AUTOIMMUNE DISEASES

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the U.S. population and disproportionately afflict women. Autoimmune diseases can be divided into two main groups: organ-specific and nonorgan-specific diseases. Organ-specific diseases are characterized by immune reactions and tissue damage localized to a single organ or tissue. Examples include type 1 diabetes and multiple sclerosis, where the primary lesions are localized in the pancreas and the central nervous system, respectively. Nonorgan-specific diseases, such as systemic lupus erythematosus (SLE), are characterized by immune reactivity against antigens distributed throughout the body, resulting in widespread damage.

NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease.

Congressional interest in autoimmune diseases was expressed in both House and Senate fiscal year 1998 Appropriations Committee Reports, encouraging the establishment of an NIH Autoimmune Diseases Coordinating Committee (ADCC). The ADCC was established in June 1998 under the direction of NIAID. Committee members include representatives of 17 NIH Institutes, Centers, and Offices, the Food and Drug Administration, Department of Veterans Affairs, Centers for Disease Control and Prevention, and private organizations that support research in this area. The ADCC facilitates maximum coordination among groups working in areas of complementary and shared interests. The ADCC Autoimmune Diseases Research Plan, which was mandated by the Children's Health Act of 2000 (Public Law 106-310), was presented to Congress in late 2002. The research plan is located at *www.niaid.nih.gov/dait/pdf/ADCC_Report.pdf.*

DAIT supports several multicenter research programs on autoimmune diseases. The Autoimmunity Centers of Excellence (ACEs) support collaborative basic and clinical research on autoimmune diseases, including single-site and multi-site pilot clinical trials of immunomodulatory therapies. This program was recently expanded to nine centers. Clinical trials are under way or in development for SLE, multiple sclerosis, Sjögren's syndrome, and other autoimmune diseases. In addition, collaborations among ACE investigators will address the immune mechanisms underlying the agents evaluated in these trials.

With co-sponsorship from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International (JDRF), NIAID supports the Immune Tolerance Network (ITN). ITN is an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in 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 immunity against infectious agents. The 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. Since its inception, the ITN has initiated more than 15 clinical protocols, a variety of state-of-the-art core facilities, and about 5 additional studies designed to explore immune mechanisms leading to the development, maintenance, or loss of clinical tolerance. Currently, the 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. More information on the ITN is available on its Web site at *www.immunetolerance.org.*

NIAID, in collaboration with NIDDK and the National Institute of Child Health and Human Development, supported the Diabetes Prevention Trial Type 1, a multi-site cooperative clinical trial for prevention of type 1 diabetes in first-degree relatives of patients with type 1 diabetes. This is the first large nationwide trial of an immunomodulatory agent for the prevention of an autoimmune disease. The arm of this trial enrolling high-risk subjects ended early with no evidence that intervention with low-dose parenteral insulin prevented the development of disease. The intermediate-risk arm, which tested the effectiveness of oral insulin to prevent the development of disease, ended in 2003, and there was no clinically significant outcome observed. These subjects will continue to be followed in the Natural History Study of TrialNet. Other studies aimed at preventing individuals from developing diabetes are under way.

Through the Stem Cell Transplantation for Autoimmune Diseases Consortium, DAIT is developing clinical trials to evaluate the safety and efficacy of hematopoietic stem cell transplantation as a treatment for several severe autoimmune diseases, including multiple sclerosis, SLE, and scleroderma. Trials involving subjects with SLE and scleroderma are expected to begin in 2004. In addition to the clinical trials, studies of the underlying mechanisms of autoimmune diseases will be performed.

DAIT supports two genetics research resources. The Multiple Autoimmune Disease Genetics Consortium collects clinical data and genetic material from families in which at least two individuals are afflicted by two or more autoimmune diseases. The data and samples will be made available to researchers studying the genetics of susceptibility or resistance to autoimmune diseases. More information can be found at *www.madgc.org.* DAIT, in collaboration with the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation, supports the North American Rheumatoid Arthritis Consortium (NARAC). NARAC collects clinical data and genetic material from families with rheumatoid arthritis. These data are made available to investigators to facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis. More information can be found at *www.naracdata.org.*

NIAID, with co-sponsorship from the National Cancer Institute, NIDDK, and JDRF, continues to support the International Histocompatibility Working Group (IHWG), a network of more than 200 laboratories in more than 70 countries that collects and shares data on genes of the human leukocyte antigen (HLA) complex. The IHWG studies five diseases for which the HLA associations have been well characterized, including type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy. In addition, NIAID supports a project within the IHWG to discover single nucleotide polymorphisms (SNPs) in immune response genes. These variations may account for the increased susceptibility of certain individuals or groups to immune-mediated diseases. To date, SNP data have been gathered for more than 100 immune-related genes.

Although considerable understanding of the immune mechanisms that mediate tissue injury in autoimmune diseases has been gained, much remains to be learned about the causes of these diseases, the underlying genetic susceptibility, the regulation of T cells and autoantibody production, and the characterization of the cells and chemical mediators of inflammation. NIAID is committed to advancing understanding of the immunopathogenesis of autoimmune diseases and to promoting the application of basic research to clinical investigations, which may result in the development of more effective therapeutic approaches and prevention strategies for these devastating diseases.