TRANSPLANTATION

Transplantation is a powerful mode of treatment for people facing a wide range of congenital and acquired diseases. Today, doctors routinely transplant more than 25 different organs and tissues to treat kidney failure, type 1 diabetes, leukemia, end-stage pulmonary disease, liver disorders, cardiovascular disease, and many other disorders.

Two major impediments to successful transplantation remain, however. The first of these is graft, or transplant, rejection by the body's immune system. Recent research advances provide a much clearer understanding of the immune mechanisms that cause graft rejection. These insights in turn led to better therapies to suppress the immune system, which allows a graft to survive and function. As a result, 1-year graft survival rates have increased for all organs and tissues, and in many cases now exceed 80 percent. But despite this improvement, long-term graft survival rates have not increased nearly as much.

The second barrier to wider use of transplantation is a critical shortage of donor organs and tissues. Nationwide, there are more than 90,000 candidates on waiting lists for organ transplantation: approximately 66,200 for kidneys; 17,500 for livers; 2,500 for pancreas or combined kidney/pancreas transplants; 3,200 for hearts or heart-lung transplants; and more than 3,000 for lung transplants.[66] The demand far outstrips the supply of donor organs in the United States. In 2005, 14,492 individuals were organ donors.[67]

Immune-Mediated Graft Rejection

To further improve both short- and long-term graft survival, the NIAID Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad portfolio of basic research in transplantation immunology, as well as preclinical evaluation and clinical trials of promising post-transplant 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 all solid organ transplants. The NIAID Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) program was first established in 1994. Its goals 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 pre-transplant immunotherapies. Ongoing CCTPT clinical trials include an evaluation of the immunosuppressive drug sirolimus for chronic graft failure and a study of the effects of steroid withdrawal in pediatric transplant recipients. CCTPT also conducts immunological studies to determine how these various interventional approaches affect the immune system.

In FY 2004, NIAID collaborated with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute to establish a clinical consortium intended to improve the success of organ transplants. The goals of the consortium are to identify genetic factors in patients that could help doctors predict transplant outcomes and responses to post-transplant therapy; to develop diagnostic tests that enable early detection and ongoing monitoring of immune-related processes; and to

test the safety and effectiveness of new, less toxic immunosuppressive drugs.

NIAID and NIDDK also cooperatively established the Genomics of Transplantation Cooperative Research Program to support interdisciplinary, large-scale genomic studies in clinical transplantation. The goals of the program are to understand the genetic factors that affect immune-mediated graft rejection and to provide a rational basis for the development of more effective strategies for long-term graft survival.

Patients with HIV infection are at high 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. HAART, however, has improved the outlook for HIV-positive patients so that many more HIV-positive patients with end-stage kidney and liver disease are potential transplant candidates. In FY 2003, DAIT and the NIAID Division of AIDS launched a clinical trial of the safety and efficacy of kidney and liver transplantation in patients with HIV. Seventeen participating centers are currently enrolling subjects in this trial.

Induction of Immune Tolerance

The drug regimens that suppress a patient's immune system usually can prevent graft rejection, but they also can cause serious side effects such as infections and malignancies. Transplant immunologists, therefore, hope to develop treatments that entail lower risks while improving graft survival. One promising alternative is to selectively modify the immune response to establish tolerance to the graft while leaving protective immune responses intact. The Nonhuman Primate Immune Tolerance Cooperative Study Group, cosponsored by NIAID and NIDDK, evaluates novel regimens intended to induce transplant tolerance in animal models. Scientists working in the study group have already demonstrated that kidney and islet transplant patients given tolerogenic regimens have increased long-term graft acceptance. In FY 2005, the program was expanded to include heart and lung transplantation. To accelerate the research conducted through this program, DAIT also supports breeding colonies of rhesus and cynomolgus monkeys.

With cosponsors NIDDK and the Juvenile Diabetes Research Foundation International, NIAID supports the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. This network clinically evaluates tolerance-inducing therapies for many immune-mediated disorders, including rejection of transplanted organs, tissues, and cells. ITN also conducts studies on the underlying mechanisms of these approaches and develops new ways to measure the induction, maintenance, and loss of immune tolerance in humans. Since its inception, ITN has established a variety of state-of-the-art core facilities, initiated more than 20 clinical protocols, and funded several basic science studies of the mechanisms of induced immune tolerance. More information on ITN is available at *www.immunetolerance.org*.

Shortage of Donor Organs

The number of organ transplants performed in the United States has increased dramatically, from 12,618 in 1988 to 28,110 in 2005.[68] These numbers would be even higher if more donor organs were available; the waiting list for transplants has quadrupled since 1988. DAIT is addressing this problem by supporting efforts to improve donor registries that identify potential donors and by developing educational initiatives to increase public understanding of organ donation, especially among minority populations.

In FY 2005, NIAID, with cosponsorship from the National Institute of Neurological Diseases and Stroke, awarded five research cooperative agreements under the new program, Human Leukocyte Antigen (HLA) Region Genetics in Immune-Mediated Diseases. The objectives

of this program are to define the association between HLA region genes or genetic markers and immune-mediated diseases, including risk and severity of disease and organ and cell transplantation outcomes. This program is the successor to the International Histocompatibility Working Group (IHWG). More information about the IHWG can be found at *http://www.ihwg.org*.

The use of nonhuman organs, tissues, or cells in human transplantation, called xenotransplantation, is another strategy DAIT is pursuing to increase the supply of transplantable organs and tissues. The potential of xenotransplantation, however, is severely limited by the violent response of the human immune system to nonhuman tissues, and some express concern that infectious agents might inadvertently be introduced from animal donors into humans. Through xenotransplantation research, DAIT supports projects that might increase understandings of the human immune response to antigens present on cells from nonhuman species and that seek to develop methods for rapid identification and treatment of any 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 most pressing challenges today include 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.