

## TRANSPLANTATION

Illnesses that affect millions of Americans, such as kidney failure, diabetes, leukemia, end-stage pulmonary disease, liver disorders, and cardiovascular disease, can often be successfully treated by transplantation of solid organs, tissues, or cells. Today, transplantation procedures are performed using more than 25 different organs and tissues, with 1-year graft survival rates often exceeding 80 percent.

Two major impediments to successful transplantation remain: immune-mediated graft rejection and the critical shortage of donor organs. Despite improvements in 1-year graft survival rates for all organs, long-term graft survival rates have not improved significantly. When a graft fails, the result is either death of the patient or a return to the organ transplant waiting list, which further increases the demand for organs.

Unfortunately, the number of patients who could benefit from transplants exceeds the supply of donor organs in the United States. Of more than 82,000 patients listed for transplantation in 2002, only 24,897 received a transplant.<sup>49</sup> Although this represents a 6-percent increase over the number of transplants performed in 2001, many patients die while awaiting a suitable donor.

### Immune-Mediated Graft Rejection

Recent advances in surgical procedures and immunosuppressive therapies have greatly increased 1-year graft survival rates for all organs and tissues. Unfortunately, however, long-term graft survival has not improved nearly as much. To further improve both short- and long-term graft survival, NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad portfolio of research that includes basic

research in transplantation immunology, preclinical evaluation of new therapies, and clinical trials of promising posttransplant therapies. The major goals of DAIT's transplantation research program are to understand the pathways whereby the immune system recognizes transplanted organs, tissues, and cells; characterize the cellular and molecular components of acute rejection and chronic graft failure; evaluate novel therapies for treating rejection and prolonging graft survival in preclinical models; develop and implement strategies for immune tolerance induction; and conduct clinical trials of new therapies to improve graft survival while minimizing the toxic side effects of immunosuppressive drugs.

Kidney transplantation, which is the preferred therapy for end-stage renal disease, accounts for 59 percent of solid organ transplants.<sup>50</sup> In fiscal year (FY) 2003, NIAID renewed a program called the Cooperative Clinical Trials in Pediatric Transplantation (CCTPT), first established in 1994. The goals of CCTPT are to support multicenter clinical trials of new ways to prevent graft rejection in pediatric kidney transplant patients, evaluate changes in drug regimens intended to limit side effects of immunosuppression, and assess pretransplant immunotherapy to improve outcomes. Ongoing CCTPT clinical trials include an evaluation of an immunosuppressive drug called sirolimus for chronic graft failure, a study of the effects of steroid withdrawal in pediatric transplant recipients, and a test of intravenous immunoglobulin as an agent to reduce existing immunity to potential donor organs and allow transplantation in high-risk kidney transplant candidates. CCTPT also conducts mechanistic studies to determine the effect of these interventional approaches on the immune system. These mechanistic studies

have led to novel approaches for noninvasive diagnosis of acute rejection and for detection of T cells that may regulate the immune response to grafts.

Patients with HIV infection are at significant risk for end-stage organ disease. Before the advent of highly active antiretroviral therapy (HAART), people with HIV were generally not considered for transplants because of their poor prognosis. With the advent of HAART, however, the outlook for HIV-positive patients has improved so much that increasing numbers of HIV-positive patients with end-stage kidney and liver disease are now potential transplant candidates. In FY 2003, DAIT and the Division of AIDS launched a study of the safety and efficacy of kidney and liver transplantation in patients with HIV.

Improvements in immunosuppressive therapy have dramatically reduced acute rejection and have increased the 1-year graft survival rate for all organ transplants. Despite this progress, however, many transplants ultimately fail due to a slow destructive process known as chronic graft failure. Little is known about what causes chronic graft failure, including the factors that determine onset and severity, the targets of immune reactivity, and the factors that control the degree of variability in the rejection process between patients. To better understand these factors, DAIT and the National Heart, Lung, and Blood Institute renewed the Immunopathogenesis of Chronic Graft Rejection program in FY 2001. This program will enhance our understanding of both the immunologic and nonimmunologic mechanisms that underlie the rejection of solid organs (the major cause of graft failure), improve diagnostic criteria to predict graft failure, and identify novel approaches for clinical intervention.

## Induced Immune Tolerance

The drug regimens that suppress a patient's immune system to prevent rejection cause serious side effects such as infections and malignancies. Reducing these risks while improving graft survival is a priority in transplantation immunology. One promising alternative to immunosuppression is to interrupt or modify the immune response to establish specific tolerance to the graft. In collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), DAIT renewed and expanded the Non-Human Primate Immune Tolerance Cooperative Study Group in FY 2002. Scientists in this program, which evaluates novel regimens intended to induce transplant tolerance in animal models, have already demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet transplant recipients. To accelerate the research conducted through this program, DAIT also supports breeding colonies of rhesus and cynomolgus macaques.

With co-sponsorship from NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), NIAID supports an international consortium of more than 80 investigators in the United States, Canada, and Europe called the Immune Tolerance Network (ITN). This network is dedicated to the clinical evaluation of tolerance-inducing therapies for both immune-mediated disorders such as autoimmune diseases, allergic diseases, and asthma, 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. ITN also

conducts studies on the underlying mechanisms of these approaches and develops new ways to measure the induction, maintenance, and loss of tolerance in humans. Since its inception, ITN has initiated more than 15 clinical protocols, has built a variety of state-of-the-art facilities, and has started several basic science studies of the mechanisms of induced immune tolerance. More information on ITN is available at [www.immunetolerance.org](http://www.immunetolerance.org).

### Shortage of Donor Organs

In 2001, almost 25,000 organ transplants were performed in the United States. The limited availability of donor organs, however, still restricts the number of transplantation procedures performed in this country. The waiting list for transplants has quadrupled in length since 1988 and now holds more than 80,000 patients; in 2002, 6,482 people died awaiting a suitable donor. To address this shortage, DAIT supports efforts to increase donation by improving donor registries that help to identify potential donors and by developing and testing educational initiatives to increase organ donation, especially among minority populations.

In collaboration with several NIH Institutes and Centers as well as the JDRF, NIAID supports the International Histocompatibility Working Group (IHWG). The IHWG is a network of more than 200 laboratories in more than 70 countries that collects data on the human leukocyte antigen (HLA) gene complex, which determines the compatibility of donor organs and tissues. The goals of this program are to improve histocompatibility testing, find HLA types that are associated with autoimmune diseases, and improve the outcomes of hematopoietic stem cell (HSC) transplantation through better donor-recipient

matching. Recently, IHWG investigators joined forces with HSC transplant centers to develop an international database of transplantation outcomes and donor-recipient HLA genotypes. This effort will help to determine optimal matching criteria for HSC transplants between unrelated individuals and increase access to this therapy for ethnically diverse populations. In addition, IHWG researchers are conducting a project to identify single nucleotide polymorphisms (SNPs) in immune response genes. SNP 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 response-related genes.

The use of nonhuman organs, tissues, or cells in human transplantation, called xenotransplantation, is another strategy that DAIT is pursuing to increase the supply of transplantable organs and tissues. Xenotransplantation is limited by the vigorous immune response to nonhuman tissues. DAIT-supported xenotransplantation research



*Organ donor who donated a kidney to her father*

focuses on increasing our understanding of the human immune response to antigens present on cells from nonhuman species, and on the development of methods to allow rapid identification and treatment of infectious diseases that might be caused by organisms present in animal donor tissue.

With each advance in transplantation, a new set of challenges emerges. The challenges facing transplantation are improving long-term graft survival, establishing long-term tolerance without immunosuppressive drugs, and reducing lengthy transplant waiting lists. NIAID's basic and clinical research programs in transplantation are committed to meeting these challenges.