EDITORIAL

The Immune Tolerance Network—An NIH/JDF-Supported Initiative to Bring Tolerance Research into the Clinic: A Major New Resource for Clinical Immunologists

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The prevalence of immune-mediated diseases in the United States, and indeed, around the world, is a significant health care problem that requires an aggressive and innovative approach to the development of new treatment solutions. Immune-mediated diseases include a broad spectrum of autoimmune diseases, such as rheumatoid arthritis, diabetes mellitus, lupus, and multiple sclerosis, as well as conditions in which excessive reactivity to exogenous agents causes asthma and various allergic diseases. These diseases affect tens of millions of Americans and result in annual medical and other indirect costs of over $100 billion. Furthermore, immune-mediated graft rejection impacts over 20,000 Americans suffering from nonimmunologic diseases who receive organ transplants each year.

Over the past 40 years, improved results in the treatment of immune-mediated diseases have been achieved primarily through the development of increasingly potent nonspecific immunosuppressive drugs that inhibit immune responses. Immunotherapies, such as steroids, cyclosporin A, and pan-reactive monoclonal antibodies have met with a degree of clinical success in treating conditions such as acute immune rejection of organ transplants and severe autoimmune diseases. However, such therapies require life-long usage and nonspecifically suppress the entire immune system, exposing patients to considerably higher risks of infection. Additionally, many of these therapies increase the risk of cancer. Thus, a major goal for treatment of immune disorders is the induction of immune tolerance—selective short-term immunotherapy targeted at eliminating only the pathogenic immune response while preserving normal, beneficial immune function. The advances in the development of tolerogenic strategies in clinical transplantation have been fueled by extensive basic research advances that have increased our conceptual understanding of the mechanisms operative in the induction of tolerance and restoration of self-tolerance. In addition, multiple preclinical studies have demonstrated the efficacy of unique and selective tolerogenic strategies.

In the past year, these developments have culminated in the development of a new initiative—the Immune Tolerance Network (ITN). Officially begun on September 30, 1999, the ITN is funded by the National Institute of Allergy and Infectious Disease, in cooperation with the National Institute for Diabetes and Digestive and Kidney Disease and the Juvenile Diabetes Foundation International. The ITN’s mandate is to initiate and oversee human clinical trials of new therapies aimed at producing stable, long-term immune tolerance in a number of disease settings. The ITN is designed to solicit and support the best ideas from any and all investigators both in the United States and throughout the world. As an integral part of clinical trials, the ITN will investigate the mechanisms of immune tolerance in order to develop and validate immune and surrogate marker assays to monitor the induction, maintenance, and loss of clinical tolerance in humans. The network will focus on a broad range of immune-related conditions, including islet transplantation, kidney transplantation, and autoimmune diseases such as rheumatoid arthritis, diabetes, lupus, multiple sclerosis, and others. The effort has recently expanded to include the study of asthma and other allergic conditions.

The ITN’s primary focus is supporting proposals for Phase I, II and potentially III trials of novel therapies that have a strong biological basis for inducing tolerance and for which preclinical investigation is complete with encouraging results. Of particular interest are trials combining existing agents that have not yet been tested together. Additional proposals for studies involving assays of immune tolerance are also examined to complement the clinical portion of the research. Partnerships with industry are encouraged and can be forged to support clinical studies in all phases of development.
The ITN is led by a steering committee of over 70 world leaders in immune tolerance and immune-mediated disease. Research is carried out under the auspices of several subgroups, each charged with overseeing clinical and mechanistic investigations in the targeted disease areas.

Islet Transplantation

The ITN will investigate novel strategies aimed at creating and maintaining long-term tolerance to transplanted islet cells. The goal of the program is the restoration of normal insulin production in Type I diabetes patients, without the need for long-term immunosuppressive therapy. A key issue in this regard is finding ways to alleviate both the alloimmune response and the ongoing autoimmune response in these affected individuals. The Islet Transplantation Clinical Subgroup is cochaired by Drs. Camillo Ricordi and Bernhard Hering. Camillo Ricordi, M.D., is the Scientific Director and Chief Academic Officer of the Diabetes Research Institute at the University of Miami and is president-elect of the International Association on Pancreas and Islet Transplantation. He developed the Ricordi method of islet isolation, in use worldwide by centers performing islet transplantation. He also studies the use of infusions of hematopoietic cells to induce tolerance of transplanted solid organs. Cochair Bernhard J. Hering, M.D., is an assistant professor of surgery and medicine and associate director of the Diabetes Institute for Immunology and Transplantation at the University of Minnesota in Minneapolis. He has extensive experience in islet transplantation and is a leader in clinical testing of new immunosuppressive agents used to prevent islet rejection.

Kidney Transplantation

The ITN’s clinical objectives in renal transplantation are closely related to those in islet transplantation. In addition, the network will test potential tolerance induction strategies against the backdrop of a maintenance immunosuppression that does not include calcineurin inhibitors. Combination drug therapies, including the use of hematopoietic stem cell chimerization, will be supported. The Kidney Transplantation Clinical Subgroup is cochaired by Dr. Christian Larsen and J. Richard Thistlethwaite, M.D., Ph.D. Christian P. Larsen, M.D., Ph.D., is an associate professor of surgery and chief of the Division of Transplantation at Emory University School of Medicine in Atlanta, Georgia. His research focuses on the pivotal role of activated T cells in the rejection of transplanted tissues and the role of co-stimulatory pathways in this process. J. Richard Thistlethwaite is a professor of surgery at the University of Chicago. He has considerable experience in transplantation of the liver, kidney, and pancreas and in laboratory and clinical studies of graft rejection and of new immunosuppressive agents.

Autoimmune Diseases

The ITN will conduct clinical trials and mechanistic studies aimed at alleviating the autoimmune responses that characterize these diseases. The disease entities studied will include systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Type I diabetes, as well as other autoimmune diseases. The Autoimmune Disease Clinical Subgroup is cochaired by David A. Hafler, M.D., and C. Garrison Fathman, M.D. Dr. Hafler is a professor of neurology (neurobiology) at Harvard Medical School and a leader in the study of human autoimmune diseases, including multiple sclerosis, Type I diabetes, and rheumatoid arthritis. His research focuses on the identification of cell surface antigens that serve as targets for autoreactive T cells. Cochair Dr. Fathman is a professor of medicine, director of the Center for Clinical Immunology, and codivation chief of immunology and rheumatology at Stanford University School of Medicine. He studies the use of immunotherapies to treat autoimmune diseases, such as arthritis, multiple sclerosis, and IDDM, and is currently targeting delivery of regulatory cytokines using retroviral-mediated gene transfer in autoreactive T cells as the delivery vehicle in animal models of autoimmune disease.

Asthma and Allergy

The goal of the proposed immunologic interventions in allergy and asthma will be to ameliorate allergen-specific Th2-driven processes and replace these processes with allergen-specific, protective immune responses. Among the diseases falling under the research mandate of the Asthma and Allergic Diseases Subgroup are allergic rhinitis (seasonal and perennial) and allergic asthma. The subgroup is cochaired by Dale T. Umetsu, M.D., and Andrew Saxon, M.D. Dr. Umetsu is a professor of pediatrics, Chief of the Division of Allergy and Clinical Immunology, and Director of the Center for Asthma and Allergic Diseases at Stanford University School of Medicine. He has been a pioneer in the basic science and clinical testing of immunotherapies for allergic disease and is currently developing improved methods for allergen immunotherapy. Dr. Saxon is professor and chief of clinical immunology at UCLA and director of the UCLA Asthma, Allergy, and Immunologic Disease Center. He has played an important role in our understanding of the regulation of human IgE production and the impact of airborne pollutants on allergic inflammation.
Tolerance Assays

In each of the four disease areas, the Tolerance Assay Group (TAG) will support the clinical trials by (i) examining the mechanism(s) that create and maintain the tolerant state and (ii) developing a set of assays that will function as a roadmap to guide clinicians in their attempts to create and monitor immune tolerance in individual patients. The TAG oversees several core facilities and the standardization of assay protocols performed at local clinical centers. The Tolerance Assay Subgroup is chaired by Terry Strom, M.D. Dr. Strom is a professor of medicine at Harvard Medical School and director of the Division of Immunology at Beth Israel Deaconess Medical Center in Boston. His research interests include the mechanisms of tolerance, testing of strategies for attaining tolerance, and the development of markers, including gene expression, as measures of graft rejection and tolerance.

The ITN’s scientists and clinicians are committed to identifying the most promising clinical trials and tolerance assays for initial support. In this regard, the highest priority of the network is to remain an open and inclusive association of academic and industry scientists, clinicians, patients, and patient advocates. With a budget of approximately $144,000,000 over a 7-year period, the ITN has begun to support clinical research based at numerous hospitals and research facilities throughout the country and around the world—the network’s first trials will begin mid-2000. The ITN is also actively soliciting industry participation in these trials to strengthen its technological base and maximize the opportunities for successful clinical intervention.

The ITN remains an inclusive collaborative effort, generating new projects through investigator-initiated research proposals. The proposal submission and review process itself is a nontraditional, two-stage process, in which applicants are first asked to submit a brief (two-page) proposal over the ITN Web site. These proposals are subjected to an expedited peer review, with successful applicants asked to submit a more complete research proposal in the following months. In evaluating new research proposals, the network has placed a high priority on its ability to respond to late-breaking discoveries—complete review of all proposals takes approximately 3 months, allowing multiple funding cycles each year. Investigators with interesting ideas should visit the ITN Web site at www.immune-tolerance.org for complete guidelines on submitting proposals.

The ITN views its greatest strength as its people and its most potent weapons, its ideas. Whatever your interest in immune tolerance research, I therefore invite you to participate in this ground-breaking endeavor.