The Immune Tolerance Network: tolerance at the crossroads

Jeffrey A. Bluestone\(^1\) and Jeffrey Matthews\(^2\)

\(^1\)Immune Tolerance Network, University of California, San Francisco, 513 Parnassus Avenue, Box 0540—HSW Room 1114, San Francisco, CA 94143-0540, USA
\(^2\)Ben May Institute for Cancer Research, MC 1089, 5841 South Maryland Avenue, Chicago, IL 60637, USA

Immune tolerance therapies are designed to reprogramme immune cells in a highly specific fashion in order to eliminate pathogenic responses but preserve normal immune function. A concept that has tantalized immunologists for decades, tolerogenic therapies would replace current lifelong immunosuppressive regimens and their often debilitating side-effects with short-term immunosuppressive regimens and their often debilitating side-effects with short-term, effective cures. Significant advances have been made over the past decade that have provided a more detailed understanding of the molecular events associated with T-cell recognition and activation. Unprecedented opportunities to test these approaches in a variety of human diseases have now emerged. As a result of these advances, the Immune Tolerance Network (ITN), a group of 70 expert immunologists spanning multiple disciplines, has been created to identify and promote the use of tolerogenic therapies in the clinic. Using a unique interactive approach designed to speed the development of clinical tolerance therapies, the ITN is examining new and innovative therapeutic approaches and bioassays in a range of autoimmune diseases and transplantation settings, as well as asthma and allergies. This work has been funded by the National Institutes of Health (in collaboration with the Juvenile Diabetes Foundation International).

Keywords: tolerance; immunology; autoimmunity; transplantation; asthma; allergy

1. THE IMMUNE TOLERANCE NETWORK

Therapies that can induce durable and clinically stable immune tolerance have been the ‘holy grail’ of clinical transplantation for several decades. To date, however, clinical success in treating organ transplant rejection has been accomplished primarily through the development of increasingly potent non-specific immunosuppressive drugs to inhibit immune responses (e.g. European Mycophenolate Mofetil Cooperative Study Group 1995). These approaches require life-long treatment and non-specifically suppress the entire immune system, exposing patients to increased risks of infection and cancer. Moreover, long-term graft survival remains problematic using these therapies (Cecka 1996). Tolerance therapies, on the other hand, are selective short-term immunotherapies targeted towards eliminating only the pathogenic immune response, leaving beneficial functions untouched. Indeed, the need for more-effective tolerogenic treatments for immune-mediated diseases has never been greater as the incidences of autoimmune, allergic and asthmatic diseases have increased at alarming rates. Kidney, liver and heart transplantation have become routine surgical procedures limited only by the shortage of organs and the risk of graft rejection. Moreover, recent developments in islet transplantation for the treatment of brittle type I diabetes provide a unique opportunity for the evaluation of tolerance protocols in a comparatively low-risk human setting where both auto- and allogeneic immune processes dominate.

Our rapidly evolving understanding of the molecular events associated with T-cell recognition and activation are generating an unprecedented breadth of new approaches towards achieving tolerance. Advances in the development of tolerogenic strategies for transplantation have been fuelled by basic immunological discoveries that have helped to unroll the fundamental processes responsible for immune regulation. In fact, as many of the articles presented in this issue elegantly illustrate, we now understand many of the normal processes that regulate tolerance in transplantation. These processes are based on four mechanisms: clonal deletion, clonal inactivation, cytokine-dependent immune deviation and suppression (Zheng et al. 1999). Each operates to varying degrees in the generation and maintenance of tolerance, although their relative contribution may vary depending upon the nature of the antigen and the location in which ‘tolerization’ occurs. This unparalleled progress in our conceptual understanding of the mechanisms at work in the induction of tolerance and the restoration of self-tolerance has led to the development of some unique and selective immunomodulatory strategies. The demonstration of long-term kidney and islet allograft survival in non-human primates receiving anti-CD154 antibody monotherapy (Kirk et al., this issue; Kenyon et al. 2001), the new generation of anti-T-cell monoclonal antibodies (Friedel et al. 1999), the use of bone marrow transplantation to tolerize (Spitzer et al. 1999) and selective inhibition

*Author for correspondence (jbluest@immunology.uchicago.edu).
of the inflammatory subset of primed autoreactive effector T cells (Chatenoud et al., 1994, 1997) are just a few examples of the various modalities of inducing tolerance that may soon become available to the clinician.

It can be argued then, that we have reached a crossroads in the quest for clinical tolerance: a point where, upon our understanding of the inherent problems, our ability to intervene, our ambition and the clinical need may have finally met. It is in fact, an opportune moment for a bold and fresh approach to clinical tolerance research.

2. A NEW PARADIGM FOR TOLERANCE RESEARCH

Typically, there have been major challenges in translating the basic science and preclinical research advances in tolerance into the clinic. There is often resistance among funding agencies to support the very expensive early-stage clinical trials involved in translational research. Study sections often regard such proposals as ‘not hypothesis driven’ or deem them more appropriate for drug company funding. Companies are often unwilling to support the trials as the financial, regulatory or intellectual property considerations often mitigate moving forward. In some instances, combination therapies or treatments like bone marrow transplantation have great difficulty finding ways into the clinic. Thus, it is with a great deal of foresight, promise and funding (US$144 million), that the US National Institutes of Health, in conjunction with the Juvenile Diabetes Foundation, created ‘The Immune Tolerance Network’ (ITN). The primary mission of the ITN is to hasten the advance of the clinical application of new tolerogenic strategies in multiple immune-mediated diseases, ranging from transplantation and autoimmunity to allergy and asthma. In addition to seeking viable clinical applications in these diseases, the ITN is committed to correlate the clinical parameters of tolerance induction with the basic processes of immune regulation through a complementary mechanistic studies and bioassay research programme (figure 1).

We believe that this value-added approach, combining clinical assessment with mechanistic investigation, will provide a new platform for innovation and a new paradigm for tolerance research.

Clinical and tolerance assay research projects pursued by the ITN are derived primarily through a continuous investigator-initiated application process. In fact, to date, the majority of the applications received and funded by the ITN have come from independent investigators with no formal association with the ITN. The application process itself takes place in two stages, designed to streamline the peer-review process while not unnecessarily burdening applicants with a large volume of additional work. Concept proposals, the first stage of this process, are designed to identify ‘ideas’ that are of interest to the ITN, and may be submitted on-line through the ITN Web site at www.immunetolerance.org. The peer-review process developed by the ITN is, itself, non-traditional, maintaining a highly interactive flavour that seeks not simply to accept or reject a given proposal, but to work with investigators to develop a comprehensive research plan with the greatest chance of success. In ITN terms, success will be measured in terms of both clinical efficacy and knowledge gained regarding the bases of clinical tolerance induction.

The interactive nature of the ITN is also maintained throughout the protocol-development process. For tolerance researchers, collaboration with the ITN means more than just research funding. It means access to wide-ranging clinical expertise and patient populations; assistance in protocol development; access to emerging biological assays such as gene microarrays, major histocompatibility complex (MHC)-peptide multimers and sophisticated gene-expression analyses that might not otherwise be available to individual researchers; a direct interface with regulatory bodies and assistance in Investigational New Drug applications; the ability to prepare and store clinical samples for future use; and a wealth of scientific and administrative support. Initially, the ITN is primarily seeking proposals for phase I–II 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. The ITN works with the investigators to develop a set of integrated tolerance assays and mechanistic studies that complement the clinical portion of the research. The ITN also accepts applications for novel tolerance or biological assays that may be of either broad clinical application or disease-, or protocol- and disease-specific. The ITN has formed a Tolerance Assay Subgroup that solicits and supports mechanistic studies that examine the mechanism(s) that creates and maintains the tolerant state or function as a road-map to guide clinicians in their attempt to create and monitor immune
tolerance in individual patients. In this regard, a set of ITN-sponsored core facilities has been developed for use in the individual trials. These core facilities include a polymerase chain reaction-based gene expression core, a gene chip Microarray core, MHC-peptide multimer core, and an ELISPOT and T-cell receptor diversity core. For each patient enrolled in ITN trials, a battery of measurements will be performed, tailored to the clinical protocols under investigation. For example, the ITN has funded a proposal to perform a battery of mechanistic studies on a cohort of tolerant liver and kidney transplant recipients (i.e. individuals who have discontinued drug treatments yet retain their organ allografts; Principle Investigator (PI), A. Thomson, University of Pittsburgh, Pittsburgh, PA, USA). We anticipate that the more detailed understanding of the tolerant state obtained by such detailed mechanistic analyses will be used to guide the development of second-generation tolerance therapies.

3. THE FOCUS IN TRANSPLANTATION

A key mandate of the ITN is to solicit and develop protocols that will promote tolerance induction in kidney and islet transplant recipients. These two organ systems were chosen for different reasons. Kidney transplantation was chosen due to the vast clinical experience that exists examining rejection and immunomodulatory drugs. However, the high success rate of current immunosuppressive protocols places some limits on the freedom to develop proactive, potentially tolerogenic strategies in the kidney setting. Yet, the serious side-effects and disappointing long-term outcomes evident with existing protocols provide impetuses for the development of more specific therapies. The Kidney Transplant Subgroup is therefore committed to moving forward to promote tolerogenic studies. To date, the ITN has approved the following proposals for implementation: (i) bone marrow transplantation trials for patients with multiple myeloma (PI, M. Sykes, Massachusetts General Hospital, Boston, MA, USA), (ii) bone marrow transplantation combined with non-ablative therapies in patients with end-stage renal disease (ESRD) (Co-PIs, D. Sachs and A. Cosimi, Massachusetts General Hospital, Boston, MA, USA), and (iii) a combination drug therapy trial using anti-CD3 plus Sirolimus™ (rapamycin) in patients with ESRD (PI, H. Kriss). As well, there is continuing interest by the subgroup to solicit and develop additional approaches using co-stimulatory blockade and other calcineurin inhibitor-free regimens. Efforts to develop a calcineurin-free therapy for kidney transplant recipients will be supported in order to develop a platform for introducing more robust tolerogenic drugs.

The Islet Transplant Subgroup is focused on developing safe and successful strategies for restoration of self-tolerance and induction of donor-specific tolerance in islet allotransplantation for type 1 diabetes. The first trial initiated by the ITN, a multicentre trial of solitary islet transplantation in type 1 diabetic patients, will be led by Dr James Shapiro of the University of Alberta. The ‘Edmonton Group’ has had exceptional success in achieving sustained insulin independence in multiple type 1 diabetic patients (Shapiro et al. 2000). This US Food and Drug Administration-approved trial will enrol c-peptide-negative type 1 diabetic patients who have failed insulin therapy. These patients will undergo solitary islet transplantation by a minimally invasive percutaneous transepiphal intra-portal approach. Fresh islets derived from a maximum of two cadaveric donors, providing at least 10,000 islet equivalents will be transplanted after minimal cold storage and without culture. The immunosuppressive therapy includes the use of a combination of daclizumab (anti-interleukin 2 receptor) induction with low-dose Tacrolimus and Sirolimus. The ITN will support 40 transplants at ten centres in this Phase II study. In addition, the ITN will support metabolic and mechanistic studies at all participating centres to ensure that a detailed analysis of islet cell quality and function can be determined to provide critical data for the second phase of the studies. In this trial, the ITN is seeking to establish new standards for human islet preparation and quality control. The ITN will identify, validate and implement immune monitoring assays tailored to the specific challenges posed by islet transplantation in autoimmune diabetes. Successful completion of the proposed multicentre trial, the first of its kind in the history of islet transplantation, will provide a platform for future tolerance-induction protocols in islet transplantation.

4. AUTOIMMUNITY, ALLERGY AND ASTHMA

In addition to the mandate to develop novel tolerogenic therapies for use in transplantation, the ITN is committed to conducting clinical trials and mechanistic studies aimed at alleviating immune-mediated diseases such as type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and other autoimmune diseases as well as asthma and allergy. The strength of this multidisciplinary approach lies in the opportunity for cross-fertilization of ideas among the various disease targets and at the levels of assay development, biomarker identification and mechanistic studies. The investigators representing the different disease areas are committed to working together to develop novel tolerogenic therapies in these areas. To date, the ITN has approved eight clinical trials in these areas (for details visit the Web site: www.immunotolerance.org).

5. LOOKING AHEAD

Since its founding in October of 1999, the ITN has progressed rapidly towards its goal of moving tolerance therapies forward into clinical application. We have established a network of over 70 leaders in the clinical and basic science of immune tolerance. We have begun to establish an array of core facilities that will provide tolerance and mechanistic assays that will yield direct feedback that will guide future directions in tolerance research. We have established close links with the government, regulatory agencies and the pharmaceutical and biotechnology industry to enhance our ability to move forward rapidly. And, we have examined over 90 proposals from investigators, selecting more than a dozen protocols for clinical application. As a result, the ITN anticipates that its first clinical protocols in transplantation...
and other immune-mediated diseases will reach the clinic in 2001. The ITN continues to strive to develop a new paradigm in clinical research of immune-mediated diseases. Through an open and interactive framework of investigator-driven research, and a broad, disease-based focus, the ITN hopes to advance our ability to create and maintain clinical tolerance and to define further the underlying mechanisms at work in the induction and loss of tolerance. Although the effort is still in its infancy, the ITN is looking towards the day when chronic therapies give way to true cures for immune-mediated diseases.

REFERENCES


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