration with NIDDK, DAIT supports the Non-Human Primate Immune Tolerance Cooperative Study Group. The goal of this program is to evaluate the safety and efficacy of novel tolerogenic regimens in preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet

allograft recipients. In fiscal year 2002, this program was renewed and several new research centers were added, which will allow a larger number of tolerance-induction strategies to be rigorously evaluated. To accelerate the research conducted through this program, DAIT supports breeding colonies of rhesus and cynomolgus macaques.

Other DAIT-supported research programs that include studies on immune tolerance are the Autoimmunity Centers of Excellence, the Human Immunology Centers of Excellence, Innovative Grants on Immune Tolerance, and program projects in basic biology, basic immunology, and transplantation tolerance.