National Institutes of Health

Action Plan for Transplantation Research

U.S. Department of Health and Human Services

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Foreword

In the 50 years since the first successful kidney transplant, solid organ and tissue transplantation have become the treatments of choice for most patients with end-stage organ failure. The benefits to patients—including children and adults—are clearly evident as demonstrated by prolonged survival and improved quality of life.

Transplantation is a routine surgical procedure and in 2005, more than 28,000 organ transplants were performed in the United States. Yet despite advances in transplantation, more than 97,000 individuals remained on transplantation waiting lists due to insufficient numbers of donor organs, and transplantation rarely, if ever, fully restores life expectancy and health-related quality of life. Major barriers to the broader application and success of transplantation include limitations on organ availability and the immunological incompatibilities between donor and recipient. Without further advances, the potential of transplantation will continue to be unfulfilled due to insufficient numbers of donor organs, the risks of acute and chronic graft rejection, graft dysfunction, and the unwanted side effects of the immunosuppressive medications currently needed to promote graft survival.

The U.S. Congress has long encouraged a coordinated approach to the many issues surrounding transplantation and organ availability, and recognized a critical role for the Federal Government through trans-agency oversight of the United Network for Organ Sharing, the United States Renal Data System, and the Scientific Registry of Transplant Recipients. Underscoring the need for comprehensive planning and a coordinated approach to ensure continued progress and the efficient use of resources, in their reports on the fiscal year (FY) 2006 budget for the Department of Health and Human Services (DHHS), the House and Senate Committees on Appropriations requested that the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), "….convene an expert panel to develop a 5-year transplantation action plan that identifies the most urgently needed research to facilitate an increase in the success of organ transplantation."

In September 2005, NIAID convened The Expert Panel on Transplantation Research to develop the NIH Action Plan for Transplantation Research. Panelists included research scientists, clinicians and surgeons, and policymakers with expertise in solid organ and hematopoietic stem cell transplantation, immunology, immune tolerance, and organ preservation. Representatives from the NIH Institutes and the DHHS also participated in the meeting. To facilitate the work of the Expert Panel, the NIH Transplantation Research Coordinating Committee (TRCC), which includes representatives of the nearly two dozen NIH Institutes and Centers, developed a draft Action Plan prior to the meeting of the Expert Panel. Under the direction of the NIAID, the TRCC summarized ongoing and planned research activities and drafted a comprehensive plan that addresses gaps in the current research portfolio and provides a roadmap for pursuing new research opportunities. The Panel, using the research goals in the four major areas set forth in the draft plan, provided the NIAID with advice and recommendations on the draft Action Plan.

NIH is deeply committed to supporting research that will improve transplantation outcomes and ensure its broader application in the coming years. We are proud of the many advances made possible through NIH-sponsored research and are hopeful about the potential of our Nation's investment in biomedical research to bring this life-saving gift to thousands of transplant recipients and their families.

Elias Zerhouni, M.D.
Director
National Institutes of Health

Anthony S. Fauci, M.D.
Director
National Institute of Allergy and Infectious Diseases

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Executive Summary

Purpose

In their reports on the FY 2006 budget for the Department of Health and Human Services (DHHS), the House and Senate Committees on Appropriations requested that the National Institute of Allergy and Infectious Diseases (NIAID) convene an expert panel to develop a 5-year transplantation research action plan that identifies the most urgently needed research to facilitate an increase in the success of organ transplantation (Senate Report 109-103, page 120, and House Report 109-143, page 77).

The National Institutes of Health (NIH) Action Plan for Transplantation Research (Action Plan) was developed by an expert panel of research scientists, clinicians and surgeons, and policymakers who gathered to develop a research plan for the next 5 years to advance efforts to improve the overall success of transplantation. The overarching goals of the Action Plan are to extend survival for transplant recipients and to improve their quality of life. The Action Plan identifies areas of scientific opportunity and suggests the direction of research resources at NIH to advance the science and practice of organ, tissue, and cell transplantation.

KEY CHALLENGES IN TRANSPLANTATION RESEARCH In the half century since the first successful kidney transplant between identical twins, transplantation has become the treatment of choice for end-stage organ failure. Despite tremendous progress, however, major barriers still remain to the overall success of transplantation. These include immunological incompatibility between donor and recipient, acute rejection, chronic graft dysfunction, and complications from long-term use of immunosuppressive drugs. Overcoming these barriers is the mission of the NIH transplantation research programs, and the Action Plan is the blueprint for accomplishing this mission.

NIH expenditures for transplantation research have grown steadily from $338 million in fiscal year (FY) 1999 to $545.4 million in FY 2005. Over the past two decades, highly productive, NIH-supported research projects have substantially increased our understanding of how to extend allograft survival and maintain graft function. In addition, NIH-supported researchers are developing and evaluating promising new strategies and treatments that, if successful, will overcome the major immunological barriers to graft acceptance while preserving the ability of transplant recipients to mount fully effective immune responses to infectious agents. This avenue of research, designated immune tolerance, has shown great promise in small animal models, but achieving robust and durable immune tolerance in larger animals and humans is proving more difficult. Meeting this long-term goal will require efforts spanning basic research in immunology and immune mechanisms, further development and evaluation of immune tolerance strategies, and clinical alternatives to organ transplantation. Success will require close collaboration between basic scientists, clinical investigators, and others from a variety of scientific, biomedical, and technological disciplines.

EXPERT PANEL ON TRANSPLANTATION RESEARCH In September 2005, NIAID, on behalf of NIH, convened such an Expert Panel. Panelists included research scientists, clinicians and surgeons, and policymakers with expertise in solid organ and hematopoietic stem cell transplantation, immunology, immune tolerance, and organ preservation. Representatives from the NIH Institutes and DHHS also participated in the meeting.

To facilitate the work of the Expert Panel on Transplantation Research, the NIH Transplantation Research Coordinating Committee (TRCC) developed a draft Action Plan. Using this plan, the panel provided NIH with advice and recommendations on the research goals in the four major areas set forth in the draft plan:

- Improve clinical outcomes for organ and cell transplantation
- Reduce morbidity and mortality by increasing organ availability and developing alternatives to organ transplantation and organ-assistive devices
- Induce immune tolerance to allografts
- Establish or improve research infrastructure and resources

Panelists discussed the current state of the science and identified critical gaps and opportunities in transplantation research. Recommendations from the panel members were incorporated into the final Action Plan.

NIH ACTION PLAN FOR TRANSPLANTATION RESEARCH The Action Plan includes a set of goals and objectives intended to advance knowledge and clinical practice in the field of organ transplantation. The Action Plan also includes examples of ongoing research and a framework that has the potential, over the next 5 years and beyond, to yield scientific advances to increase the success of organ transplantation, and, ultimately, lead to cures for a variety of diseases for which organ transplantation is the best treatment option.

The following principles guided the development of the Action Plan:

- Emphasize the importance of basic research in making fundamental advances in transplantation research
- Capitalize on the bidirectional nature of translational research
  - ▸ Translate findings from basic research into practical approaches to diagnosis, prevention, treatment, and cure
  - ▸ Translate findings from clinical research to refine directions of basic research
- Realize the full potential of scientific and technological breakthroughs and advances
  - ▸ Synergize research efforts by fostering multidisciplinary research teams and communications
  - ▸ Maximize trans-NIH transplantation research activities by providing a forum for the exchange of information and ideas, as well as contacts in specific program areas to facilitate collaboration.

Action Plan Research Goals and Objectives

I. Improve Clinical Outcomes for Organ and Cell Transplantation

GOAL 1: Improve the health of patients through better strategies for immunosuppression by optimizing and improving current therapies and developing novel therapies.

Key Research Objective

- Conduct clinical trials to evaluate how modified and novel immunosuppressive regimens affect health outcomes.

GOAL 2: Improve the health of patients by identifying clinical strategies and medical procedures that modify immune and nonimmune risk factors that increase the risk of graft dysfunction, graft rejection, graft-versus-host disease (GVHD), and other posttransplant morbidities.

Key Research Objectives

- Characterize the innate and adaptive immune responses that contribute to rejection and GVHD.
- Identify donor and recipient factors that predict the risk of GVHD, graft rejection, and other posttransplant morbidities.
- Identify organ-specific and non-organ-specific mechanisms of chronic allograft dysfunction.
- Identify causes and predictors of mortality in the presence of a functioning transplant.
- Conduct clinical trials to evaluate strategies aimed at preventing recurrence of organ-damaging disease after transplantation.

GOAL 3: Improve the health of patients by developing methods and diagnostic assays for early detection of graft rejection and GVHD.

Key Research Objective

- Develop surrogate markers, imaging techniques, and peripheral blood and/or urinary assays for early detection of impending or ongoing allograft rejection and GVHD.

GOAL 4: Improve the outcome of hematopoietic stem cell transplantation (HSCT) as currently used and extend its use to the treatment of cancer and autoimmune diseases by understanding immunological mechanisms by which HSCT can control cancer and autoimmune diseases, and also can induce the unwanted side effect of GVHD.

Key Research Objectives

- Identify mechanisms by which HSCT can contribute to the immunological control of cancer and autoimmunity.
- Identify the mechanisms whereby HSCT induces chronic GVHD.

II. Reduce Morbidity and Mortality by Increasing Organ Availability and by Developing Alternatives to Organ Transplantation and Organ-Assistive Technologies

GOAL 1: Reduce the morbidity and mortality of those on waiting lists through research to increase organ availability and develop technologies that improve and prolong the function of failing organs.

Key Research Objectives

- Improve the health of patients on transplant waiting lists by advancing and developing assistive/replacement devices.
- Support programs to educate and encourage organ donation by minorities.
- Improve the health of live donors through increased understanding of the short- and long-term health outcomes for live organ donors.

GOAL 2: Reduce the morbidity and mortality of those on waiting lists through development of alternatives to whole organ transplantation and the need for human organ donors.

Key Research Objectives

- Explore the potential of xenotransplantation as a transplantation-alternative to human donor organ or cell transplantation and advance our understanding of physiological and immunological barriers to xenotransplantation by conducting preclinical research in trials using large animal models, such as nonhuman primates, as recipients.
- Explore the potential of using stem and progenitor cells to repair, maintain, or replace vital organ functions as alternatives to donor whole organ transplantation.
- Investigate tissue engineering as a means to repair, maintain, or replace vital organ function.

III. Induce Immune Tolerance to Allografts

GOAL 1: Improve our understanding of immune tolerance by investigating the underlying mechanisms.

Key Research Objectives

- Develop multiple animal models that reliably induce immune tolerance.
- Identify the mechanisms of and targets for the induction, maintenance, and loss of immune tolerance.
- Determine the impact of immune tolerance on protective immunity to pathogens.

GOAL 2: Identify and validate surrogate biomarkers of induction, maintenance, and loss of immune tolerance.

Key Research Objectives

- Identify and validate surrogate biomarkers of immune tolerance or its absence.
- Conduct clinical trials in which biomarkers are used to guide withdrawal of immunosuppressive drugs.

GOAL 3: Conduct clinical trials of immune tolerance strategies in adults and children.

Key Research Objectives

- Conduct clinical trials of immune tolerance strategies in adults and children based on results from promising animal model studies.
- Pursue international collaborations on immune tolerance research.

IV. Establish or Improve Research Infrastructure and Resources

GOAL 1: Enable and facilitate cutting-edge research by providing access to state-of-the-art technologies for cellular, genetic, and molecular research; identification of alloreactive MHC-peptide complexes important to regulating immune response; and bioinformatics platforms for data analysis.

GOAL 2: Enable and facilitate cutting-edge research by providing access to unique rodent strains and large animal models, and resources such as cells, tissues, and reagents, for transplantation research.

GOAL 3: Enable and facilitate cutting-edge research by enhancing the pace, productivity, and quality of NIH-sponsored clinical trials through access to various clinical trial support services.

Next Steps

The Action Plan for Transplantation Research sets a flexible, collaborative, and comprehensive course for NIH transplantation programs for the next 5 years and beyond. It is anticipated that, over the next 5 years, pursuit of the goals and objectives set forth in the Action Plan will lead to substantial improvements in the success of organ transplantation and, it is hoped, ultimately will contribute to the cure of a variety of chronic diseases. Success is measured within each initiative, based on whether it met its stated goals and objectives. The Action Plan is a dynamic tool, and periodic evaluations and "mid-course" corrections will be undertaken to ensure that our overall goal of improving the success of organ transplantation is being met.

Introduction

In their reports on the Fiscal Year 2006 budget for the Department of Health and Human Services, the Committees on Appropriations stated:

> The Committee is aware that while 1-year organ transplantation survival has improved remarkably over the last 15 years, there has been little success in reversing the decline in long-term graft and patient survival. Therefore, the Committee urges NIAID to convene an expert conference during fiscal year 2006, in collaboration with NIDDK and NHLBI, to develop a 5-year Transplantation Research Action Plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation. The expert conference is also urged to focus on promising new technologies in pre-transplant organ care and post-transplant patient therapies. The Committee requests a report by May 1, 2006, on the results of this conference including a trans-NIH breakdown of resources committed to this category of research. The Committee also urges the initiation of a cohort study to assess the health outcomes of living donors not only for the period immediately following the donation, but for the quality-of-life implications in the decades post donation (Senate Report 109-103, page 120).
>
> The Committee is aware that while 1-year organ transplantation survival has improved remarkably over the last 15 years, there has been little success in reversing the decline in long-term graft and patient survival. The Committee suggests that NIAID convene an expert conference, in collaboration with NIDDK and NHLBI, to develop a 5-year Transplantation Research Action Plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation. The expert conference should also focus on promising new technologies in pre-transplant organ care and post-transplant patient therapies. The Committee also suggests the initiation of a cohort study to assess the health outcomes of living donors, not only for the period immediately following the donation, but for the quality-of-life implications in the decades post donation (House Report 109-143, page 77).

In their reports on the Fiscal Year 2005 budget for the Department of Health and Human Services, the Committees on Appropriations stated:

> The Committee encourages NIAID to convene an expert conference to develop a transplantation research action plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation (House Report 108-636, page 82).
>
> The Committee urges NIAID to convene an expert conference during fiscal year 2005 to develop a Transplantation Research Action Plan identifying the most urgently needed research to facilitate an increase in the success of organ transplantation. The Committee requests a report on the results of this conference including a breakdown of resources committed to this category of research (Senate Report 108-345, page 127).

The following report has been prepared by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) of the Department of Health and Human Services in response to this request.

Background

Transplantation is among the most promising forms of medical treatment developed in the 20th century. Few other interventions can so profoundly and dramatically revitalize a life of chronic illness and decline as transplantation. The benefits of transplantation—prolonged survival and/or improved quality of life—have been clearly demonstrated for

children and adults suffering from a wide range of life-threatening congenital and acquired diseases. Since the first successful kidney transplant in 1954, organ transplantation has evolved from being exceedingly rare to the preferred treatment for many forms of irreversible organ failure. In 2005, more than 28,000 organ transplants were performed in the United States (Table 1).

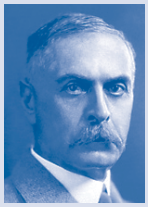
However, return to normal life expectancy and health-related quality of life is rarely, if ever, fully achieved by organ transplantation. One-year survival after organ transplantation has improved markedly over the last 15 years, but long-term graft and patient survival continue to decline in recipients of any organ transplant. The major barriers to short- and long-term success of transplant procedures include incompatibility between donor and recipient, acute rejection, chronic graft dysfunction, and complications from long-term use of immunosuppressive drugs. Overcoming these barriers is the mission of the NIH transplantation research programs. The NIH Action Plan for Transplantation Research is the blueprint for accomplishing this mission.

Nobel Prizes in Physiology or Medicine Related to Transplantation

1912
"in recognition of his work on vascular suture and the transplantation of blood vessels and organs"

Alexis Carrel
FRANCE

1930
"for his discovery of human blood groups"



Karl Landsteiner
AUSTRIA

TABLE 1: Transplants and Waiting List Registrants in 2005

ORGAN	NUMBER OF TRANSPLANTS	REGISTRANTS ON WAITING LIST
Kidney	16,477	68,429
Liver	6,444	17,831
Heart	2,125	3,004
Lung	1,406	3,192
Kidney-Pancreas	903	2,571
Pancreas	541	1,706
Intestine	178	205
Heart-Lung	35	143
TOTAL	**28,109**	**97,081**

1901
Karl Landsteiner discovers human blood groups.

From 1902
Alexis Carrel develops techniques for suturing blood vessels together; later, he is the first to describe transplant rejection.

1905
First successful human corneal transplant performed by Eduard Zirm.

1914–1918
Major steps in skin transplantation occurred during WWI, e.g., the tubed pedicle graft.

1930s
Peter Gorer and George Snell, at The Jackson Laboratory, discover histocompatibility antigens in mice.

Nobel Prizes in Physiology or Medicine Related to Transplantation

1960 "for the discovery of acquired immunological tolerance"

Sir Frank Burnet
AUSTRALIA

Peter Medawar
UNITED KINGDOM

1980 "for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions"

Baruj Benacerraf
USA

Jean Dausset
FRANCE

George Snell
USA

Historical Overview of Transplantation

For centuries, physicians have recognized the potential of replacing diseased organs and tissues with healthy ones. However, only in recent decades has this potential been realized, enabling transplantation to save the lives of thousands of people who otherwise had no hope of survival. Several key discoveries made in the 1940s set the stage for the first successful transplantation, a kidney transplant performed in 1954 between identical twins. At this time, scientists had little understanding of the molecular basis of graft acceptance or rejection. Trial-and-error studies in animals and humans had shown that transplants from one individual to another resulted in aggressive inflammation and organ rejection, whereas transplants within the same individual (e.g., skin grafts) often succeeded. The chief impediment was the immunologic barrier—the body's own response to substances that it identified as foreign.

An important breakthrough in understanding the immunologic barrier came not from clinical research, but from a series of experiments in mice that could never have been performed in humans. Beginning in the 1930s, researchers at The Jackson Laboratory, in Bar Harbor, Maine, repeatedly mated sibling and other closely related mice until the offspring were genetically alike. By transferring cells and tissues from one mouse to another, scientists eventually discovered that transplant success depended on the similarity of cell-surface structures, or antigens, between donor and recipient. The Jackson Laboratory researchers then identified a single genetic region on a specific chromosome that encoded these mouse transplantation antigens. By the 1960s, similar molecules had been identified on one of the human chromosomes. These molecules are called human leukocyte antigens (HLA). The HLA serve as the basis for human tissue-typing techniques that match compatible transplant recipients and donors, thus greatly enhancing graft acceptance and the recipients' chances of survival.

While basic scientists pieced together the functions of the HLA, clinical investigators made important advances

1939–1945	1953	1954	1956	1957
Major advances in reconstructive surgical techniques during WWII.	Peter Medawar, Rupert Billingham, and Leslie Brent publish their seminal paper, "Actively Acquired Tolerance of Foreign Cells."	First successful kidney transplant performed, between identical twins, by Joseph Murray.	First successful bone marrow transplant performed in recipient twin with leukemia, by Donnall Thomas. The recipient twin was treated with total body irradiation before the transplant; the procedures resulted in complete remission of leukemia.	George Hitchings and Gertrude Elion develop the immunosuppressive drug azathioprine.

Nobel Prizes in Physiology or Medicine Related to Transplantation

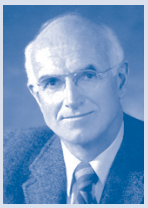
1988 "for their discoveries of important principles of drug treatment"

1990 "for their discoveries concerning organ and cell transplantation in the treatment of human disease"

Sir James Black
UNITED KINGDOM

Gertrude Elion
USA

George Hitchings
USA



Joseph Murray
USA

E. Donnall Thomas
USA

in transplanting organs between unrelated individuals through the use of drugs that suppress the recipient's immune response.

Early immunosuppressant drugs, such as azathioprine and prednisone, enabled successful transplantation of the human heart, liver, lungs, pancreas, and kidneys. These procedures not only extended the lives of the transplant recipients, but expanded the knowledge of surgeons throughout the world, giving them the impetus to continue these ground-breaking operations.

The introduction of the immunosuppressant drug cyclosporine, in the early 1980s, further revolutionized the field by dramatically improving graft survival. Immunosuppressive drugs have greatly increased the short-term success rate, particularly in kidney and other solid organ transplants. However, these drugs are highly toxic and require adherence to a lifelong regimen that suppresses the entire immune system, thereby increasing the susceptibility of patients to developing infections, cancer, and other complications. In addition, immunosuppressive drugs have not had a significant effect on increasing long-term graft survival.

A major goal of modern clinical immunology is to develop new strategies and treatments that will induce a state of immune tolerance—the lack of a harmful immune response. Tolerance induction strategies aim to selectively block or prevent deleterious immune responses, while leaving protective immunity intact. In transplantation, donor-specific immune tolerance—a selective blockade of immune responses directed against the graft—would enable long-term graft survival without the complications and risks of systemic immunosuppressive therapy.

The substantial advances in transplantation illustrate how interdisciplinary efforts—among molecular biologists, geneticists, animal researchers, and clinical investigators—lay a solid foundation for improving human health. Basic immunology research has helped unravel the fundamental processes responsible for self-tolerance and immune regulation, and the prospects for tolerizing therapies are now quite promising. A variety of therapeutic strategies to induce or restore immune tolerance are now entering clinical trials and, if successful, will be applied in a range of clinical settings, including transplantation, autoimmune diseases, and allergies.

1958	1962	1966	1967
Discovery of the first HLA antigen by Jean Dausset.	First successful reimplantation—reattachment of severed limb, resulting in limited function and feeling—performed by a surgical team led by Ronald Malt.	First successful pancreas transplant performed by William Kelly and Richard Lillehei.	First successful heart transplant performed by Christiaan Barnard. First successful liver transplant performed by Thomas Starzl.

Research Coordination

Improving the success of transplantation requires a combined effort from agencies within the Department of Health and Human Services (DHHS). DHHS supports a broad array of activities in transplantation, ranging from basic research to translational and clinical research to allocation of donated organs. Research coordination occurs on a variety of levels—trans-NIH activities that facilitate complementary programs and collaborative efforts; participation in a broad range of Federal policymaking efforts, including those related to organ procurement organizations (OPOs) and insurance reimbursement for transplant procedures; and interactions with patient advocacy groups and other stakeholders.

Government Agencies

DHHS AGENCIES SUPPORTING TRANSPLANTATION ACTIVITIES

- **NIH**—basic, translational, and clinical research in transplantation
- **Health Resources and Services Administration (HRSA)**—procurement and distribution of deceased donor organs in the United States, as well as oversight of the National Bone Marrow Donor Registry
- **Centers for Medicare & Medicaid Services (CMS)**—sets the standards for certification of organ procurement organizations in the United States and provides Medicare coverage and payment poliices for transplantation
- **Agency for Healthcare Research and Quality (AHRQ)**—supports projects focused on improving organ donation and allocation, and reducing medication errors
- **Centers for Disease Control and Prevention (CDC)**—focuses on public health interventions to improve transplant safety, including rapid detection and prevention of infectious agents transmitted through organ and tissue transplantation
- **Food and Drug Administration (FDA)**—evaluates safety and efficacy of new therapeutic agents, and regulates human tissue, e.g., bone, skin, and corneas, intended for transplantation, as well as xenotransplantation and research programs to address the safety and efficacy of xenotransplantation products

TRANS-NIH COORDINATION In 1989, NIH established the Transplantation Research Coordinating Committee (TRCC), which today includes 19 NIH Institutes, Centers, and Offices, and is under the leadership of NIAID. The TRCC facilitates trans-NIH transplantation research activities by providing a forum for the exchange of information and ideas as well as contacts in specific program areas to facilitate collaboration. Nearly one-half of the solicited research programs described in the Action Plan are trans-NIH initiatives, illustrating the importance of intra-agency coordination and collaboration at NIH. The TRCC developed the draft Action Plan, which was reviewed by the Expert Panel for Transplantation Research convened in September 2005.

DHHS-INTERAGENCY COORDINATION

- **Secretary's Advisory Committee on Organ Transplantation (ACOT) Working Group:** The Working Group is composed of Federal scientists and policymakers from the Office of the Secretary, National Institutes of Health, Health Resources and Services

1968	1971	1973	1981
First bone marrow transplant using related donor for treatment of a noncancerous condition (severe combined immunodeficiency syndrome).	Cyclosporin, a metabolite of the fungus *Tolypocladium inflatum*, is recognized to have immunosuppressive properties.	First bone marrow transplant using an unrelated donor. The recipient was a child with severe combined immunodeficiency syndrome. After the seventh bone marrow infusion, hematologic function normalized.	First successful heart/lung transplant performed by Bruce Reitz.

Administration, Food and Drug Administration, and the Centers for Disease Control and Prevention. The Working Group facilitates the activities of the ACOT.

- **Health Resources and Services Administration:** NIH is a member of the HRSA Advisory Committee for the Scientific Registry of Transplant Recipients.
- **Centers for Medicare & Medicaid Services:** NIH has been instrumental in the development of CMS policies on transplant-related reimbursement, including "Medicare Proposed Rules: Organ Procurement Organization Conditions of Coverage and Transplant Center Conditions for Participation" and "CMS Pharmacy Reimbursement Policy for Immunosuppressive Medications." NIH works with CMS to establish consistency between CMS policy and NIH clinical trials activities to ensure appropriate coverage of patients participating in NIH-sponsored transplantation trials.
- **Interagency Working Group on Hematopoietic Stem Cells**

Patient Advocacy Groups, Stakeholders, Scientific/Technical Advisory Committees

NIH scientists participate in forums and committees organized by patient groups and other stakeholders, including the:

- Juvenile Diabetes Research Foundation International
- National Kidney Foundation
- American Society of Transplant Surgeons
- American Society of Transplantation
- Collaborative Islet Transplant Registry
- Post-Transplant Tumor Registry Technical Advisory Committee
- Scientific Registry of Transplant Recipients Scientific Advisory Committee
- Council of American Kidney Societies

The Importance of Investigator-Initiated Research

Dr. M. Louise Markert, standing on the right in the picture to the left, is a NIAID-funded investigator whose work on thymus transplantation led to a life-saving procedure for children with a rare congenital immune system defect, and new insights into the process of immune reconstitution.

ML Markert et al. Postnatal thymus transplantation with immunosuppression as treatment for DiGeorge syndrome. *Blood*, 104:2574-81, 2004.

ML Markert et al. Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. *Blood*, 102:1121-30, 2003.

1983	1990	1995	1997
First successful lung transplant performed by Joel Cooper. Cyclosporin (Sandimmune) approved for prevention of transplant rejection.	Tacrolimus (Prograf) approved for prevention of transplant rejection—has immunosuppressive properties very similar to cyclosporin but is 10 to 100 times more potent on a per gram basis.	Mycophenolate (CellCept) approved for the prevention of transplant rejection.	Daclizumab (Zenapax) approved for preventing transplant rejection.

U.S. Transplant Games

The U.S. Transplant Games is a four-day athletic competition among recipients of organ transplants that is open to anyone who has received a lifesaving solid organ transplant, such as a heart, liver, kidney, lung, or pancreas. Bone marrow recipients are also eligible to participate.

The Games were first held in Texas in 1982 but attracted only a small number of participants. In 1990, the National Kidney Foundation was approached by Sandoz Pharmaceuticals (Novartis) and asked to assume the task of organizing and rejuvenating the Games and, as a result, that year the Games in Indianapolis hosted more than 400 athletes and 600 supporters.

The success of the Games and the message they engendered began to spread to the entire transplant community. By introducing the concept of local teams, the Games helped to bring the message of organ donation to the immediate community. They became the seed for the largest organized transplant support group in the nation, and they invited donor families to participate directly. Two years later, the Games in Los Angeles attracted 850 athletes and 2,000 supporters.

The Games are held every two years and have continued to grow at an exponential rate. By 2004, which marked the 50th anniversary of the first successful transplantation, the Games were attended by approximately 7,000 participants. New competitive events have been added with an emphasis on team sports, such as team golf, team bowling, and volley ball. Activities have expanded to include special programs for children, educational symposia, and programs recognizing donor families and living donors. The Games have now become more than an athletic event that calls attention to the success of organ and tissue transplantation—they have also become a celebration of life among recipients, their families, and friends.

Parker Milbrath, 7, who had a liver transplant when he was 2, won 3 medals in swimming and track and field events at the 2004 U.S. Games.

Sandy Webster with her partner Abby Lorica won gold at the 2004 U.S. Games in doubles tennis. Both are kidney transplant recipients.

1998	1999	2005	2005
First successful cord blood stem cell transplant from an unrelated donor to a child with sickle cell anemia.	First successful transplants of pancreatic islets using the Edmonton Protocol, by James Shapiro. The transplant recipients had complications of Type I diabetes that could not be managed with insulin injections.	First living donor pancreatic islet transplant from a 56-year-old woman to her 27-year-old diabetic daughter. The transplanted cells began producing insulin within minutes.	First successful partial face transplant.

NIH Funding for Transplantation Research

Transplantation research has been vigorously supported by NIH. Nineteen NIH Institutes, Centers, and Offices currently support and collaborate on transplantation research with a total investment of $545.4 million in fiscal year 2005 (Table 2).

TABLE 2. FY 2005 NIH Funding for Transplantation Research

NIH INSTITUTE	FY 2005 DOLLARS (M)
National Institute of Allergy and Infectious Diseases	162.6
National Institute of Diabetes and Digestive and Kidney Diseases	125.5
National Heart, Lung, and Blood Institute	103.1
National Cancer Institute	66.3
National Institute of Neurological Disorders and Stroke	24.5
National Center for Research Resources	17.1
National Institute of Child Health and Human Development	9.0
National Institute of Dental and Craniofacial Research	7.7
National Eye Institute	7.6
National Institute on Aging	5.0
National Institute of Arthritis and Musculoskeletal and Skin Diseases	3.9
National Institute of Nursing Research	3.2
National Institute of Mental Health	2.7
National Institute on Alcohol Abuse and Alcoholism	2.4
NIH Office of the Director and Roadmap	1.6
National Institute of Biomedical Imaging and Bioengineering	1.3
National Institute on Drug Abuse	1.2
National Human Genome Research Institute	0.5
National Center for Complementary and Alternative Medicine	0.2
TOTAL	**545.4**

NIH investments in basic and clinical research in transplantation enable the work of individual investigators and collaborative research partnerships, and support the infrastructure and research resources needed to facilitate this research. NIH expenditures for transplantation research have grown steadily from $338 million in fiscal year 1999 to $545.4 million in fiscal year 2005 (Table 3).

TABLE 3. NIH Transplantation Expenditures

FISCAL YEAR	FUNDING (MILLIONS)
1999	338.4
2000	372.5
2001	414.4
2002	489.8
2003	504.2
2004	530.1
2005	545.4

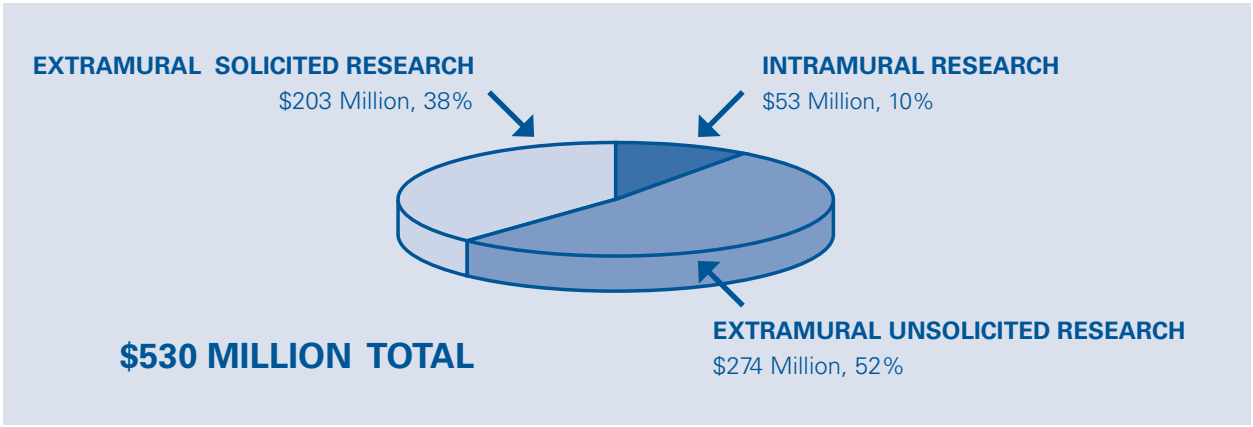
Over the past two decades, NIH-supported investigator-initiated and solicited research projects have substantially increased our understanding of how to extend allograft survival and function, and have yielded promising strategies and treatments to induce a state of immune tolerance that will eliminate pathogenic responses while preserving protective immunity. Continued efforts to support research in basic immunology and immune mechanisms, immune tolerance strategies, and alternatives to organ transplantation are necessary to improve the outcomes for all patients for whom replacing a diseased organ is the only viable treatment option. Success will require close collaboration between basic scientists, clinical investigators, and individuals from a host of other technological disciplines, ranging from bioinformatics to the development of new imaging approaches.

NIH FUNDING MECHANISMS The major mechanisms of research funding include investigator-initiated research project grants, program project grants, cooperative agreements, and contracts. These mechanisms support projects ranging from basic research to multi-center, international clinical trials of novel therapies. NIH-supported extramural research includes grants and contracts awarded to medical schools, academic institu-

tions, and other research organizations throughout the United States. Most NIH-funded research is through investigator-initiated, unsolicited grants that have been judged to be of extremely high scientific merit and technical feasibility by the NIH two-tiered review system. This peer review system includes initial review groups of scientific experts, as well as National Advisory Councils of each Institute and Center.

In FY 2004, nearly 90 percent of NIH transplantation research expenditures supported extramural research and training programs at universities and research organizations in the United States, Canada, and Europe (Figure 1). The remaining 10 percent supports intramural research, that is, research conducted at NIH laboratories in Bethesda, Maryland. The majority (57.4 percent) of the extramural research portfolio consists of investigator-initiated (unsolicited) research projects (52 percent of the total budget), which are critical to maintain a strong basic science foundation and promote innovation. Translation of basic research advances into therapeutic or diagnostic applications generally requires solicited research programs that support clinical research networks and may also encourage high-risk, highly innovative projects and studies in emerging scientific areas.

FIGURE 1: FY 2004 NIH Transplantation Budget: Intramural and Extramural Research



The NIH Action Plan for Transplantation Research

The NIH Action Plan represents the coordinated efforts of the NIH Institutes and Centers to improve the health and quality of life for all transplant recipients by achieving the following goals:

- Improve clinical outcomes for organ and cell transplantation
- Reduce morbidity and mortality by increasing organ availability and by developing alternatives to organ transplantation and organ-assistive devices
- Induce immune tolerance to allografts
- Establish or improve research infrastructure and resources

The goals described in the Action Plan are applicable across all organs and diseases. The magnitude of the impact and promise of transplantation research is best illustrated by Table 4 (page 15), which gives examples of the organs and associated diseases for which transplantation is a treatment option.

The significance of the goals of the Action Plan is evident when one considers that the first successful solid organ transplant occurred just over 50 years ago, and that, in 2005 alone, more than 28,000 organs were transplanted in the United States.

SOLICITING INPUT FROM NIH CONSTITUENCIES
Identifying Research Opportunities and Priorities

NIH convenes panels, working groups, and conferences to gather input from a wide range of scientific and lay communities. Many of these efforts have contributed to the present Action Plan. Examples include:

GRAFT-VERSUS-HOST DISEASE In June 2005, NCI, NHLBI, and the Office of Rare Diseases (ORD) sponsored "Chronic GVHD: The Next Frontier in Transplantation Research," a consensus meeting to discuss and develop criteria for clinical trials in chronic GVHD. Six working groups presented recommendations that will be published in a series of articles in *Biology of Blood and Marrow Transplantation*.

HEART AND LUNG TRANSPLANTATION NHLBI convened the following conferences, which have influenced the priorities of NIH in transplant research:

- In July 2001, the Heart and Lung Xenotransplantation Working Group (Platt et al. *Circulation*, 106:1043-7, 2002); and
- In June 2004, a workshop of research experts to discuss priorities in lung allograft transplantation research (*http://www.nhlbi.nih.gov/meetings/workshops/lung-transplant.htm*).

HIV/HEPATITIS C VIRUS COINFECTION In April 2004, NIDA sponsored a meeting on HIV and Hepatitis C Virus Coinfection in Injection Drug Users (Khalsa et al. Medical Management of HIV/Hepatitis C Coinfection in Injection Drug Users. *Clinical Infectious Diseases,* 41:S1-S6, 2005). Recommendations from this meeting included further research on liver transplantation.

IMMUNE TOLERANCE In September 1998, NIAID released reports based on the findings of two NIAID Expert Panels:

- The "Report of the NIAID Task Force on Immunology" (*http://www.niaid.nih.gov/publications/immunology/pdf/immunology.pdf*); and
- "The NIAID Plan for Research on Immune Tolerance" (*http://www.niaid.nih.gov/Publications/immune/bookcover.htm*).

"Recommendations of the NHLBI Heart and Lung Tolerance Working Group" provided similar recommendations (*Transplantation*, 72:1467-70, 2001).

ISLET TRANSPLANTATION From 2003 to 2005, NIDDK convened two Advisory Meetings and one workshop to address key issues in islet transplantation research:

- Islet Transplantation Advisory Meeting (May 2003);
- Islet Kidney Transplantation Advisory Meeting (February 2005); and
- Workshop on Immunobarriers for Pancreatic Islet Transplantation (March 2004):

A report is available at *http://www.niddk.nih.gov/fund/other/Encapsulation_Report_Final.pdf.*

LIVER DISEASE In December 2004, NIDDK issued the Action Plan for Liver Disease Research, a Report of the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee (*http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm*). The report was based on recommendations provided by expert panels at several meetings.

RENAL TRANSPLANTATION

- In December 1998 and in February 1999, NIDDK and the Council of American Kidney Societies convened two research planning conferences to address research priorities and barriers in renal disease and its treatment. Their conclusions are highlighted in the NIDDK Renal Disease Research Plan (*http://www.niddk.nih.gov/fund/reports/wholeRDRC.pdf*).

  In July 2004, NIDDK and NIAID co-sponsored the Workshop on Late Renal Allograft Dysfunction (Meyers CM, Kirk, AD. Workshop on late renal allograft dysfunction. *American Journal of Transplantation* 5:1600-50, 2005).

  Both reports helped to define research priorities in renal transplantation.

- In October 2002, NIDDK convened a workshop to discuss the unique clinical issues related to Hepatitis C and Renal Disease (Meyers CM et al., Hepatitis C and Renal Disease: An Update. *American Journal of Kidney Diseases* 42:631-57, 2003).

STEM CELL TRANSPLANTATION From 2002 to 2005, NHLBI convened several workshops to address key research areas in stem cell transplantation:

- Cell-Based Therapies for Regenerative & Reparative Medicine: Vision, Scope, and Directions (2002) (*http://www.nhlbi.nih.gov/meetings/stemcell_wg.htm*);
- Translation of Cardiovascular Cell Based Therapies, NHLBI Working Group Interim Summary (2004) *(http://www.nhlbi.nih.gov/meetings/workshops/translation.htm*); and
- Workshop on Adult Stem Cells, Lung Biology, and Lung Disease, Executive Summary (2005) (*http://www.nhlbi.nih.gov/meetings/workshops/stem-cell.htm*).

TYPE 1 DIABETES In April 2004, the NIDDK issued the Special Statutory Funding Program for Type 1 Diabetes Research, a Report on Progress and Opportunities (*http://www.niddk.nih.gov/federal/planning/type1_specialfund/*). Scientific experts provided recommendations for the report at meetings convened in April 2000 and May 2002.

TABLE 4. Organs and Diseases: US Transplant Data: 1988 - 2005 (United Network For Organ Sharing)

ORGAN	# TRANSPLANTS	RELATED DISEASES
Kidney	217,033	Diabetes, hypertension, glomerulonephritis, polycystic kidney disease
Liver	74,981	Hepatitis, biliary atresia, neonatal cholestatic liver disease, acute liver failure
Heart	38,710	Coronary artery disease, cardiomyopathy, congenital heart disease
Lung	13,763	Emphysema, cystic fibrosis, pulmonary hypertension, pulmonary fibrosis, bronchiectasis, sarcoidosis
Pancreas	4,776	Type 1 diabetes
Intestine	1,145	Short bowel syndrome, irritable bowel syndrome
Eye	546,798*	Corneal diseases
Hematopoietic Tissue	45,000/year ** (autologous and allotransplants)	Aplastic anemia, sickle cell anemia, beta thalessemia, acute and chronic leukemias, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma
Neurologic Tissues From Stem Cells	*(in experimental stage)*	Parkinson's Disease, multiple sclerosis, spinal cord injuries

* 1990-2005 DATA FROM THE EYE BANK ASSOCIATION OF AMERICA

** NEJM 354:1813-26, 2006

Development and Organization of the Action Plan

The NIH Transplantation Research Coordinating Committee met early in 2005 to establish a process for developing the Action Plan. The Committee members gathered and analyzed the data and information and developed a draft plan for consideration by an Expert Panel. In September 2005, NIAID convened the Expert Panel on Transplantation Research to review the draft plan and make recommendations for improving and strengthening the Action Plan. Members of the Panel included international experts in the field of transplantation research and practice, public policy, and patient advocacy.

The Action Plan is organized into four chapters, corresponding to each major goal. Each chapter includes a brief introduction, a description of the current research challenge, specific goals and objectives, and a research plan to achieve these goals. Reference material is contained in the appendices. It is anticipated that the Action Plan will be reviewed and revised to incorporate new knowledge and progress.

NIAID Explores the Many Faces of Transplantation

The statistics are compelling. In 2005, more than 97,000 men, women, and children are waiting for life-saving organ transplants, and thousands more are in need of bone marrow transplants. Every 13 minutes another name is added to transplant waiting lists, and every day 17 people die nationwide waiting for donor organs. To bring these statistics to life and to promote awareness of organ and tissue donation, NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) convened a Transplantation Fair in the Spring of 2004 in which donors and recipients shared their experiences. Most of the speakers at the fair — themselves donors or recipients — also happen to work at NIAID. They shared their stories of courage and joy, fear and promise, heartbreak and hope.

One father-daughter transplant team told their story:

Jennifer Pasternak, a grants technical assistant at NIH, is the kidney donor for her dad, Stephen. After more than 5 years of watching her father's health fail and his medical options dim, Pasternak had a conversation with her father. "Dad, you and I are going through this together," she said.

"Not a good idea," he tells the audience, as his eyes start to well up. "My own flesh and blood stepped up to the plate to be my angel and saw me through this. When I think of the alternatives, that's when my daughter really shines."

With a smile, he jokes, "My only regret is that when my daughter gets up to go to the bathroom, I get up, too!"

On a serious note, Jennifer says, "It does not take a remarkable person to be a donor. This was my one chance in life to do something for my dad. Without him, I wouldn't even be here. My parents have done so much for me throughout my entire life."

For more information on the Gift of Life Donation initiative, visit *www.organdonor.gov,* and on NIAID-sponsored clinical trials in transplantation, visit *www.niaid.nih.gov/clintrials*.

CHAPTER I
Improve Clinical Outcomes for Organ and Cell Transplantation

Research to improve clinical outcomes of transplantation strives to develop better diagnostic tools, design superior transplantation protocols, manipulate the immune response to avoid transplant rejection, and develop clinical practices that maintain healthy function of transplanted organs, tissues, and cells, and improve overall survival of transplant recipients.

Current Research Challenge

Organ transplantation has been shown clearly to prolong survival and greatly improve quality of life for children and adults suffering from a wide range of congenital and acquired diseases. However, normal life expectancy and health-related quality of life are rarely, if ever, restored by organ transplantation. Although 1-year survival rates after organ transplantation have improved markedly over the last 15 years, there has been little success in reversing the decline in long-term graft acceptance and patient survival. Barriers to long-term patient health after a transplant include incompatibility between donor and recipient; chronic adverse reactions to powerful immunosuppressive drugs; chronic rejection; infection; and the recurrence or persistence of the disease that caused the original organ to fail.

NIH continues to support research to improve long-term graft survival and patient outcomes by increasing our understanding of the immune response to transplanted organs, evaluating innovative strategies for modulating the immune response, evaluating and modifying risk factors for poor outcome after transplantation, and identifying early markers of graft rejection. Research is needed to identify causes of graft failure and to eliminate or reduce the need for immunosuppressive drugs, which have detrimental side effects. In addition, research in basic immunology and transplantation biology is needed to provide fundamental knowledge from which future translational and clinical research can benefit.

Research Goals for Improving Clinical Outcomes for Organ and Cell Transplantation

The Expert Panel recommended four key goals to improve outcomes for organ and cell transplantation. These goals reflect NIH's effort to improve patient health by determining clinical strategies and medical procedures that modify nonimmune and immune risk factors and thus reduce complications that contribute to graft dysfunction, graft rejection, and other posttransplant morbidities.

GOAL 1: Improve the health of patients through better strategies for immunosuppression by optimizing and improving current therapies and developing novel therapies.

A major reason transplantation fails is that the body's own immune system attacks the donated tissue, causing acute and/or chronic rejection. During the 1980s, doctors began to prescribe immunosuppressive drugs, such as cyclosporine, to block rejection, and this practice dramatically boosted 1-year graft survival rates. However, immunosuppressive drugs, which must be taken throughout the patient's life, also have undesirable side effects, including an increased risk of infection and malignancy, and conditions such as diabetes and hypertension.

Researchers are designing a new generation of immunosuppressive drugs that they hope will be able to block the immune system response against the transplant while still maintaining its ability to mount a defense against pathogens. Other strategies aim to minimize the harmful side effects of immunosuppressive drugs by tailoring the dosage and length of administration of the drugs.

Key Research Objective

- Conduct clinical trials to evaluate how modified and novel immunosuppressive regimens affect health outcomes.

GOAL 2: Improve the health of patients by identifying clinical strategies and medical procedures that modify immune and nonimmune risk factors that increase the risk of graft dysfunction, graft rejection, graft-versus-host disease (GVHD), and other posttransplant morbidities.

Effective immunosuppressive therapies have reduced the rates at which transplanted organs fail due to acute rejection, chronic rejection, GVHD, graft dysfunction, and other posttransplant morbidities, such as infection. However, hypertension and diabetes continue to contribute to poor outcomes. The underlying causes of these problems include characteristics of the organ donor, the condition of the organ at the time of transplant, immunologic incompatibility, chronic immune suppression, and drug toxicity. A greater understanding of these underlying immune and nonimmune factors will help clinicians devise strategies to better manage transplant patients. Researchers aim to improve long-term graft acceptance and patient outcomes through maintaining the health of transplanted organs or cells, circumventing chronic rejection, and characterizing risk factors for poor outcome after transplantation.

Key Research Objectives

- Characterize the innate and adaptive immune responses that contribute to rejection and GVHD.
- Identify donor and recipient factors that predict the risk of GVHD, graft rejection, and other posttransplant morbidities.
- Identify organ-specific and non-organ-specific mechanisms of chronic allograft dysfunction.
- Identify causes and predictors of mortality in the presence of a functioning transplant.
- Conduct clinical trials to evaluate strategies aimed at preventing recurrence of organ-damaging disease after transplantation.

GOAL 3: Improve the health of patients by developing methods and diagnostic assays for early detection of graft rejection and GVHD.

A major difficulty for transplant recipients and the doctors who care for them is that there are few reliable and simple ways to predict that rejection is occurring or will occur in the future. If it were possible to identify markers of rejection—for example, by doing a blood test or urine test—then the type and dose of immunosuppressive drugs could be individually tailored. In this way, patients would be less likely to receive too much or too little immunosuppression, and their health would be improved.

Key Research Objective

- Develop surrogate markers, imaging techniques, and peripheral blood and/or urinary assays for early detection of impending or ongoing allograft rejection and GVHD.

GOAL 4: Improve the outcome of hematopoietic stem cell transplantation (HSCT) as currently used and extend its use to the treatment of cancer and autoimmune diseases by understanding immunological mechanisms by which HSCT can control cancer and autoimmune diseases, but can induce the unwanted side effect of GVHD.

Hematopoietic stem cell transplantation (HSCT) is the practice of using cells from bone marrow or umbilical cord blood to replace cells that have been destroyed either by disease or as part of disease treatment. The hematopoietic stem cells may be the patient's own cells, collected before the injury caused by disease or drugs (autologous cells), or cells collected from someone else (allogeneic cells). HSCT is used to treat nonmalignant diseases such as aplastic anemia, sickle cell anemia, and autoimmune disorders. The stem cells are also used to treat multiple myeloma and many forms of blood cell cancers, including acute and chronic leukemia, and Hodgkin's and non-Hodgkin's lymphoma.

One unique feature of HSCT is that the transplanted cells are part of the body's immune system. A benefit of HSCT is that the donor graft can transfer immune functions to the recipient to fight cancer or overcome autoimmunity. A downside of transplanting a component of the immune system is that the graft can recognize the recipient's body as foreign and mount an immune response (GVHD). Research is needed to determine the immunological mechanisms by which transplanted hematopoietic stem cells attack cancer cells, cause autoimmunity, and induce chronic GVHD. These findings will increase the efficacy

of HSCT for current clinical applications and provide new therapeutic opportunities.

Key Research Objectives

- Identify mechanisms by which HSCT can contribute to the immunological control of cancer and autoimmunity.
- Identify the mechanisms whereby HSCT induces chronic GVHD.

Improving Clinical Outcomes—Story of Discovery

BIOMARKER IN URINARY CELLS AS A PREDICTOR OF KIDNEY TRANSPLANT REJECTION Kidney transplantation is a life-saving procedure for many patients with end-stage renal disease, but these patients must continuously take drugs to prevent rejection of their transplant. When acute rejection episodes occur, there is damage to the kidney, and in addition the patient must be treated with more aggressive immunosuppressive regimens that increase the risk of toxicity. Recently, NIH-supported investigators showed that messenger RNA encoding a specific protein of the immune system, FOXP3, could be detected in cells obtained from urine specimens, and that the presence and amount of this RNA would predict immunologic events in the setting of acute kidney rejection and its aftermath. These findings suggest there may be ways to monitor transplant recipients noninvasively to predict onset of a rejection episode before damage occurs.

Achieving Research Goals

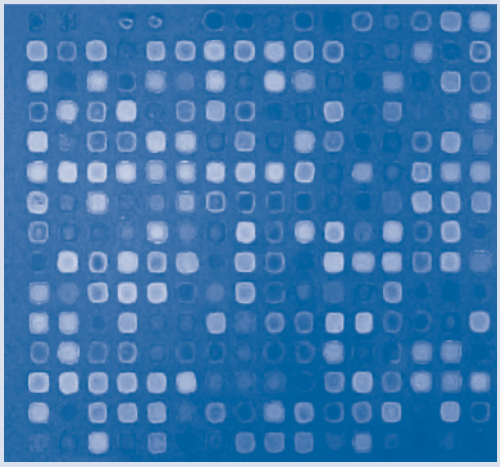
Many of the goals for improving clinical outcomes for cell and organ transplantation can be accomplished only through large clinical trials that include a diverse patient pool whose members may be scattered around the world. In response to input from previous expert panels and advisory committees, NIH has created consortia and networks that coordinate and prioritize transplantation research. This approach has multiple advantages that include increasing the pool of eligible research volunteers and patients, enabling participation of researchers from a range of disciplines and institutions, and effectively managing the allocation of research resources.

The Expert Panel concurred that advances in clinical outcomes of transplantation depend on the success of research networks and consortia and recommended that these be continued. The Panel also endorsed investigator-initiated proposals as a means to respond quickly to research opportunities and novel discoveries that might enhance clinical outcomes of transplantation.

Solicited programs in NIH's transplantation research portfolio are likely to be modified in response to innovative research opportunities and newly identified goals. For example, some NIH-sponsored programs are slated for expansion or shift in focus directly related to the goals specified in this report. Examples of updated programmatic initiatives include:

- "Adult-to-Adult Living Liver Transplant Cohort Study" will develop studies investigating the long-term health effects of live organ donation (NIDDK, NIAID, NHLBI).
- "Clinical Trials in Organ Transplantation" will, among other research goals, focus on the identification of non-biopsy-based markers for active and impending rejection (NIAID, NHLBI, NIDDK).
- "Blood and Marrow Transplant Clinical Trials Network" will be competitively renewed and will shift its focus to emphasize Phase II trials and follow-on Phase III studies on transplantation methodologies that improve long-term outcomes for transplant recipients, especially children and patients with rare diseases (NHLBI, NCI).

Microarray Technology



Technological advances in genomics research, including the use of "gene chips" to characterize gene expression, genotypes, single nucleotide polymorphisms, microsatellite polymorphisms, and haplotypes, have shown wide applicability to many areas of biomedical research. The Genomics of Transplantation Cooperative Research Program supports the wide application of these approaches to the field of transplantation, including studies of:

- Gene expression profiles in donor organs and recipients at all stages of transplantation;
- Surrogate biomarkers of acute and chronic graft rejection;
- Genetic variations and responses to immunosuppressive therapy;
- Graft survival/rejection correlated with gene regulation; and
- Development of noninvasive diagnostic/prognostic tests based on gene expression that will predict or confirm acute and chronic rejection.

The Expert Panel also identified additional approaches to improve clinical outcomes for organ and cell transplantation:

- Continue NIH programmatic support to assist in resource and protocol development for clinical trial design and liaison to regulatory agencies.
- Support basic research and animal studies to understand the cellular and molecular mechanisms that underlie the clinical outcomes after transplantation.
- Establish formal collaborative efforts among transplant programs, focusing on the identification of genomic determinants of transplant outcomes in adult and pediatric transplant recipients.
- Initiate coordinated, multicenter, large-scale mechanistic studies to develop reliable, non-biopsy-based markers of impending rejection and test preemptive therapy to diminish immunologic injury to transplanted organs.
- Expand industry partnerships with NIH-funded clinical trial networks.
- Initiate randomized clinical trials to evaluate innovative interventions to prevent allograft deterioration due to humoral rejection in renal transplant recipients.
- Encourage transplantation research in special populations such as children, individuals with preexisting immune deficiencies, and those with chronic infectious diseases or metabolic disorders.
- Develop imaging technologies through individual research project and specialized center grants.
- Develop standard mechanisms to evaluate the feasibility of clinical trials.
- Develop metrics to evaluate subject accrual, data integrity, Good Clinical Practice, and achievement of trial endpoints.
- Advance clinical trials in human islet transplantation, conducted with input from the appropriate regulatory authorities. Goals include (1) improvements in islet manufacture and islet transplant outcomes by testing innovative investigational agents, and (2) establishment of an islet manufacture process that will satisfy FDA requirements for licensure.

Table 5 highlights programs related to improving clinical outcomes for organ and cell transplantation that advance NIH goals in transplantation research.

Selected Programs

NIDDK INTRAMURAL KIDNEY TRANSPLANTATION PROGRAM conducts clinical trials to test strategies (T-cell depletion, bone marrow infusion) for more precise immune management of transplant recipients with the aim to reduce or eliminate the requirement for chronic immunosuppressive medications.

COOPERATIVE CLINICAL TRIALS IN PEDIATRIC TRANSPLANTATION (NIAID) is a consortium for clinical studies of pediatric kidney transplantation with the goal to (a) reduce or eliminate the need for immunosuppressants in pediatric kidney transplant recipients; (b) develop less toxic immunosuppressive regimens, focusing on toxicities that are unique to childhood such as growth; (c) define pharmacokinetic properties of immunosuppressive medications in children; and (d) identify markers of rejection.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK (NHLBI, NCI) conducts multicenter Phase II and III clinical trials to improve outcomes after bone

TABLE 5: Improve Clinical Outcomes for Organs and Cell Transplantation

PROGRAMS	GOAL 1 Improve immuno-suppression strategies	GOAL 2 Modify risk factors	GOAL 3 Improve early detection of graft rejection	GOAL 4 Improve efficacy of HSCT
NIDDK Intramural Kidney Transplantation Program	x	x		
Cooperative Clinical Trials in Pediatric Transplantation (NIAID)	x	x	x	
Blood and Marrow Transplant Clinical Trials Network (NHLBI, NCI)		x		x
Immune Reconstitution Consortium (NCI, NIAID)	x			
Clinical Islet Transplantation Consortium (NIDDK, NIAID)	x			
Long-Term Deterioration of Kidney Allograft Function (NIAID)		x	x	
Angiotensin II Blockade in Chronic Allograft Nephropathy Trial (NIDDK)		x	x	
Renal Senescence and Transplantation Studies (NIDDK)			x	
Genomics of Transplantation Cooperative Research Program (NIAID)	x	x	x	
Pathogenesis of Polyomavirus-Associated Nephropathy (NIAID)	x	x		
Folic Acid for Vascular Outcome Reduction in Transplantation (NIDDK)		x		
Clinical Trials in Organ Transplantation (NIAID, NHLBI, NIDDK)	x	x	x	
Specialized Centers of Clinically Oriented Research in Pediatric Heart Development and Disease (NHLBI)	x		x	
Specialized Centers of Research in Hematopoietic Stem Cell Biology (NHLBI)				x
Cord Blood Transplantation Study (NHLBI)				x
Adult-to-Adult Living Liver Transplant Cohort Study (NIDDK)		x		
International Histocompatibility Working Group (NIAID, NIDDK, NCI, NHGRI, JDRF)		x		

marrow transplant for treatment of multiple myeloma, acute myelogenous leukemia, relapsed follicular and diffuse large B cell non-Hodgkin's lymphoma, and severe aplastic anemia. Aims include the prevention of complications such as GVHD and fungal infection and comparing peripheral blood stem cell or bone marrow transplantation using unrelated donors.

IMMUNE RECONSTITUTION CONSORTIUM (NCI, NIAID) is an international, multi-institutional research enterprise that conducts basic and clinical research on the biochemical and cellular basis of immune recovery after transplantation and investigates clinical/laboratory relationships that ultimately may permit improved clinical evaluation of individual patients and/or assist in the evaluation of responses to novel therapies.

CLINICAL ISLET TRANSPLANTATION CONSORTIUM (NIDDK, NIAID) conducts Phase II and III clinical trials of pancreatic islet transplantation in subjects with type I diabetes. The goals are to provide the research-based evidence necessary for licensure of an islet product, and to develop innovative approaches to human islet transplantation.

LONG-TERM DETERIORATION OF KIDNEY ALLOGRAFT FUNCTION (NIAID) is a clinical trial that is recruiting both retrospective and prospective patient cohorts to study the factors that contribute to chronic allograft dysfunction.

ANGIOTENSIN II BLOCKADE IN CHRONIC ALLOGRAFT NEPHROPATHY (NIDDK) is a multicenter randomized clinical trial assessing the impact of chronic losartan therapy on preventing delayed kidney allograft loss.

RENAL SENESCENCE AND TRANSPLANTATION STUDIES (NIDDK) uses serial physiologic and morphometric analyses, plus mathematical modeling and magnetic resonance angiography (MRA), to assess the relationship between renal senescence and acceleration of chronic allograft nephropathy.

GENOMICS OF TRANSPLANTATION COOPERATIVE RESEARCH PROGRAM (NIAID) is an interdisciplinary research program for large-scale, broad-scope genomic studies in clinical transplantation to determine the genetic basic of immune-mediated graft rejection and transplantation outcomes.

PATHOGENESIS OF POLYOMAVIRUS-ASSOCIATED NEPHROPATHY (NIAID) supports basic, clinical, and epidemiological research on the risk assessment and preventive, diagnostic, and treatment strategies for polyomavirus-associated nephropathy, a complication of immune suppression.

FOLIC ACID FOR VASCULAR OUTCOME REDUCTION IN TRANSPLANTATION (NIDDK) project conducts a nationwide, multicenter clinical trial to determine whether total homocysteine-lowering treatment with a high-dose combination of folic acid, vitamin B12, and vitamin B6 will reduce the rate of cardiovascular disease outcomes among stable renal transplant recipients.

CLINICAL TRIALS IN ORGAN TRANSPLANTATION (NIAID, NHLBI, AND NIDDK) is a multisite consortium to conduct interventional and observational clinical studies with accompanying mechanistic studies to understand and reduce the immune-mediated morbidity and mortality of organ transplantation. These studies include evaluation of new therapeutic regimens and development of diagnostic tests and surrogate biomarkers to facilitate routine surveillance and allow preemptive therapy of rejection.

SPECIALIZED CENTERS OF CLINICALLY ORIENTED RESEARCH IN PEDIATRIC HEART DEVELOPMENT AND DISEASE (NHLBI) supports clinical and basic research related to long-term survival in pediatric heart transplantation by testing ways to decrease immunosuppression and post-transplantation complications such as lymphomas. This program also supports research to identify predictive genetic markers.

SPECIALIZED CENTERS OF RESEARCH IN HEMATOPOIETIC STEM CELL BIOLOGY (NHLBI) is a program to advance knowledge of basic stem cell biology. Clinical applications are focused on treatment of genetic and acquired diseases and the use of HSCT for gene transfer.

CORD BLOOD TRANSPLANTATION STUDY (NHLBI) established ethnically diverse, unrelated allogeneic umbilical cord blood banks and aims to determine (1) the suitability of umbilical cord blood cells for transplantation into patients with malignant and nonmalignant blood diseases who do not have a suitable donor, and (2) whether two or three antigen differences in HLA matching can be tolerated in pediatric leukemia patients as measured by overall survival at 6 months post-transplant.

International Histocompatibility Working Group

ADULT-TO-ADULT LIVING LIVER TRANSPLANT COHORT STUDY (NIDDK) is an epidemiologic study of adult-to-adult living donor liver transplantation. The study examines the informed consent process, morbidity, and quality of life among live donors of a lobe of liver, and compares the effectiveness of living donor transplantation with deceased donor transplantation.

INTERNATIONAL HISTOCOMPATIBILITY WORKING GROUP (NIAID, NIDDK, NCI, NHGRI, JDRF) is a network of laboratories focused on HLA genetics and reagents for HLA-typing. The network has projects to characterize HLA diversity throughout the world, maintains the Major Histocompatibility Complex database (dbMHC), and identifies distinct, well-tolerated HLA mismatches that allow expansion of the pool of compatible donors.

CHAPTER II

Reduce Morbidity and Mortality by Increasing Organ Availability and by Developing Alternatives to Organ Transplantation and Organ-Assistive Technologies

Programs in organ donation, public education, and biomedical research strive to reduce the morbidity and mortality of patients awaiting organ transplants. In addition, NIH supports basic research to develop alternative approaches to organ donation, such as tissue and stem cell engineering and xenotransplantation.

Current Research Challenge

The number of patients waiting to receive organ transplants far exceeds the number of available organs. In 2005, more than 28,000 organ transplants were performed in the United States, yet more than 97,000 individuals remained on organ transplant waiting lists. Although active donor recruitment and education programs have increased organ donation, the organ shortage is growing more severe. As a consequence, 5,895 patients on the waiting lists died in 2005, and this figure does not include patients who were too ill to be placed on the waiting lists. The Department of Health and Human Services (DHHS) takes a two-pronged approach toward reducing the morbidity and mortality of patients on the waiting lists: public education and biomedical research. The lead DHHS agency for organ donor and education programs is the Health Resources and Services Administration (HRSA). NIH is the lead agency for biomedical research programs that address waiting list morbidity and mortality in the longer term by supporting studies to make organ donation safer for living donors; to develop devices to maintain and extend vital organ function in individuals awaiting a transplant; and to develop alternatives to human organ donation through tissue and stem cell engineering and xenotransplantation research.

Another challenge is overcoming the racial and ethnic disparities in the prevalence of end-stage organ failure, rates of transplantation, and outcomes following transplantation. Compared with the general U.S. population, African Americans are at an increased risk for the development of, and complications from, many of the diseases leading to end-stage organ failure and the need for transplant. They also experience less successful outcomes after transplantation. In contrast, other minority groups (e.g., Hispanics and Asians) do not have such a disparity in transplant outcomes. The African American disparity in outcomes may be related to fewer numbers of African American organ donors, resulting in fewer opportunities for successful donor-patient tissue matches; other immunologic and genetic factors, including greater immune responsiveness in African Americans; access to health care; and socioeconomic factors. Considerable research effort is focused on understanding and resolving this racial disparity in transplantation outcomes and finding more closely matched donors, by increasing the numbers of African American donors. One notable success is the steady increase in minority donation over more than a decade, with African Americans comprising 13.6 percent of all organ donors in 2004, comparable to their overall representation in the U.S. population (12.8 percent).

Research Goals for Reducing Morbidity and Mortality by Increasing Organ Availability and by Developing Alternatives to Organ Transplantation and Organ-Assistive Technologies

The Expert Panel recommended two key goals to reduce morbidity and mortality among those on waiting lists: (1) increase organ availability and improve technologies that prolong and improve the function of failing organs; and (2) explore alternatives to organ transplantation.

GOAL 1: Reduce the morbidity and mortality of those on waiting lists through research to increase organ availability and develop technologies that improve and prolong the function of failing organs.

This goal aims to keep those on transplantation waiting lists alive and their impaired organ functioning while they await a suitable organ, and to decrease the waiting time by increasing organ availability.

One way to reduce the patient morbidity and mortality due to waiting times is to develop or improve assistive devices that can augment function of the impaired organ. Such devices are particularly important for pediatric patients and those with end-stage heart failure. Research is also being conducted to more precisely determine the latitude of acceptable matching of HLA tissue markers between recipient and donor. This research may increase the likelihood that a suitable donor can be found for individuals with less common HLA types.

In 2002, the DHHS Secretary's Advisory Committee on Transplantation agreed upon a set of recommendations that addressed specific concerns about organ donation and transplantation, including those relating to living donors. As a result, NIH has developed an epidemiologic program to study the outcomes and health care needs of living donors. This is generating an expanded, reliable dataset on the risks to living organ donors and the short- and long-term health outcomes for the donors.

Key Research Objectives

- Improve the health of patients on transplant waiting lists by advancing and developing assistive/replacement devices.
- Support programs to educate and encourage organ donation by minorities.
- Improve the health of live donors through increased understanding of the short- and long-term health outcomes for live organ donors.

Goal 2: Reduce the morbidity and mortality of those on waiting lists through development of alternatives to whole organ transplantation and the need for human organ donors.

One strategy to relieve the growing need for human organs suitable for transplantation is to develop alternative sources of organs and cells. Xenotransplantation, or cross-species transplantation, offers a potential solution to the severe shortage of human organs. Currently, swine are of primary interest as a potential source of donor organs, tissues, and cells due to their favorable reproductive capacity, as well as anatomical and physiological similarities to humans. However, xenotransplantation poses significant challenges, including the immune response against the xenograft, the physiological limitations of organs or cells functioning in a xenogeneic environment, and the potential transmission of zoonotic infectious agents, such as porcine endogenous retroviruses. Currently, considerable research effort is focused on addressing the immunological and physiological issues critical to the engraftment, survival, and function of xenografts.

Stem cells also hold promise as alternatives to donor cell or tissue transplantation and offer new strategies for treating or preventing a variety of diseases that affect the gastrointestinal tract, liver, and exocrine pancreas. Recently, transplantation of donor pancreatic islets has been successful in the treatment of brittle type 1 diabetes. The ability to generate islets from stem cells could potentially provide a virtually unlimited source of these cells.

Key Research Objectives

- Explore the potential of xenotransplantation as an alternative to human donor organ or cell transplantation and advance our understanding of physiological and immunological barriers to xenotransplantation by conducting preclinical research in trials using large animal models, such as nonhuman primates, as recipients.
- Explore the potential of using stem and progenitor cells to repair, maintain, or replace vital organ functions as alternatives to donor whole organ transplantation.
- Investigate tissue engineering as a means to repair, maintain, or replace vital organ function.

Achieving Research Goals

The Expert Panel concurred that NIH should have a diverse approach to alleviating the growing need for human organs and tissues suitable for organ donation. Goal 1 will have a more immediate impact on addressing the morbidity and mortality of patients on waiting lists compared to Goal 2, which entails longer-term basic and preclinical research. This research is inherently higher risk; however, if successful, it will have the greatest impact on reducing the need for donor organs. The Expert Panel also endorsed investigator-initiated proposals as a means to respond quickly to research opportunities and novel discoveries that might enhance clinical outcomes of transplantation.

The Expert Panel identified additional approaches to advance research to increase organ availability and develop alternatives to organ transplantation. Short- to medium-term activities to achieve the goals are to:

- Establish the Clinical Outcomes of Live Organ Donors program (FY 2006 Initiative).
- Encourage and expand solicited and investigator-initiated research on the health outcomes of live organ donors.
- Maintain programs to educate and encourage organ donation by minorities. Identify factors contributing to the recent success of minority donor programs and facilitate the dissemination and broader implementation of successful strategies.
- Facilitate research on pig-to-nonhuman-primate xenotransplantation to address key immunological, physiological, and viral transmission issues.
- Advance promising product leads for organ-assistive/replacement technologies to address needs of patients on transplant waiting lists. Maximize the use of SBIR/STTR grants in support of these activities.

TABLE 6: Reduce Morbidity and Mortality by Increasing Organ Availability and by Developing Alternatives to Organ Transplantation and Organ-Assistive Technologies

PROGRAMS	GOAL 1 Improve organ availability	GOAL 2 Develop alternatives to transplantation
Immunobiology of Xenotransplantation (NIAID, NIDDK)		x
Minority Organ and Tissue Donation (NIDDK)	x	
Clinical Outcomes of Live Organ Donors (NIAID, NHLBI)	x	
Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH, NHLBI)	x	
Pediatric Circulatory Support Devices (NHLBI)	x	x
Specialized Centers for Cell-Based Therapy (SCCT) for Heart, Lung, and Blood Diseases (NHLBI)		x
Stem Cell Plasticity in Hematopoietic and Nonhematopoietic Tissue (NHLBI, NIDDK, NINDS)		x
Beta Cell Biology Consortium (NIDDK)		x
Development of the Gut, Liver, and Exocrine Pancreas (NIDDK)		x
Progenitor Cell Genome Anatomy Projects (NIDDK)		x
Innovative Concepts and Approaches to Developing Functional Tissues and Organs: Heart, Vascular, Lung, and Blood Applications (NHLBI)		x
Stem Cell Biology and Cell-Based Therapies for Heart, Lung, Blood, and Sleep Disorders (NHLBI)		x
Research Opportunities in Tissue Engineering (NIBIB, NIDDK)		x
Pilot and Feasibility Program in Hematological Diseases (NIDDK)		x
Pilot and Feasibility Program in Diabetes Endocrinology and Metabolism (NIDDK)		x

- Continue investment in tissue engineering and stem cell technologies as a means to repair, maintain, or replace vital organ function through the trans-NIH coordinating groups, e.g., BECON (*http://www.becon.nih.gov/becon.htm*) and the Stem Cell Task Force (*http://stemcells.nih.gov/policy/taskforce*).
- Initiate the Innovative Technologies for Engineering Small Blood Vessels program in FY 2006.

Table 6 highlights programs related to reducing morbidity and mortality, alternatives to organ transplantation, and organ-assistive technologies that advance NIH goals in transplantation research.

Selected Programs

IMMUNOBIOLOGY OF XENOTRANSPLANTATION (NIAID, NIDDK) undertakes studies of porcine-to-nonhuman-primate xenotransplantation to address immunological and physiological issues critical to the engraftment, survival, and function of xenografts.

MINORITY ORGAN AND TISSUE DONATION (NIDDK) spurs increased participation of targeted groups in organ donor programs through development of culturally appropriate educational programs to improve understanding of the benefits of organ and tissue transplantation, and the need, especially in racial and ethnic minority communities, to donate organs and tissues for transplantation.

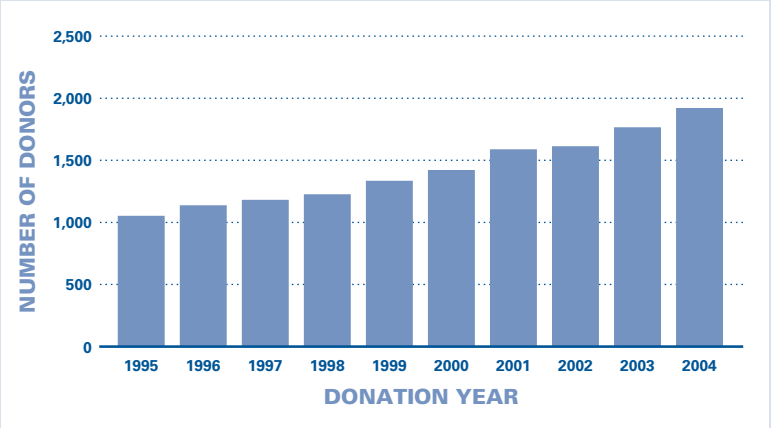
CLINICAL OUTCOMES OF LIVE ORGAN DONORS (NIAID, NHLBI) will investigate the outcomes and health care needs of living donors by developing an expanded, reliable set of demographic and clinical data that will allow exploratory epidemiologic research into the risks to, and outcomes of, living organ donors.

RANDOMIZED EVALUATION OF MECHANICAL ASSISTANCE FOR THE TREATMENT OF CONGESTIVE HEART FAILURE (REMATCH, NHLBI) evaluates the safety, efficacy, and cost-effectiveness of the HeartMate ventricular assist device as compared to intensive medical care to improve survival of patients with end-stage heart failure who are ineligible for transplantation.

PEDIATRIC CIRCULATORY SUPPORT DEVICES (NHLBI) develops devices that provide circulatory support for infants and children weighing less than 25 kilograms with congenital or acquired heart disease, while minimizing risks related to infection, bleeding, and thromboembolism.

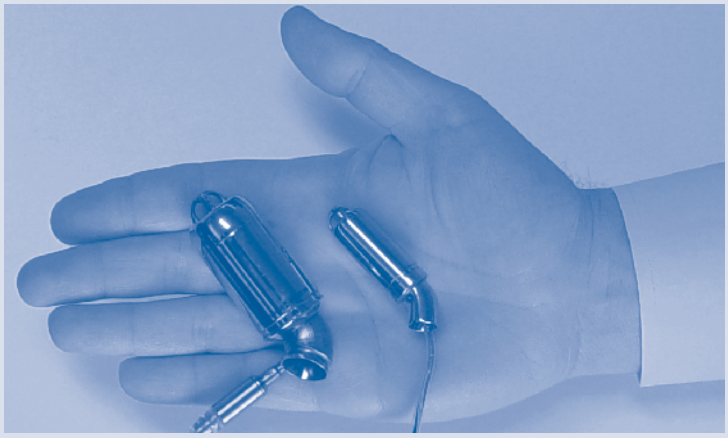
SPECIALIZED CENTERS FOR CELL-BASED THERAPY (SCCT) FOR HEART, LUNG, AND BLOOD DISEASES (NHLBI) encourages translation of basic research advances into the clinical arena by conducting preclinical studies to meet the requirements for an Investigational New Drug application prior to initiating clinical trials.

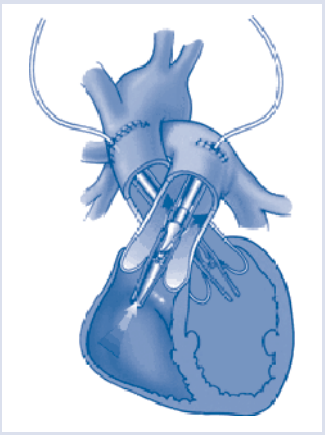
African American Organ Donation, 1995-2004



Over the past decade, organ donation by African Americans has steadily increased, providing organs for many recipients who might otherwise not have received a transplant. This success highlights the value of programs to inform and educate minority communities, and the willingness of individuals to participate in this lifesaving cause.

Pediatric Circulatory Support Systems





Assistive devices that support the functioning of vital organs are an important focus of research and development in transplantation research. The capability to support failing or insufficient function of organs while awaiting transplantation would greatly reduce waiting list morbidity and mortality. [Photos courtesy of Cleveland Clinic and Jarvik Heart, Inc.]

STEM CELL PLASTICITY IN HEMATOPOIETIC AND NONHEMATOPOIETIC TISSUE (NHLBI, NIDDK, NINDS) will advance knowledge of stem cell plasticity and will elucidate the potential signals required for differentiation of hematopoietic stem cells into nonhematopoietic tissues.

BETA CELL BIOLOGY CONSORTIUM (NIDDK) aims to increase the supply of islet cells for transplantation use by conducting basic research on the differentiation of islet cell progenitors, exploring the use of embryonic stem cells or other tissue-specific stem cells in the formation of pancreatic beta cells, and generating reagents to identify and purify stem cells.

DEVELOPMENT OF THE GUT, LIVER, AND EXOCRINE PANCREAS (NIDDK) focuses on the gastrointestinal tract and related organs that share a common embryological origin from the endoderm. The program seeks to increase our understanding of molecular regulation of organ genesis and cell renewal, with the ultimate goal of providing new strategies for treating or preventing a variety of diseases that affect the GI tract, liver, and exocrine pancreas.

PROGENITOR CELL GENOME ANATOMY PROJECTS (NIDDK) advance research on the molecular and cellular characteristics of stem cells during and following development of the pancreas, liver, stomach and intestine, kidney and genitourinary tract, bone, and hematopoietic tissues. The research strives for new insights into the pathologic processes underlying disordered development and maintenance, neoplastic transformation of the targeted organs, and new strategies for repairing or replacing damaged organs in individuals of all ages.

INNOVATIVE CONCEPTS AND APPROACHES TO DEVELOPING FUNCTIONAL TISSUES AND ORGANS: HEART, VASCULAR, LUNG, AND BLOOD APPLICATIONS (NHLBI) advances efforts to engineer tissue *in vitro* as a biological substitute for implantation, or to foster tissue regeneration *in vivo* to replace, repair, maintain, or enhance organ function, including cardiovascular, lung, and blood tissues.

STEM CELL BIOLOGY AND CELL-BASED THERAPIES FOR HEART, LUNG, BLOOD, AND SLEEP DISORDERS (NHLBI) supports fundamental research on cell-based therapies directed at regenerative and reparative medicine for heart, lung, blood, or sleep disorders or diseases.

RESEARCH OPPORTUNITIES IN TISSUE ENGINEERING (NIBIB, NIDDK) provides resources to overcome barriers to advancing research in tissue engineering through multidisciplinary collaborations among clinicians, engineers, and scientists. Specific areas of opportunity include: identification of an optimal cell source and biomaterial for a particular tissue; rational engineering design principles to tissue-engineered constructs; and technologies for commercialization of tissue engineering applications.

PILOT AND FEASIBILITY PROGRAM IN HEMATOLOGICAL DISEASES (NIDDK) supports the development of high-risk pilot and feasibility studies of hematopoietic stem cells to establish a foundation for future research and applications in hematological diseases and their complications.

PILOT AND FEASIBILITY PROGRAM IN DIABETES ENDOCRINOLOGY AND METABOLISM (NIDDK) focuses on protection of pancreatic islets by the anti-apoptosis protein, survivin; PDX-1 expression and embryonic stem cells; insulin production by genetically engineered gut K-cells; and islet cells from bone-marrow-derived progenitor cells.

CHAPTER III
Induce Immune Tolerance to Allografts

Immune tolerance induction strategies aim to selectively prevent deleterious immune responses directed against the transplanted organ, while leaving the protective immune response against pathogens intact. Such a selective blockade would enable long-term graft survival without the complications and risks of broadly immunosuppressive therapy.

Current Research Challenge

Transplanted tissues provoke immune responses in the recipient that are among the most powerful known—up to a thousand times stronger than those that develop in response to vaccination or infection. Better tissue matching reduces these deleterious responses, but only the continued use of broadly immunosuppressive drugs can keep powerful rejection responses under control at the present time. Broad immunosuppression brings with it many harmful side effects, including damage to organ systems and reduced capability to respond to infection. To circumvent the need for drugs that affect immunity in such a general way, research on immune tolerance seeks to find approaches that target specifically those immune cells that participate in the unwanted graft rejection process or in graft-versus-host disease. Developing therapies that would allow control of the immune system in such a specific manner requires both basic understanding and practical tools. The considerable success that has been achieved in animal models and in early pioneering studies in humans strongly supports the prospects for continued major strides in the development of highly specific therapies to induce immune tolerance to the transplant.

Research Goals for Inducing Immune Tolerance

The Expert Panel recommended three key goals for immune tolerance research: (1) further understand the underlying mechanisms of immune tolerance; (2) identify early biomarkers of tolerance or loss of tolerance; and (3) develop potential clinical strategies to induce transplantation tolerance.

GOAL 1: Improve our understanding of immune tolerance by investigating the underlying mechanisms.

Research objectives in this goal aim to elucidate the cellular and molecular reactions that underlie immune tolerance in experimental animal models. Detailed knowledge of the basic biology and biochemistry of immune tolerance will enable development of improved therapeutics for use in the clinic.

Key Research Objectives

- Develop multiple animal models that reliably induce immune tolerance.
- Identify the mechanisms of and targets for the induction, maintenance, and loss of immune tolerance.
- Determine the impact of immune tolerance on protective immunity to pathogens.

GOAL 2: Identify and validate surrogate biomarkers of induction, maintenance, and loss of immune tolerance.

The research objectives to meet this goal aim to define biochemical compounds produced by the body or genes expressed differently under conditions of immune tolerance or loss of tolerance that could serve as markers, capable of rapidly revealing the underlying state of immune system activity in the transplant recipient.

Key Research Objectives

- Identify and validate surrogate biomarkers of immune tolerance or its absence.
- Conduct clinical trials in which biomarkers are used to guide withdrawal of immunosuppressive drugs.

GOAL 3: Conduct clinical trials of immune tolerance strategies in adults and children.

This goal encompasses several important components: advancement of promising immune tolerance strategies through stages of preclinical studies in small animal models and nonhuman primates; Phase I clinical trials for safety; and assessment of efficacy in Phase II and Phase III trials. In the next 5 years, we anticipate that several promising strategies from the preclinical studies will advance to Phase I/II trials.

Key Research Objectives

- Conduct clinical trials of immune tolerance strategies in adults and children based on results from promising animal model studies.
- Pursue international collaborations on immune tolerance research.

Investigator-Initiated Basic Research in Transplantation Immunology

Providing investigators the funding to freely follow their scientific instincts and promising leads in their research programs remains the key strategy for encouraging discovery in transplantation immunobiology. Recent selected accomplishments of investigator-initiated research include:

- Development of a method to expand mouse T regulatory cells *in vitro* for inhibition of unwanted immune responses.
- Tolerance induction through peripheral deletion of alloreactive T cells and preservation of regulatory T cells.
- Discovery of a human receptor for porcine endogenous retrovirus, key to facilitating xenotransplantation research.
- Identification of a potential mechanism for islet allograft rejection.
- Novel costimulatory blockade to prevent graft-versus-host disease and significantly prolong organ graft survival.
- Tolerance induction to fully mismatched renal allografts by cotransplantation of the donor thymus in a miniature swine model.

Achieving Research Goals

Accelerating research on immune tolerance has been a major priority of transplantation research at NIH for several years. NIAID, NHLBI, and NIDDK have previously identified major opportunities for research in immune tolerance as described in research initiatives and planning documents, such as the "NIAID Plan for Research on Immune Tolerance" (*http://www.niaid.nih.gov/publications/immune/contents.htm*), and "Recommendations of the National Heart, Lung, and Blood Institute Heart and Lung Working Group" (*Transplantation* 72:1467-70, 2001).

The Expert Panel identified the following programs, many of them previously initiated by NIH Institutes, to advance immune tolerance research:

- Renew the Innovative Grants in Immune Tolerance program, which focuses on mechanisms of tolerance in the neonatal and early stages of immune development (FY 2006 Initiative).
- Renew the Islet and Kidney Model Grants of the Nonhuman Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) program and continue the heart and lung transplant animal models, focusing on (1) the development and evaluation of novel tolerance induction strategies, and (2) the identification of biomarkers of tolerance and rejection (FY 2007 Initiative).
- Maintain a pilot project/opportunities program for the NHPCSG to fund short-term, innovative pilot projects related to transplantation for type 1 diabetes and allow the NHPCSG to capitalize on new opportunities.
- Renew the Immune Tolerance Network to: (1) continue the network of academic and industry collaborations; (2) expand the scope of work to include transplantation of all organs and cells; and (3) allow focused product manufacturing and nonclinical toxicity and pharmaco-

kinetic studies when industry sponsorship is lacking. Notable examples include certain cell-based therapies and "proof-of-principle" studies of novel monoclonal antibodies or fusion proteins (FY 2007 Initiative).

- Continue small-scale, closely monitored studies of promising approaches to the induction of immune tolerance in human transplant recipients, including drug withdrawal trials in stable transplant recipients maintained on traditional regimens of immunosuppressive drugs, and evaluation of potentially tolerance-inducing strategies such as lymphocyte-depleting agents; mixed chimerism-inducing regimens using a variety of lymphocyte-depleting protocols followed by the infusion of donor bone marrow or isolated donor hematopoietic progenitor cells; and costimulatory blockade.
- In association with the above clinical studies, perform immunologic mechanistic assays, with standardization and coordination of assays across trials, to allow for cross-trial exploratory comparisons and analyses. A major goal will be to define molecular "signatures" of the induction, absence, or loss of tolerance.

Table 7 highlights programs related to inducing immune tolerance to allografts that advance NIH goals in transplantation research.

TABLE 7: Induce Immune Tolerance to Allografts

PROGRAMS	GOAL 1 Determine underlying mechanisms of immune tolerance	GOAL 2 Identify biomarkers	GOAL 3 Conduct clinical trials
Immune Tolerance Network (NIAID, NIDDK, JDRF)	x	x	x
Nonhuman Primate Transplantation Tolerance Cooperative Study Group (NIAID, NIDDK)	x	x	
Innovative Grants on Immune Tolerance (NIAID, NIDDK, NHLBI)	x	x	

Selected Programs

IMMUNE TOLERANCE NETWORK (ITN) (NIAID, NIDDK, JDRF) is an international consortium dedicated to (1) the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma, and allergic diseases, and (2) the prevention of graft rejection following kidney, liver, and pancreatic islet transplantation. ITN clinical trials include mechanistic studies to investigate the basic biological features of clinical tolerance and are supported by a wide range of scientific and technical expertise and core laboratories. In addition to clinical trials, the ITN directs more than a dozen state-of-the-art core facilities to assess the general immunocompetence of potentially tolerant transplant recipients and to monitor induction, maintenance, and loss of tolerance.

NONHUMAN PRIMATE TRANSPLANTATION TOLERANCE COOPERATIVE STUDY GROUP (NIAID, NIDDK) supports the breeding and use of rhesus and cynomolgous macaques for investigations of tolerance induction strategies for kidney, pancreatic islets, heart, and lung transplantation. In addition, the Group conducts research to determine the immunological mechanisms of tolerance induction in nonhuman primates and to identify and validate biomarkers for tolerance induction that may be applied to human transplant recipients.

INNOVATIVE GRANTS ON IMMUNE TOLERANCE (NIAID, NIDDK, NHLBI) support innovative, high-risk, high-impact research on mechanisms of tolerance induction. A major goal is to identify new molecular targets and strategies for tolerance induction through relatively short-term pilot projects.

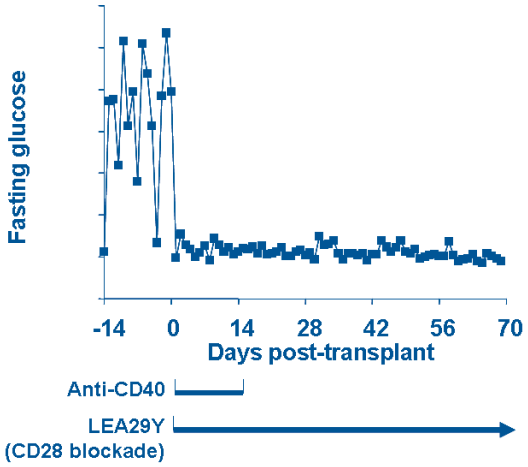
ITN CORE FACILITIES

CORE FACILITY	LOCATION
HLA Typing	University of California, San Francisco, CA
High-Throughput Real Time PCR	Applied Biosystems, Foster City, CA
Real Time PCR (Innovation)	Harvard University, Boston, MA Cornell University, New York, NY
RNA Preparation	University of Pittsburgh, PA McKesson Biosciences, Rockville, MD
MHC-Peptide Tetramer	Virginia Mason Research Center, Seattle, WA
Type 1 Diabetes Autoantibody Facility	University of Colorado, Boulder, CO
Flow Cytometry – United States	Roswell Park Cancer Institute, Rochester, NY
Flow Cytometry – Europe	Thymed GmbH, Mainz, Germany
Alloantibody and Flow Cross-Match	Emory University, Atlanta, GA
Allo-ELISPOT	Cleveland Clinic Foundation, Cleveland, OH
Luminex	Wilhelmina Children's Hospital, Utrecht, Netherlands
Trans-vivo Delayed Type Hypersensitivity	University of Wisconsin, Madison, WI
ELISA	Johns Hopkins Allergy and Asthma Center, Baltimore, MD
Liver-Tissue Analysis	University of Pittsburgh, PA
Renal Pathology	Harvard University, Boston, MA
CMV/EBV Viral Load	ViraCore, Lee's Summit, MO
Clinical Specimen Repository	McKesson Biosciences, Rockville, MD
Bioinformatics/Data Analysis	ITN, Bethesda, MD

ITN Clinical Trials in Transplantation

- Edmonton Protocol – A multisite replication of the Edmonton Islet Transplant Steroid-Free Immunosuppression Protocol
- Tolerogenic Effects of Anti-CD3 and Sirolimus Immunotherapy in Islet Transplantation
- Sirolimus Withdrawal in Renal Transplantation
- Costimulatory Blockade with LEA29Y and Immunosuppression Withdrawal in Renal Transplantation
- Immunosuppression Withdrawal in Liver Transplantation
- Immunosuppression Withdrawal in Liver Transplant Recipients with HCV Infection
- Immunosuppression Withdrawal in Stable Pediatric Liver Transplant Recipients
- Renal Allograft Tolerance through Mixed Chimerism
- Donor Stem Cells and Campath-1H to Induce Renal Transplant Tolerance
- Combined Bone Marrow and Kidney Transplantation for Multiple Myeloma with Renal Failure

Prolonged Islet Allograft Survival With Costimulatory Blockade



NHPCSG member Dr. Christian Larsen and colleagues at Emory University established long-lasting islet allografts in nonhuman primates treated with a combination of experimental drugs targeting costimulatory pathways. Their studies led to new insights into the complexities of tolerance induction and to human transplant trials with one of the experimental agents, LEA29Y.

CHAPTER IV
Establish or Improve Research Infrastructure and Resources

NIH is dedicated to ensuring that transplantation researchers have the infrastructure and resources they need to advance the overall goals of the NIH transplantation research agenda.

Current Research Challenge

Biomedical research is changing rapidly, most notably in the emergence of new technologies and the need for large-scale collaborations to tackle many of the key questions in contemporary science. Examples include the ability to examine the genetic and molecular make-up of cells and tissues; characterize, in detail, complex patterns of gene and protein expression; and analyze vast amounts of information using new computational platforms and analytical tools. The costs of such tools, however, are often beyond the capabilities of single investigators or academic institutions.

In the field of transplantation, research that depends on animal models and human clinical studies requires other enabling resources, especially when the research crosses scientific disciplines and geographic and institutional boundaries. Preclinical transplantation research requires access to unique, genetically engineered mice; high-quality or genetically engineered swine; high-quality, specific pathogen-free nonhuman primates; and unique reagents. Clinical transplantation research requires academic infrastructure and clinical research networks, biostatistical and regulatory support, clinical site monitoring, and training in Good Clinical Practices. Through a variety of mechanisms, NIH strives to ensure that these and other resources are available to NIH-sponsored researchers in transplantation.

Research Goals for Research Infrastructure and Resources

The Expert Panel recommended three key goals for research infrastructure and resources. These goals reflect the NIH effort to enable and facilitate cutting-edge research by providing access to (1) state-of-the-art technologies, (2) unique animal models, and (3) clinical trial support services.

GOAL 1: Enable and facilitate cutting-edge research by providing access to state-of-the-art technologies for cellular, genetic, and molecular research; identification of alloreactive MHC-peptide complexes important to regulating immune response; and bioinformatics platforms for data analysis.

NIH supports a range of programs to develop and facilitate the use of state-of-the-art technologies for molecular, genetic, and cellular research. Other programs are developing and providing researchers access to bioinformatics platforms for data analysis. To advance this goal, NIH supports projects including the NIH Tetramer Facility, which provides custom synthesis and distribution of major histocompatibility complex (MHC)-peptide tetramer reagents to detect antigen-specific T cells; the Immune Epitope Database and Analysis Program, a comprehensive database on antibody and T-cell epitopes and their functions; and a multidisciplinary partnership that is developing a comprehensive picture of innate immunity using a "systems biology" approach.

GOAL 2: Enable and facilitate cutting-edge research by providing access to unique rodent strains and large animal models, and resources such as cells, tissues, and reagents for transplantation research.

NIH supports the development, distribution, and use of high-quality animal models, such as transgenic mice, swine, and nonhuman primates that are essential for transplantation research. Additional programs support the development and distribution of state-of-the-art reagents.

By providing access to these animal models and specialized research reagents, NIH will facilitate cutting-edge research; moreover, the research community will benefit from the wider use of well-standardized materials and protocols and economies of scale.

GOAL 3: Enable and facilitate cutting-edge research by enhancing the pace, productivity, and quality of NIH-sponsored clinical trials through access to various clinical trial support services.

NIH sponsors clinical research to facilitate translation of basic research advances into therapeutic and diagnostic applications. Most NIH-sponsored clinical trial networks receive support from contract research organizations that provide assistance with protocol design and development, site selection and training, data collection, monitoring for compliance with Good Clinical Practice, statistical analysis, and preparation of regulatory documents. Other support services include drug distribution and tracking, and production and dissemination of educational and recruitment materials aimed at physicians and the public. NIH staff negotiate clinical trial agreements with industry partners, provide guidance on study design and regulatory matters, and may serve as the official representatives to the Food and Drug Administration (FDA) or foreign regulatory authorities. NIH Institutes charter and support Data Safety and Monitoring Boards and Study Monitoring Committees that review the progress of clinical trials and provide independent advice to the research sponsor.

TABLE 8: Advantages of SPF Breeding Colonies

- High production rates
- Low infant mortality
- Low viral conversion rates
- SPF assurances, investigator-specified special testing
- Detailed pedigree history and analyses
- MHC typing of the colony
- Directed breeding program; haploidentical donor-recipient pairs
- Bone marrow collection available
- Predictable delivery schedules
- Flexibility for selection of animals

TABLE 9: Current and Projected Species Populations at Breeding Colonies

		RESEARCH OFFSPRING BY YEAR			
SPECIES	CURRENT POPULATION	2004	2005	2006*	2007*
Rhesus	990	122	140	145**	150
Cynomolgus	563	38	60	87	145**

* Offspring numbers for 2006–2007 are projected

** Output at full-strength colony

Achieving Research Goals

The Expert Panel strongly endorsed the continued support of these programs and recommended that NIH periodically evaluate existing programs and consider future opportunities as new technologies and areas of research emerge.

The Expert Panel recommended the creation of an NIH Transplant Centers Program that would provide support to major academic and research institutions in the United States to sustain broad-based, coordinated, interdisciplinary programs in transplant clinical and basic research. The program would target specific activities necessary for continued growth and productivity in transplantation research, including:

- Promotion of scientific interaction between researchers in diverse areas of organ, tissue, and cellular transplantation;
- Formal education of transplant clinicians and basic scientists to prepare them for careers in basic, translational, and clinical transplantation research; and
- Infrastructure support for clinical research.

Table 10 highlights individual infrastructure and resource programs that advance NIH goals in transplantation research.

TABLE 10: Research Infrastructure and Resources

PROGRAMS	GOAL 1 State-of-the-art technologies	GOAL 2 Animal models	GOAL 3 Clinical trial support
Specific Pathogen-Free Macaque Breeding Colonies (NIAID)	x	x	
Development of Immune Monitoring Reagents and Major Histocompatibility Typing Technologies for Nonhuman Primates (NIAID)	x	x	
National Swine Research and Resource Center (NCRR, NIAID, NHLBI)	x	x	
National Primate Research Centers (NCRR)	x	x	
Gene Knockout/Transgenic Mice (NIAID)	x	x	
NIH Knockout Mouse Project (KOMP) (15 NIH ICs)	x	x	
NIH Tetramer Facility (NIAID, NCI)	x		
Immune Epitope Database and Analysis Program (NIAID)	x		
Systems Approach to Innate Immunity, Inflammation, and Sepsis (NIAID)	x		
Clinical Research Networks			x
Collaborative Islet Transplant Registry (NIDDK)	x		x
Islet Cell Resource Centers (NCRR, NIDDK, JDRF)	x		x
United States Renal Data System (USRDS) (NIDDK)			x
Center for International Blood and Marrow Transplantation Research (NCI, NIAID, NHLBI)	x		x
dbMHC (NLM)	x		x
Studies in Pediatric Liver Transplantation (NIDDK)			x
The Type 1 Diabetes - Rapid Access to Intervention Development (T1D-RAID) program (NIDDK)	x		x
Assays for Viral Detection in Donated Organs (NHLBI)	x		x
Production Assistance for Cellular Therapies (NHLBI)	x		x
Bioinformatics Integration Support Contract (NIAID)	x		x

Selected Programs

PRECLINICAL PROGRAMS

SPECIFIC PATHOGEN-FREE (SPF) MACAQUE BREEDING COLONIES (NIAID) supports specific pathogen-free Indian rhesus macaque (*Macaca mulata*) and cynomolgus macaque (*Macaca fasicularis*) breeding colonies to provide a reliable source of high-quality research animals, allowing investigators to undertake long-range planning of immune tolerance research (Tables 8 and 9, page 38).

DEVELOPMENT OF IMMUNE MONITORING REAGENTS AND MAJOR HISTOCOMPATIBILITY TYPING TECHNOLOGIES FOR NONHUMAN PRIMATES (NIAID) supports programs to develop (1) specific reagents to accelerate mechanistic and *in vivo* studies in nonhuman primate models (*http://nhpreagents.bidmc.harvard.edu/NHP/default.aspx*) and (2) high-throughput techniques for MHC typing.

NATIONAL SWINE RESEARCH AND RESOURCE CENTER (NCRR, NIAID, NHLBI) provides biomedical investigators across a variety of disciplines with access to swine models, serves as a central resource for reagents, creates new genetically modified swine, and provides expertise and training to investigators (*http://www.nsrrc.missouri.edu*).

NATIONAL PRIMATE RESEARCH CENTERS (NCRR) provide infrastructure, animals, and expertise to investigators studying various aspects of regenerative medicine and transplantation.

GENE KNOCKOUT/TRANSGENIC MICE (NIAID) increases the availability of immunologically related, gene-targeted mouse strains to the scientific community. Twenty-one mouse strains are currently available through this program; the mice are listed on the Taconic Emerging Models Web site at *http://www.taconic.com/emerging/listing.htm*.

NIH KNOCKOUT MOUSE PROJECT (KOMP) (15 NIH ICS) aims to provide a null mutation for every protein-coding gene in the mouse genome. The use of these "knockout" mice will increase our understanding of mammalian gene function and human disease.

NIH TETRAMER FACILITY (NIAID, NCI) provides custom synthesis and distribution of major histocompatibility complex (MHC)-peptide tetramer reagents to detect antigen-specific T cells. As of August 2005, the Tetramer Facility had provided more than 2,000 tetramers to nearly 500 researchers in 23 countries (*http://www.niaid.nih.gov/reposit/tetramer/index.html*).

IMMUNE EPITOPE DATABASE AND ANALYSIS PROGRAM (NIAID) provides the scientific community with a central source of comprehensive information on antibody and T-cell epitopes, and their functions (*http://www.immuneepitope.org*).

SYSTEMS APPROACH TO INNATE IMMUNITY, INFLAMMATION, AND SEPSIS (NIAID) is a multidisciplinary partnership between Scripps Research Institute and the Institute for Systems Biology that provides a comprehensive and detailed picture of innate immunity using a "systems biology" approach by developing and using proteomics, genomics, and bioinformatics to define the transcription and signaling networks responsible for innate immune function (*http://www.systemsbiology.org*).

CLINICAL PROGRAMS

CLINICAL RESEARCH NETWORKS support many NIH-funded clinical networks. These contract organizations serve as data coordinating centers, assist in biostatistical analysis and clinical trial design, and provide regulatory expertise, clinical site training, and monitoring. In addition, NIH has chartered a number of Data and Safety Monitoring Boards (DSMBs) that review the progress of NIH-sponsored clinical trials.

COLLABORATIVE ISLET TRANSPLANT REGISTRY (NIDDK) collects and disseminates clinical information on islet and beta cell transplantation and related information on pancreatic islet isolation and islet characterization (*http://spitfire.emmes.com/study/isl/index.html*).

ISLET CELL RESOURCE CENTERS (NCRR, NIDDK, JDRF) make up a consortium that generates and distributes Good Manufacturing Practices (GMP)-grade human pancreatic islets to clinical investigators for transplantation; optimizes techniques for isolation, purification, storage, shipment, and characterization of human pancreatic islets for use in clinical protocols; and generates and distributes human pancreatic islets to investigators for use in laboratory-based research studies (*http://www.ncrr.nih.gov/clinical/cr_icr.asp*).

UNITED STATES RENAL DATA SYSTEM (USRDS) (NIDDK) collects and analyzes information on the incidence, prevalence, treatment, morbidity, and mortality of end-stage renal disease (ESRD) in the United States. The U.S. Renal Data System contains information on 250,000 kidney transplants dating from 1978 and provides a variety of reports and online tools for data mining and generation of custom reports.

CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANTATION RESEARCH (NCI, NIAID, NHLBI) is a resource that provides the biomedical community with information on transplantation outcomes by combining data from many centers; identifies uncommon events in long-term survivors; evaluates organizational factors that affect outcome; and provides assistance with protocol design (*www.cibmtr.org*).

dbMHC (NLM) is a public access database resource for hypothesis-driven research on the association of human MHC (HLA) and disease. dbMHC consists of an interactive Alignment Viewer for HLA and related genes, an MHC microsatellite database, a sequence interpretation site for Sequencing-Based Typing (SBT), and a Primer/Probe database (*http://www.ncbi.nlm.nih.gov/mhc/*).

STUDIES IN PEDIATRIC LIVER TRANSPLANTATION (NIDDK) is a data repository that provides to the research community information addressing clinical outcomes after transplantation; degree of immune suppression complications in children, such as renal failure, cardiovascular disease, and cancer; and influence of liver disease on school performance and growth.

THE TYPE 1 DIABETES - RAPID ACCESS TO INTERVENTION DEVELOPMENT (T1D-RAID) PROGRAM (NIDDK) (*http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D-RAID/*) is a program designed to assist in the translation to the clinic of novel therapeutic interventions for type 1 diabetes and its complications. Investigators who are approved gain access to the drug development contract resources of the National Cancer Institute's Developmental Therapeutics Program (*http://dtp.nci.nih.gov/docs/raid/raid_index.html*).

ASSAYS FOR VIRAL DETECTION IN DONATED ORGANS (NHLBI) is a program to validate nucleic acid-based viral detection techniques for use in clinical laboratories. These techniques are used in the filing of FDA Investigational New Drug exemptions and product license applications.

PRODUCTION ASSISTANCE FOR CELLULAR THERAPIES (NHLBI) consists of a consortium that manufactures clinical-grade cellular products for translational research and clinical trials, provides investigators with the data needed to support Investigational New Drug applications, and offers assistance in meeting regulatory requirements.

BIOINFORMATICS INTEGRATION SUPPORT CONTRACT (NIAID) is the cornerstone of the NIAID immunology bioinformatics program. Its overarching goals are to support the advancement, discovery, and testing of new therapies for immune-mediated diseases and to further our understanding of innate and adaptive immunity. The Bioinformatics Integration Support Contract provides online, advanced computer support for archiving, analyzing, and sharing scientific data (*http://www3.niaid.nih.gov/about/organization/dait/bisc.htm*).

APPENDIX A: Abbreviations and Acronyms

ACOT	Advisory Committee on Organ Transplantation
AHRQ	Agency for Healthcare Research and Quality
BMT CTN	Bone and Marrow Transplant Clinical Trials Network
CCTPT	Cooperative Clinical Trials in Pediatric Transplantation
CDC	Centers for Disease Control and Prevention
CITS	Clinical Islet Transplantation Consortium
CMS	Centers for Medicare & Medicaid Services
COBLT	Cord Blood Transplantation Study
CTOT	Clinical Trials in Organ Transplantation
dbMHC	Major Histocompatibility Complex Database
DHHS	Department of Health and Human Services
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
FY	Fiscal Year
ITN	Immune Tolerance Network
JDRF	Juvenile Diabetes Research Foundation International
HRSA	Health Resources and Services Administration
LDLT	Living Donor Liver Transplant
NCBI	National Center for Biotechnology Information
NCCAM	National Center for Complementary and Alternative Medicine
NCI	National Cancer Institute
NCMHD	National Center on Minority Health and Health Disparities
NCRR	National Center for Research Resources
NEI	National Eye Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NHPCSG	Nonhuman Primate Transplantation Tolerance Cooperative Study Group
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases

NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
OPTN	Organ Procurement and Transplantation Network
ORD	Office of Rare Diseases (NIH)
ORWH	Office of Research on Women's Health (NIH)
SBIR/SBTT	Small Business Innovation Research and Small Business Technology Transfer Awards
TRCC	Transplantation Research Coordinating Committee (NIH)

APPENDIX B: Glossary

Adjuvant A component of vaccines used to increase the potency of an antigen in inducing an immune response.

Adult stem cell An undifferentiated cell found in a differentiated tissue that can renew itself and (with certain limitations) differentiate to yield all the specialized cell types of the tissue from which it originated.

Allogeneic Tissues, organs, or cells of the same species, but genetically different.

Allograft A graft of tissue obtained from a donor of the same species as, but with a different genetic make-up from, the recipient.

Allotransplant See allograft.

Antibody A molecule produced by B cells in response to an antigen. Also called an immunoglobulin.

Antigen A substance or molecule that is recognized by the immune system. The molecule can be from a foreign material such as a bacterium or virus, or the molecule can be from one's own body and called a self-antigen.

Antigen-presenting cells Specialized cells, such as macrophages, dendritic cells, and B cells, that capture and display antigens on their surfaces for interactions with T or B cells. For T cells, the antigens are displayed in combination with MHC molecules.

Autoimmune disease Condition in which the immune system mistakenly attacks the body's own organs and tissues.

Autologous Related to self, the components of the same individual.

B cell A type of lymphocyte. B cells secrete antibodies and express them on their cell surfaces.

BMT Bone marrow transplantation, see HSCT.

Central tolerance Process by which potentially autoreactive immune system cells are eliminated before they can mature and be released to circulate in the body.

Chimerism The presence in an individual of a population of cells derived from a genetically dissimilar individual.

Cord blood Blood present in the umbilical vessels at the time of infant delivery.

Cohort In epidemiology, a group of individuals who share a common characteristic. In cohort studies, subjects are followed over time in order to study the incidence of a disease and the relative risk of incurring the disease (the ratio of disease incidence in subjects exposed to certain predictors, risk factors, against those not exposed).

Complement system A set of plasma proteins that act together to attack extracellular pathogens.

Co-stimulation A signal required for complete activation of lymphocytes, required to generate many immune responses.

Epitope The specific part of the antigen that is recognized by an antibody or T-cell receptor.

Genome Complete genetic complement of an organism.

Genotype The genetic constitution of an individual.

GVHD Graft-versus-host disease. A common complication of hematopoietic cell transplantation caused by the reaction of mature T cells from the donor to the allogeneic tissues of the recipient.

Haplotype A group of linked genes contributed by either parent.

HCT Hematopoietic cell transplantation, see HSCT.

HSCT Hematopoietic stem cell transplantation, also called HSCT or bone marrow transplantation. Transplantation of autologous or allogeneic blood cell progenitors to replace bone marrow that is diseased or damaged by therapy; also used in some tolerance induction protocols. Also called HCT or BMT.

HLA Human leukocyte antigen, the major histocompatibility complex (MHC) in humans (see MHC).

Humoral rejection Rejection caused by antibodies produced in the recipient against the donor tissue.

Immune tolerance The safeguards that the immune system naturally possesses to protect from harming self.

Innate immune system Cells and soluble factors that are constitutively present to respond to microorganisms in a non-antigen-specific way.

KIR Killer cell immunoglobulin-like receptor. Activating or inhibitory receptors for HLA molecules; expressed on NK cells.

Leukocyte A white blood cell.

Lymphocytes Small white blood cells that are critical components of the immune system. There are several types of lymphocytes: B cells are primarily involved in the production of antibodies; T cells attack infected cells or release chemicals that activate and direct the movements of other cells to help fight infection or attack foreign matter.

Islets Clusters of cells within the pancreas made up of two types of cells: alpha cells that make glucagon, a hormone that raises the level of glucose (sugar) in the blood, and beta cells that make insulin. In type 1 diabetes, the beta cells are destroyed by the person's immune system.

MHC Major histocompatibility complex, a gene complex that encodes molecules that are found on cell surfaces and display antigen to T cells, see also HLA.

Monoclonal antibody Antibody derived from a single B-cell clone.

NHP Nonhuman primate.

NK cells Natural killer cells. A non-T, non-B lymphocyte with the intrinsic ability to recognize and kill certain tumor and virally infected cells.

Peripheral tolerance The process by which potentially autoreactive cells are controlled after they reach the bloodstream.

Polymorphism The presence of multiple alleles at a specific locus of a chromosome.

Proteomics State-of-the-art methods that combine genomics, molecular biology, and protein chemistry.

Receptor A structure on the surface of a cell with the capability of combining specifically with a structurally matched cognate molecule. Depending on the specific receptor, the latter may be a drug, a cytokine, or an antigen.

Stem cell Cell with the ability to divide for indefinite periods in culture and to give rise to specialized cells.

T cell A type of lymphocyte. T cells develop in the thymus and have receptors that bind specific antigen-MHC complexes. Different types of T cells help to orchestrate the immune response and can issue orders for other cells to make cytokines and chemokines.

Thymus A primary lymphoid organ located in the upper chest area; the site of T-cell maturation.

Tolerogenic Producing immunological tolerance.

Type 1 diabetes A condition in which the pancreas makes little or no insulin because the beta cells have been destroyed by an autoimmune reaction. Because the body is unable to use glucose for energy, insulin must be replaced through injection or by another mechanism.

Xenotransplantation Transplantation of organs, tissues, or cells from one species to another.

APPENDIX C: Immunology of Transplantation

NIH transplantation research engages scientists from a wide range of disciplines, including surgery, pediatric and adult medicine, physiology, infectious diseases, and immunology. This appendix provides a conceptual overview of the major themes in transplantation immunology and a framework in which to view many of the NIH programs highlighted in Chapters I-IV. In the past 30 years, the development of immunosuppressive agents and the refinement of surgical and ancillary therapies have made transplantation the preferred treatment for end-stage disease of the kidneys, heart, liver, lungs, pancreas, and hematopoietic system. NIH programmatic activities and funding mechanisms, including support for innovative basic research projects, preclinical research programs, and clinical trial networks, promote the translation of new basic science discoveries to clinical research and application.

Immunological Barriers to Transplantation

T-CELL IMMUNITY AND ALLOGRAFT TRANSPLANTATION. The major biological barrier to transplantation is the cellular immune response of the recipient against the genetically distinct donor graft. Cellular immune responses are mediated primarily by the recipient's T lymphocytes, which have cell-surface receptors that recognize the "non-self" antigens (alloantigens) of the graft. T cells recognize non-self antigens bound to and presented by the major histocompatibility complex (MHC) molecules (also called human leukocyte antigens, or HLA, in humans). In transplantation, the recipient's T cells may also recognize the donor's MHC molecules as non-self. Two types of T cells are $CD4^+$ T cells and $CD8^+$ T cells. In general, $CD4^+$ T cells function in a regulatory or helper capacity. They produce cytokines that induce B cells to produce antibody or activate nonspecific inflammatory responses, or they activate cytotoxic $CD8^+$ T lymphocytes for cell killing. In contrast, $CD8^+$ T cells function largely as cytotoxic T cells. Both T-cell subsets are involved in graft rejection, although $CD4^+$ and $CD8^+$ T cells may act in concert or singly depending on the organ or tissue transplanted.

In the setting of protective immunity to pathogens, the individual's antigen-presenting cells process the foreign proteins of the infectious agent and present these foreign protein fragments to T cells. In contrast, during allograft rejection, donor antigen-presenting cells that are present in the transplanted organs or cells mediate the first encounters between alloantigens on the surface of the donor cells and the recipient's T cells, a unique feature of allograft recognition termed "direct" presentation. Later, donor antigen presentation is mediated primarily through the uptake and processing of donor proteins by the recipient's antigen-presenting cells, a process called "indirect" presentation. The donor's MHC molecules are the major targets for allorecognition, but responses directed against minor histocompatibility antigens, which represent other genetic variations between individuals, can cause rejection even in HLA-matched individuals. Another unusual property of the allograft reaction is that the response to allogeneic (donor) MHC molecules is several orders of magnitude greater than responses to most other foreign proteins. In allogeneic bone marrow transplantation, donor T cells within the graft may attack the recipient, resulting in acute or chronic graft-versus-host disease (GVHD). T-cell activation occurs shortly after transplantation and, in the absence of immunosuppression, leads to graft rejection or graft-versus-host disease within days to weeks. Strategies to induce transplant tolerance must address both this heightened level of T-cell reactivity and the presentation of alloantigens via the direct and indirect routes.

ANTIBODY-MEDIATED GRAFT REJECTION. Alloreactive antibodies (alloantibodies) can cause rejection even when cellular rejection is prevented by immunosuppressive drugs. Alloantibodies are generated as a consequence of organ and tissue allotransplants, but also from prior exposure to non-self antigens through blood transfusions. A pathologic process called "vascular rejection" is thought to be mediated by the recipient's antidonor antibodies and the complement system. If a recipient has preformed antidonor antibodies at the time of transplantation, hyperacute, immediate rejection is likely to occur. Such antibody-mediated hyperacute rejection is a current obstacle to xenotransplantation, where the best candidate donor species, swine, possesses an antigen not present in humans to which all humans have preformed

antibodies. Alloantibodies are also components of chronic graft rejection and the accumulation of damage that leads to organ dysfunction. B cells may also play a role in allograft rejection by acting as antigen-presenting cells that display non-self antigens for recognition by T cells.

POTENTIAL ROLE OF NATURAL KILLER CELLS IN SETTING THE STAGE FOR ALLOGRAFT REJECTION. Natural killer (NK) cells are triggered by an array of activating receptors, but the killing of autologous or "self" cells is prevented by the presence of a family of inhibitory receptors, the killer cell immunoglobulin-like receptors (KIRs). Individual KIRs recognize shared portions of various self or similar MHC molecules. In bone marrow transplantation, the donor NK cells may play a key role in antileukemia effects when the KIRs are not shared by donor and recipient leukemia cells; however, NK cells may also contribute to deleterious graft-versus-host disease when the KIRs are not shared. Thus, the degree of KIR matching and mismatching between donor and recipient influences bone marrow transplant outcomes in a complex fashion and is an emerging area of study. In solid organ and islet transplantation, the role of recipient NK cells in graft rejection is unknown. However, some studies suggest that NK cells may play a significant role in these settings.

Immune-Based Approaches to Control Chronic Allograft Rejection

Chronic rejection of transplants is currently the major cause of delayed allograft loss, and measures that are highly successful in preventing acute rejection frequently fail to prevent chronic rejection. Loss of organ transplants beyond the first year may also result from recurrence of the primary disease, autoimmune responses, deleterious effects of the immunosuppressive therapy, or viral infections. Immunological approaches to chronic rejection include the development of assays that define the recipient's state of immune responsiveness to a graft, thus predicting rejection before severe organ damage occurs; identification of mechanisms of chronic rejection and other late problems; and development of appropriate therapies for prevention. Major areas of immunological research on prevention of graft rejection are (1) development of improved immunosuppressive drugs and (2) the induction of donor-specific immune tolerance.

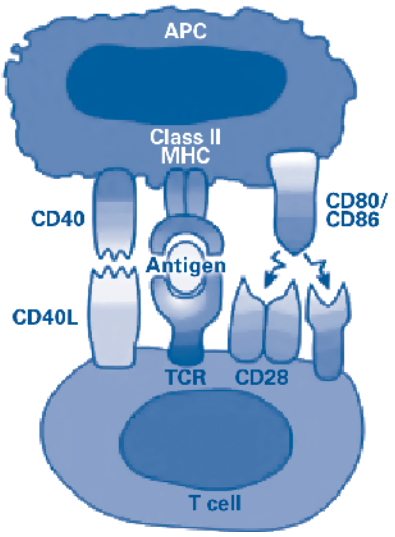
IMPROVED IMMUNOSUPPRESSIVE DRUGS. Better immunosuppressive drugs would continue to target T cells, B cells, or antigen-presenting cells that are active in rejection, but without unwanted side effects. For example, inhibitors of the signaling molecule calcineurin are highly effective by interfering with a cellular factor needed to activate genes in T cells, but have significant kidney, cardiac, and vascular toxicity. Potentially, development of drugs that are more specific for particular target cells or signaling/activation pathways may have fewer deleterious effects. As an example, a growing understanding of T-cell development and activation underpins a number of improved immunosuppressive agents and novel investigational agents, including those that target the T-cell receptor, costimulatory pathways, or cytokines vital to T-cell function. Nevertheless, interfering with any T cells undergoing activation may unintentionally impair responses needed to combat infections or tumors. Current therapeutics lack the ability to target only those cells that are involved in rejection, a need that is being addressed by research into new methods for generating donor-specific immune tolerance.

IMMUNE TOLERANCE. Immune tolerance is the selective modulation of the immune system to prevent or inhibit harmful immune responses while keeping protective responses intact. Induction of immune tolerance should result in long-term graft acceptance without the continued use of immunotherapy, the ultimate goal of transplantation immune tolerance research. Immune tolerance strategies are based upon the natural processes by which the body avoids immunological harm to itself. There are two general mechanisms of immune tolerance, **central** and **peripheral** immune tolerance, both of which appear to be applicable to transplantation tolerance. Approaches directed at central and peripheral immune tolerance have shown striking success in rodent transplantation models, and academic investigators and the pharmaceutical and biotechnology industries are developing candidate drugs for evaluation in larger animals and in early-phase human clinical studies. However, durable transplant tolerance has been difficult, and in most cases impossible, to establish in larger animal models including nonhuman primates, highlighting the need for additional basic, developmental, and applied research.

- **CENTRAL TOLERANCE.** Developing T and B lymphocytes undergo rigorous selection processes based upon receptor binding strength for self-antigens. T-cell selection occurs initially in the thymus, where those T cells with receptors that cannot bind at all to self-antigens die before maturing. T cells with T-cell receptors that bind very strongly to self peptide-MHC complexes also die, while those that bind with a lesser affinity survive to populate the body. Central tolerance processes eliminate a great number of T cells in the thymus, and those that survive constitute the entire population of T cells that can recognize foreign antigens with high affinity. Similarly, in the bone marrow, B cells with receptors that bind self-antigens strongly are also eliminated. The thymus and bone marrow express antigens from many tissues of the body, enabling removal of the majority of potentially dangerous autoreactive cells before they mature. Direct introduction of antigens to the thymus prior to transplantation may be of very limited applicability to human transplants. However, a central tolerance approach termed "mixed chimerism" may be achievable in hematopoietic cell transplantation or as a conditioning approach before organ transplantation.

  Mixed chimerism refers to the coexistence of significant percentages of both donor and host (recipient) hematopoietic cells within the body. In individuals with mixed chimerism, donor hematopoietic cells entering the recipient thymus can tolerize newly developing recipient-derived T cells. Thus, T cells positively selected in the thymus after chimera formation will not be able to mount a strong response against the antigens present on the foreign donor cells that functioned in their selection. At least in some circumstances, the result is a very effective method for reducing or eliminating the potential for unwanted T-cell responses. However, T cells already present in the periphery before chimera formation need to be eliminated or controlled. Therefore, mixed chimerism without other ablative treatments is only partially effective. Potentially, a combination of central tolerance and peripheral tolerance could provide powerful control over a wide range of T-cell-mediated immune responses.

Targeting Costimulatory Pathways



Costimulatory pathways come into play only when the T-cell receptor engages antigen/MHC on the APC, thereby targeting T cells involved in antigen-specific responses. Blocking costimulation or engaging receptors that counteract costimulatory signals block T-cell activation. Molecules involved in costimulation that function in transplant rejection/and tolerance include CD28, CTLA-4, ICOS, PD-1, CD154, CD137, CD134, and CD27.

- **PERIPHERAL TOLERANCE.**
  - **T-Cell Antigen Receptors.** Delivery of soluble peptides or proteins (antigens) without an adjuvant usually does not elicit immune responses, and has been shown in many animal studies to down-modulate T-cell responses in an antigen-specific manner. Approaches include intravenous injections or oral delivery of antigens. These approaches may lead to anergy in antigen-specific T cells or the triggering of regulatory T cells (see below). Although antigen targeting may appear to be the ideal approach for manipulating peripheral tolerance, there are important problems that currently limit this approach for therapy of existing disease. The major problem is practical: knowing which antigens to use. For T cells, there is insufficient knowledge of the exact alloantigens presented by MHC molecules. The great potential for T-cell receptor diversity makes controlling existing responses by antigen targeting a formidable task, but this remains an important goal being pursued by researchers in basic transplantation immunology.
  - **Costimulatory and Other Molecules.** For T cells, binding of the T-cell receptor to antigen-MHC alone is insufficient to mount an immune response; a simultaneous signal from another group of cell-surface molecules, termed costimulatory molecules, must also be present. These costimulatory molecules include B7-1 (CD80) and B7-2 (CD86), which are expressed on the surface of activated antigen-presenting cells. For B cells, sufficient quantity of antigen is required to aggregate their B-cell receptors, and most B cells also require signals from activated "helper" T cells in order to develop into potent antibody-secreting cells.

    The approach using costimulatory blockade bypasses the need to identify antigen-specific cells. In this approach, broad inhibition of T-cell costimulation will include those T cells undergoing activation toward alloantigens, resulting in T-cell anergy or deletion, thus circumventing transplant rejection.
  - **Immunoregulatory T Cells.** Subsets of T cells, called regulatory T cells, are now known to be a key effector of antigen-specific tolerance in humans. The prospect that methods may be devised to generate and manipulate regulatory T cells in an antigen-specific manner suggests many possibilities for new tolerogenic treatments.

    T cells expressing the cell surface molecules CD4 and CD25 ($CD4^+CD25^+$ T cells) have recently been defined in humans and are known to play a major regulatory role. $CD4^+CD25^+$ T cells develop in the thymus like conventional T cells, and respond to antigens. When activated *in vitro*, they respond with a low level of cell division, but become potent suppressors of other T cells nearby. Other subsets of regulatory T cells with somewhat different cell surface molecules, termed Tr1 and Th3, respond to antigens by releasing cytokines that counteract cytotoxic T-cell activity. Tr1 and Th3 cells release the cytokines interleukins-4, -10, -13, and transforming growth factor-beta, each of which has potent anti-inflammatory effects. Most likely, these regulatory cells respond to specific antigens presented by activated antigen-presenting cells in affected tissues and act to suppress local inflammatory responses.
  - **NK T Cells.** Another distinct regulatory population, NK T cells, bears surface molecules commonly found on both natural killer cells (NK) and T cells. NK T cells produce the cytokines interleukins-4, -10, and interferon-gamma, probably influencing the activation of other regulatory T-cell populations. NK T cells recognize the antigen-presenting cell surface molecule CD1, which presents lipid antigens, in contrast to the peptide-presenting MHC molecules. While the role of NK T cells in immune responses has been the subject of much controversy, these cells appear to play an important regulatory role in maintenance of transplant tolerance. In rodent models of cardiac and islet transplantation, immune tolerance to cardiac allografts or islet xenografts (rat islets transplanted into mice) induced by blocking T-cell costimulatory signals could not be maintained if the animals lacked NK T cells. In bone marrow transplantation, recipient NK T cells may also play an important role in reducing graft-versus-host disease. Further investigations are necessary to elucidate the physiologic role of NK T cells in transplantation.

Innate Immunity and Graft Rejection

The innate immune system provides the initial responses to infection, taking both immediate defensive actions as well as upregulating costimulatory molecules that lead to the activation of T and B cells. Langerhans cells of the skin, tissue dendritic cells and macrophages, and tissue-associated lymphocytes such as NK cells and gamma-delta receptor T cells, are components of the innate immune system that trigger these early responses to infection.

A family of innate immune receptors, known as the Toll-like molecules, has recently been shown to function in the early detection and response to infection by recognizing microbial components that include bacterial cell wall molecules, viral double-stranded RNA, and bacterial nucleic acids. In addition, innate immune responses may be involved in endogenous pathways of inflammation, and may play a role in graft rejection. New information indicates that Toll-like molecules may also detect molecules of stress or tissue damage, such as those that may be associated with allografts. Cellular necrosis, occurring as a result of tissue damage, can trigger immature dendritic cells to become highly activated and to function as antigen-presenting cells for T cells. Thus, allo- or potentially even self-antigens that happen to be presented in the context of innate immune activation may trigger unwanted T-cell responses. Innate immune activation appears to be a significant characteristic of brain death of the donor; this may be one of the reasons that outcomes of transplants from deceased donors have poorer outcomes than those utilizing organs from living donors, and is an area of active research. The importance of innate immune responses in graft rejection is not yet well understood; however, the cellular pathways and genes involved in innate immunity are rapidly becoming well characterized. Advances in this area may open additional strategies for conquering chronic graft rejection.

Investigator-initiated Basic Research in Transplantation Immunology

Providing investigators the funding to freely follow their scientific instincts and promising leads in their research programs remains the key strategy for encouraging discovery in transplantation immunobiology. Recent selected accomplishments of investigator-initiated research include:

- Development of a method to expand mouse T regulatory cells *in vitro* for inhibition of unwanted immune responses.
- Tolerance induction through peripheral deletion of alloreactive T cells and preservation of regulatory T cells.
- Discovery of a human receptor for porcine endogenous retrovirus, key to facilitating xenotransplantation research.
- Identification of a potential mechanism for islet allograft rejection.
- Novel costimulatory blockade to prevent graft-versus-host disease and significantly prolong organ graft survival.
- Tolerance induction to fully mismatched renal allografts by cotransplantation of the donor thymus in a miniature swine model.

APPENDIX D: Expert Panel on Transplantation Research

Charles B. Carpenter, M.D., Panel Chair
Harvard University
Boston, MA

Hugh Auchincloss, M.D.
Massachusetts General Hospital
Boston, MA

Bruce Blazar, M.D.
University of Minnesota
Minneapolis, MN

Kelvin Brockbank, Ph.D.
Organ Recovery Systems
Charleston, SC

James Burdick, M.D.
U.S. Department of Health and Human Services
Rockville, MD

Joel Cooper, M.D.
Washington University Center for Advanced Medicine
St. Louis, MO

R. Duane Davis, M.D.
Duke University
Durham, NC

Mary Ellison, Ph.D.
United Network for Organ Sharing
Richmond, VA

Margaret A. Goodell, Ph.D.
Center for Cell and Gene Therapy
Baylor College of Medicine
Houston, TX

Mary Horowitz, M.D., M.P.H.
Center for International Blood and Marrow Transplant Research
Medical College of Wisconsin
Milwaukee, WI

Marc Jenkins, Ph.D.
Center of Immunology
University of Minnesota
Minneapolis, MN

Chris Larsen, M.D., Ph.D.
Emory University
Atlanta, GA

Joren Madsen, M.D., D.Phil.
Massachusetts General Hospital
Boston, MA

Arthur Matas, M.D.
Department of Surgery
University of Minnesota
Minneapolis, MN

Kim Olthoff, M.D.
University of Pennsylvania
Philadelphia, PA

Camillo Ricordi, M.D.
University of Miami
Miami, FL

Daniel P. Schuster, M.D.
Washington University School of Medicine
St. Louis, MO

Abraham Shaked, M.D., Ph.D.
University of Pennsylvania
Philadelphia, PA

Megan Sykes, M.D.
Transplantation Biology Research Center
Massachusetts General Hospital
Boston, MA

Laurence Turka, M.D.
University of Pennsylvania
Philadelphia, PA

Kathryn D. Wood, D.Phil.
Transplantation Research Immunology Group
Nuffield Department of Surgery
University of Oxford
Oxford, England

APPENDIX E: NIH Transplantation Research Coordinating Committee

Shiv A. Prasad, Ph.D., Chair
Chief
Transplantation Immunobiology Branch
Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases

Debra J. Babcock, M.D., Ph.D.
Neural Systems Psychopathology Program
Experimental Therapeutics Branch
National Institute of Mental Health

Dorynne Czechowicz, M.D.
Division of Clinical Neuroscience and Behavioral Research
National Institute on Drug Abuse

Eleni Kousvelari, D.D.S., D.Sc.
Acting Director
Center for Biotechnology and Innovation
National Institute of Dental and Craniofacial Research

Judith Massicot-Fisher, Ph.D.
Heart Research Program
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute

Catherine M. Meyers, M.D.
Director
Inflammatory Renal Diseases Program
Division of Kidney, Urologic and Hematologic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases

Alan N. Moshell, M.D.
Branch Chief
Skin Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Denise A. Russo, Ph.D.
Division of Metabolism and Health Effects
National Institute on Alcohol Abuse and Alcoholism

D. Stephen Snyder, Ph.D.
Etiology of Alzheimer's Disease
Neuroscience and Neuropsychology of Aging
National Institute on Aging

Ursula Utz, Ph.D., M.B.A.
Program Director
National Institute of Neurological Disorders and Stroke

Fei Wang, Ph.D.
Program Director
Tissue Engineering Program
Division of Discovery Science and Technology
National Institute of Biomedical Imaging and Bioengineering

Roy S. Wu, Ph.D.
Chief
Clinical Grants and Contracts Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute

APPENDIX F: NIH-Solicited Programs in Transplantation

I. Improve Outcomes for Organ and Cell Transplantation

ADULT-TO-ADULT LIVING LIVER TRANSPLANT COHORT STUDY supports research on living donor liver transplantation (LDLT), including informed consent for the donor; donor recovery, morbidity, and quality of life; the benefits of LDLT versus being placed on the waiting list for a deceased donor transplant; the severity of hepatitis C recurrence after LDLT; and recovery of liver function after LDLT (NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01DK062531	Adult-to-Adult Living Donor Liver Transplantation	Fisher, Robert A. Virginia Commonwealth University
U01DK062444	Adult-to-Adult Living Donor Liver Transplantation Cohort	Freise, Chris University of California, San Francisco
U01DK062496	ADLDT: An Opportunity To Expand the National Donor Pool	Ghobrial, Rafik M. University of California, Los Angeles
U01DK062498	Living Donor Liver Transplant Data Coordinating Center	Merion, Robert M. University of Michigan, Ann Arbor
U01DK062494	Adult-to-Adult LDLT Cohort Study	Shaked, Abraham University of Pennsylvania
U01DK062505	Right Lobe Living Donor Liver Transplantation in Adults	Shrestha, Roshan University of North Carolina, Chapel Hill
U01DK062484	Living Donor Liver Transplantation Cohort Study	Berg, Carl University of Virginia
U01DK062483	Adult-to-Adult Living Donor Liver Transplantation Cohort	Emond, Jean Columbia University
U01DK062467	Adult Live Donor Liver Transplant: A Comparative Analysis	Abecassis, Michael Northwestern University
U01DK062536	Adult-to-Adult Living Donor Liver Transplantation Cohort	Trotter, James F. University of Colorado

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK (BMT CTN) conducts multicenter trials to improve transplant outcomes and allow promising therapies to be developed/evaluated using high-quality studies that provide definitive answers to significant problems in HCT (NHLBI, NCI).

AWARD	NETWORK	PRINCIPAL INVESTIGATOR INSTITUTION
U01 HL069233	Nebraska Blood And Marrow Transplant Research Network	Vose, Julie University of Nebraska Medical Center
U01 HL069278	Blood and Marrow Transplant Clinical Research Network	Forman, Stephen City of Hope/Beckman Research Institute
U01 HL069286	Bone Marrow Transplant Clinical Network	Stadtmauer, Edward University of Pennsylvania
U01 HL069291	BMT Clinical Trial Network at Stanford	Negrin, Robert Stanford University
U01 HL069294	BMT Clinical Research Network Data Coordinating Center	Horowitz, Mary Medical College of Wisconsin
U01 HL069249	Randomized Trial of CD8 T-Cell Depletion in PBSC Transplantation	Antin, Joseph Dana-Farber Cancer Institute
U01 HL069273	CTLA-4 Blockade To Stimulate Allogeneic Graft Vs Tumor	Ball, Edward University of California, San Diego
U01 HL069330	University of Michigan Core Clinical Center for The BMT Clinical Research Network	Ferrara, James University of Michigan, Ann Arbor
U01 HL069348	Phase III Trial of UUCB +/- MSCs in Hematologic Cancers	Lazarus, Hillard Case Western Reserve University
U01 HL069290	Enhanced GVHD Prophylaxis in Allogeneic Stem Cell Transplantation	Weisdorf, Daniel University of Minnesota
U01 HL069246	Blood and Marrow Transplant Clinical Research Network	Applebaum, Fred Fred Hutchinson Cancer Institute
U01 HL069310	Translational Research in Blood and Marrow Transplantation	Jones, Richard Johns Hopkins University
U01 HL069301	Core Clinical Center for BMT Clinical Research Network	Wingard, John University of Florida, Gainesville
U01 HL069315	IL-7 for Immune Recovery After Hematopoietic Allograft	O'Reilly, Richard Memorial Sloan Kettering Cancer
U01 HL069334	Reduced Intensity Versus Myeloablative Conditioning	Giralt, Sergio MD Anderson Cancer Center
U01 HL069274	Core Clinical Center Application for Duke University	Kurtzberg, Joanne Duke University
U01 HL069254	Pediatric Blood and Marrow Transplant Consortium	Gamis, Alan/Schultz, Kirk Children's Mercy Hospital

BMT CTN CLINICAL TRIALS	STATUS
Fluconazole Versus Voriconazole for the Prevention of Invasive Fungal Infections in Allogeneic Blood and Marrow Transplant Recipients	Active
Tandem Autologous Stem Cell Transplants +/- Post Second Autologous Transplant Maintenance Therapy Versus Single Autologous Stem Cell Transplant Followed by Matched Sibling Non-Myeloablative Allogeneic Stem Cell Transplant for Patients with Multiple Myeloma	Active
Phase III Randomized Multicenter Study Comparing G-CSF Mobilized Peripheral Blood Stem Cell With Marrow Transplantation From HLA-Compatible Unrelated Donors	Active
Autologous Versus Nonmyeloablative Hematopoietic Cell Transplantation (HCT) for Patients with Relapse Follicular Non-Hodgkin's Lymphoma	Active
Transplants of HLA-Matched, CD34+ Enriched, T-Cell-Depleted Peripheral Blood Stem Cells Isolated by the CliniMACS System in the Treatment of Patients with AML in Second Complete Remission	Active
Initial System Treatment of Acute GVHD: A Phase II Randomized Trial Evaluating Etanercept, Mycophenolate Mofetil (MMF), Denileukin Diftitox (Ontak), and Pentostatin in Addition to Corticosteroids	In development
Purine Analog-Based Conditioning for Allogeneic Stem Cell Transplantation in Patients with Severe Aplastic Anemia	In development
Two Targeted Monoclonal Antibody Therapies (Rituxan versus Bexxar) Combined with BEAM Conditioning Followed by Autologous Transplant for Patients with Persistent or Relapsed Chemotherapy Sensitive Diffuse Large B-Cell Non-Hodgkin's Lymphoma	In development

CLINICAL TRIALS IN ORGAN TRANSPLANTATION (CTOT) supports interventional or observational clinical studies, accompanied by mechanistic studies, to enhance the understanding of and ultimately reduce the immune-mediated morbidity and mortality of organ transplantation (NIAID, NHLBI, NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 AI063623	Noninvasive Markers and Transplant Outcome in Humans	Sayegh, Mohamed Harvard University
U01 AI063589	Novel Therapies of Chronic Allograft Dysfunction	Shaked, Abraham University of Pennsylvania
U01 AI063594	Noninvasive Markers and Transplant Outcome in Humans	Heeger, Peter Cleveland Clinic Lerner College of Medicine
U01 AI067067	Data Coordinating Center for Organ Transplant Clinical Trial Networks	Ikle, David PPD, Inc.

CTOT CLINICAL TRIALS	STATUS
Noninvasive Monitoring To Predict Outcome in *De Novo* Kidney Transplant Recipients	In development
B-cell Depletion by Anti-CD20 in Renal Allograft Recipients Who Develop *De Novo* Anti-HLA Antibodies	In development
Noninvasive Diagnosis of Renal Allograft Rejection by Urinary Cell mRNA Profiling	In development
Molecular Profiling of Donor and Recipient Proinflammatory and Alloimmune Response	In development
Safely Limiting Long-Term Renal and Cardiac Toxicity in Stable Heart Allograft Recipients Through Drug Substitution/Calcineurin Inhibitor Withdrawal	In development

CLINICAL ISLET TRANSPLANTATION CONSORTIUM supports research to design and implement human islet transplantation studies that will result in improved treatment of T1D. A priority of CITC researchers is to achieve licensure of an islet product. The CITC is also undertaking a clinical investigation of islet transplantation in Medicare beneficiaries as directed by the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 (NIDDK, NIAID).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 AI065193	Advancing Islet Transplants for Type 1 Diabetes Care	Hering, Bernhard University of Minnesota
U01 AI065192	Innate Immunity in Clinical Islet Transplantation	Korsgren, Olle Uppsala University
U01 AI065191	Islet Transplant – Costimulatory Blockade with LEA29Y	Shapiro, A. M. James University of Alberta
U01 DK070430	B-Lymphocyte Immunotherapy in Islet Transplantation	Naji, Ali University of Pennsylvania
U01 DK070460	Strategies To Improve Long-Term Islet Graft Survival	Ricordi, Camillo University of Miami
U01 DK070431	Clinical Islet Transplantation: Data Coordinating Center	Clarke, William University of Iowa

CIT CLINICAL TRIALS	STATUS
Open Randomized Multicenter Study To Evaluate Safety and Efficacy of Low Molecular Weight Sulfated Dextran in Islet Transplantation	In development
Strategies To Improve Long-Term Islet Graft Survival	In development
Multicenter, Open-Label Clinical Trial of the Efficacy of Peritransplant Administration of Deoxyspergualin in Promoting Restoration of Insulin Independence After Single-Donor Islet Allotransplantation in Nonuremic Type 1 Diabetic Recipients	In development
Islet Transplantation in Type 1 Diabetes with LEA29Y (Belatacept) Maintenance Therapy	In development
B-Lymphocyte Immunotherapy in Islet Transplantation: Toward Calcineurin-Inhibitor Free Immunosuppression	In development
Islet Transplantation Versus Standard Medical Therapy in Type 1 Diabetic Kidney Allograft Recipients	In development
Islet Transplantation in Type 1 Diabetes	In development

COOPERATIVE CLINICAL TRIALS IN PEDIATRIC TRANSPLANTATION (CCTPT) conducts clinical trials of immunosuppressive agents in pediatric kidney recipients (NIAID).

AWARD	PROJECT TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 AI055795	New NAPRTCS Trials in Steroid-free Immunosuppression	Salvatierra, Oscar Stanford University
U01 AI055801	B7 Costimulatory Blockade in Pediatric Transplantation	Harmon, William Children's Hospital (Boston)
N01 AI15432	Clinical and Statistical Coordinating Center for the CCTPT	Stablein, Donald M. The EMMES Corporation

CCTPT CLINICAL TRIALS	STATUS
Calcineurin Inhibitor Sparing Protocol in Living Donor Pediatric Kidney Transplantation	Followup
A Randomized Trial of Immunomodulatory Diet with Arginine and Omega-3 Fatty Acids in Renal Transplant Recipients	Closed
Evaluation of Intravenous Gamma Globulin as an Agent to Lower Allosensitization and Improve Allograft Survival in Highly Sensitized Pediatric ESRD Recipients	Closed
Evaluation of IGIV-C as an Agent to Reduce Anti-HLA Antibodies and Improve Transplantation Results in Cross-Match Positive Living Donor Kidney Allograft Recipients	Closed
Controlled Therapy if Induction Therapy in Renal Transplantation	Closed
A Randomized, Multicenter Comparative Trial of Tacrolimus with Steroids and Standard Daclizumab Induction Versus a Novel Steroid-Free Tacrolimus-Based Immunosuppression Protocol with Extended Daclizumab Induction in Pediatric Renal Transplantation	Active
An Open-Label, Comparative Study of the Effect of Sirolimus Versus Standard Treatment on Clinical Outcomes and Histologic Progression of Allograft Nephropathy in High-Risk Pediatric Renal Transplant Patients	Followup
A Double-Blinded Randomized Trial of Steroid Withdrawal in Sirolimus and Cyclosporine-Treated Primary Transplant Recipients	Followup
Evaluation of the Safety and Immunogenicity of Varivax (Live-Attenuated Varicella-Zoster Virus Vaccine) in Pediatric Renal Transplant Recipients	Closed
Safety in Immunomodulatory Functions of Campath-1H	Active

CORD BLOOD TRANSPLANTATION STUDY established ethnically diverse, unrelated allogeneic cord blood banks and determined the utility of umbilical cord blood cells for transplantation of patients with malignant and nonmalignant blood diseases who did not have a matched related or unrelated donor, or who must receive a transplant quickly. The clinical trial has been completed and data analysis is ongoing (NHLBI).

GENOMICS OF TRANSPLANTATION COOPERATIVE RESEARCH PROGRAM supports cooperative, interdisciplinary research for large-scale, broad-scope genomic studies in clinical transplantation. The goal is to understand the genetic basis of immune-mediated graft rejection and differences in transplant outcomes, and provide a rational basis for the development of more effective treatment and prevention strategies to improve long-term graft survival and provide better quality of life for transplant recipients (NIAID).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U19 AI063603	Genomics for Kidney Transplantation	Salomon, Daniel Scripps Research Institute

HLA GENETICS IN IMMUNE-MEDIATED DISEASES conducts research to generate high-quality HLA-disease association data for public use that will be submitted to and maintained by dbMHC. Awards will be made in FY2005 (NIAID, NINDS).

HYPERACCELERATED AWARD/MECHANISMS IN IMMUNOMODULATION TRIALS supports mechanistic studies in conjunction with clinical trials of immunomodulatory interventions for immune-mediated diseases, including asthma and allergy, chronic inflammatory and autoimmune disorders, transplant rejection, and primary immunodeficiency diseases (NIAID, NHLBI, NIA, NIAMS, NIDCR, NIDDK, NINDS, ORWH).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
R01 AI049156	Pharmacodynamic Thresholds of Immunosuppression	Sindhi, Rakesh K. Children's Hospital University of Pittsburgh
R01 AI054115	Gene Polymorphisms and Kidney Transplant Outcome	Oetting, William S. University of Minnesota
R01 AI055234	Immunological Monitoring of Heart Allograft Recipients	Suciu-Foca, Nicole Columbia University
R01 AI061739	Defining Biomarkers in Pediatric Renal Transplantation	Sarwal, Minnie M. Stanford University
R01 DK064588	Immune Parameters in a Steroid Paring Clinical Trial	Reinsmoen, Nancy L. Duke University
R01 DK070632	Campath-1H and Calcineurin-Inhibitors in Renal Transplant	Knechtle, Stuart J. University of Wisconsin, Madison

IMMUNOPATHOGENESIS OF CHRONIC GRAFT REJECTION supports research on the immunological mechanisms of chronic allograft dysfunction (NIAID, NHLBI).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
P01 AI050153	Transplant Arteriosclerosis: Viral and Host Mechanisms	Mocarski, Edward Stanford University
P01 AI050157	Immunopathogenesis of Chronic Allograft Rejection	Sayegh, Mohamed H. Children's Hospital, Boston
P01 AI050162	Gene Expression Microarrays in Lung Rejection	Hertz, Marshall I. University of Minnesota, Twin Cities
P01 HL070294	Mechanisms of Chronic Pathobiology In Allografts	Strauch, Arthur Ohio State University
P01 HL070295	Chronic DTH And IFN-Gamma In Human Graft Arteriosclerosis	Pober, Jordan S. Yale University

INTERNATIONAL HISTOCOMPATIBILITY WORKING GROUP conducts studies to catalog the human leukocyte antigen (HLA) gene complex, and characterize the relationship between certain HLA genes and immune-mediated diseases, including autoimmunity and transplant-related diseases (NIAID, NIDDK, NCI, NHGRI, NLM, JDRF).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U24 AI049213	13th International Histocompatibility Working Group	Hansen, John Fred Hutchinson Cancer Research Center

INTRAMURAL KIDNEY TRANSPLANTATION PROGRAM develops (1) therapies that avoid chronic immunosuppressive medications and their inherent complications and (2) techniques that allow more precise immune management of transplant patients. Present clinical trials are investigating the effects of T-cell depletion, alone or in combination with donor bone marrow infusion, to reduce the need for immunosuppressive medications. Multiple new agents and approaches are moving toward clinical trials from nonhuman primate models. Diagnostic assays are being developed to better predict graft rejection in order to guide clinical decision making (NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR
DK 062005	Kidney/Pancreas Allograft Rejection	Kirk, Allan D.
DK 062006	Bone Marrow Conditioning In Solid Organ Transplantation	Hale, Douglas
DK 062007	Methods For Inducing Solid Organ Transplant Tolerance	Kirk, Allan D.
DK 062008	Allograft Neuropathy and Connective Tissue Growth Factor	Mannon, Roslyn B.

NIDDK INTRAMURAL CLINICAL PROTOCOLS	STATUS
Screening Protocol for Patients Needing a Kidney, Kidney-Pancreas, or Islet Cell Transplant	Active
Monitoring for Donor-Specific Hyporesponsiveness Following Renal and Pancreatic Allotransplantation	Active
Live Donor Renal Donation for Allotransplantation	Active
Sirolimus Monotherapy To Optimize Activation-Induced Cell Death (AICD) in Renal Transplants Following Lymphocyte Depletion Induction With Thymoglobulin	Followup
Tolerance Induction Following Human Renal Transplantation Using Treatment With a Humanized Monoclonal Antibody Against CD52 (Campath -1H)	Followup
The Expression of Connective Tissue Growth Factor and Other Mediators in the Pathogenesis of Chronic Allograft Nephropathy	Active
Renal Transplantation in Recipients With Nephropathic Cystinosis	Active
Depletional Induction With Rabbit Antithymocyte Globulin, Followed by Two Approaches Toward Monotherapy Immunosuppression in Kidney Transplant Recipients	Active
Identification and Mechanistic Investigations of Tolerant Kidney Transplant Patients (Collaboration With the ITN)	Active

PATHOGENESIS OF POLYOMAVIRUS-ASSOCIATED NEPHROPATHY supports basic, preclinical, clinical, and epidemiological research projects on polyomavirus-associated nephropathy (NIAID).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
R01 AI060584	Parameters Governing Kidney Cell Infection with BKV	Imperiale, Michael J. University of Michigan
R21 AI060597	Characterization of BKV Infection in Hematopoietic Cells	Doerries, Kristina University of Würzburg, Germany
R01 AI060602	Biomarkers Based Studies of Polyomaviruses	Vats, Abhay N. Children's Hospital, Pittsburgh
R21 AI060609	Pathogenesis/Murine Polyomavirus Allograft Nephropathy	Larsen, Christian P. Emory University
R01 AI060706	Noninvasive Diagnosis of BKV Nephropathy	Suthanthiran, Manikkam Weill Medical College of Cornell University

RECURRENT HEPATITIS B AFTER LIVER TRANSPLANTATION is a prospective, randomized controlled trial to determine whether lamivudine and short-term hepatitis B immune globulin (HBIG) is as effective as lamivudine and long-term HBIG in preventing recurrent hepatitis B. Additionally, this study will evaluate whether another antiviral agent, adefovir dipivoxil, can suppress HBV replication in patients who have developed lamivudine-resistant strains of the virus (NIDDK).

SICKLE CELL ANEMIA projects listed below are focused on establishing resources and conducting basic, translational, and clinical research on hematopoietic cell transplantation for sickle cell anemia (NHLBI).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 HL067877	Sibling Donor Cord Blood Banking and Transplantation	Lubin, Bertram Children's Hospital, Oakland Research Institute
U01 HL068091	Induction of Stable Chimerism for Sickle Cell Anemia	Walters, Mark Children's Hospital, Oakland Research Institute
U54 HL070769	Nonmyeloablative Therapy for Sickle Cell Disease	Rizzieri, David Duke University

SPECIALIZED CENTERS OF CLINICALLY ORIENTED RESEARCH IN PEDIATRIC HEART DEVELOPMENT AND DISEASE support basic and clinical research related to congenital and acquired pediatric heart diseases (NHLBI).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
P50 HL074732	Optimizing Outcome After Pediatric Heart Transplantation	Webber, Steven A. University of Pittsburgh

SPECIALIZED CENTERS FOR CELL-BASED THERAPY (SCCT) FOR HEART, LUNG, AND BLOOD DISEASES AND DATA AND COORDINATING CENTER (DCC) establish and maintain (1) Specialized Centers for Cell-based Therapy (SCCT) to perform preclinical and clinical studies for cell-based therapy and (2) a Data and Coordinating Center (DCC) for the program. The clinical and basic research supported under this program will be related to cell-based therapy for the treatment of heart, lung, and blood diseases (NHLBI).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U54 HL081007-01	Improving the Safety and Efficacy of Cell Therapies	Brenner, Malcolm Baylor College of Medicine
U54 HL081021-01	Specialized Centers for Cell-Based Therapy (SCCT) for Heart, Lung, and Blood Diseases and Data and Coordinating Center (DCC)	Carter, Shelley EMMES Corporation
U54 HL081208-01	Cellular Cardiomyoplasty for Acute and Chronic Ischemic	Hare, Joshua Johns Hopkins University
U54 HL081030-01	Specialized Center for Cell-Based Therapy	Scadden, David Massachusetts General Hospital

SPECIALIZED CENTERS OF RESEARCH IN TRANSFUSION BIOLOGY AND MEDICINE conduct studies to improve the safety and efficacy of blood and blood components, to determine the indications for their use, to evaluate and possibly modify immunological responsiveness following their administration, and to develop and evaluate alternative treatment strategies that substitute for certain of their functions or stimulate their endogenous production so as to reduce transfusion needs (NHLBI).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
P50 HL054476	Microchimerism in Transfusion Medicine and Organ Transplant Rejection	Busch, Michael P. University of California, San Francisco

STUDIES IN PEDIATRIC LIVER TRANSPLANTATION support research to address the degree of immune suppression complications in children such as renal failure, cardiovascular disease, and cancer; survival of the patient after transplantation; and the influence of liver disease on school performance and growth. SPLIT has supported the development of the Pediatric End-Stage Liver Disease score for allocation of organs to pediatric transplant candidates (NIDDK).

AWARD	PROJECT TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 DK061693	Studies in Pediatric Liver Transplantation	Lindblad, Anne The EMMES Corporation

UNITED STATES RENAL DATA SYSTEM collects and analyzes information on the incidence, prevalence, treatment, morbidity, and mortality of ESRD in the United States (NIDDK).

AWARD	PROJECT TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
N01 DK92343	USRDS: Data Coordinating Center	Collins, Alan Minneapolis Medical Research Foundation
N01 DK02401	USRDS: Economic Special Studies Center	Hunsicker, Lawrence University of Iowa
N01 DK92344	USRDS: Cardiovascular Disease Studies Center	Herzog, Charles Minneapolis Medical Research Foundation
N01 DK12471	USRDS: Quality of Life/Rehabilitation Special Studies Center	Kutner, Nancy Emory University
N01 DK22498	USRDS: Nutrition/Malnutrition Special Studies Center	Chertow, Glen University of California, San Francisco

II. Reduce Morbidity and Mortality by Increasing Organ Availability and by Developing Alternatives to Organ Transplantation and Organ-Assistive Technologies

CLINICAL OUTCOMES OF LIVE ORGAN DONORS is a FY2006 program in response to recommendations made by the Secretary's Advisory Committee on Transplantation to investigate the outcomes and health care needs of living donors (NIAID, NHLBI).

IMMUNOBIOLOGY OF XENOTRANSPLANTATION conducts preclinical pig-to-NHP transplantation studies to address immunological and physiological issues that are critical to the survival and function of xenotransplants (NIAID, NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 AI068642	Thromboregulation To Prevent Thrombotic Microangiopathy	Cooper, David University of Pittsburgh
U01 AO066310	Studies in Pig-to-Primate Cardiac Xenotransplantation	Mc Gregor, Christopher Mayo Clinic
U01 AI066331	Thromboregulatory Strategies To Prolong Xenograft Survival	Robson, Simon Beth Israel Deaconess Medical Center
U19 AI067151	Pig-to-Nonhuman-Primate Islet Allografts	Thomas, Judith University of Alabama at Birmingham
U01 AI066335	Mechanisms of GalTKO Lung Xenograft Injury	Pierson, Richard N. III University of Maryland, Baltimore

LEFT VENTRICULAR ASSIST DEVICES AS DESTINATION THERAPY: A NEW LOOK AT SURVIVAL supports the development of a family of pediatric circulatory support devices. The common objective for these devices is to reliably provide circulatory support for infants and children less than 25 kg with congenital or acquired heart disease while minimizing risks related to infection, bleeding, and thromboembolism (NHLBI).

DEVICE	AWARDEE
PediPump	The Cleveland Clinic Foundation
PediaFlow	University of Pittsburgh
Pediatric Cardiopulmonary Assist System	Ension, Inc.
Jarvik 2000 VADs	Jarvik Heart, Inc.
Penn State Pediatric Ventricular Assist Device	Milton S. Hershey Medical Center, Penn State University

MINORITY ORGAN AND TISSUE DONATION supports educational programs to improve the understanding and the benefits of organ and tissue transplantation, and the need, especially in racial and ethnic minority communities, and other underserved populations to participate in giving organs and tissues for transplantation (NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
R01 DK062659	Bayanihan (Working Together to Help): A Filipino Education Program	Wong, Linda L. University of Hawaii at Manoa
R01 DK062642	Physician Peer Minority Organ Donation Education Model	Ojo, Akinlolu University of Michigan at Ann Arbor
R01 DK062619	Increasing Blood and Cord Blood Donation in Blacks	DeBaun, Michael R. Washington University
R01 DK062596	A Program to Increase Living Donations in African Americans	Baliga, Prabhakar K. Medical University of South Carolina
R01 DK062617	Organ Donation in the Black Community: A Focus on Family	Arriola, Kimberly R. Emory University

MINORITY ORGAN AND TISSUE TRANSPLANTATION EDUCATION PROGRAM (MOTTEP) supports programs to broaden and deepen the knowledge of organ/tissue donation and transplantation among minorities, increase the number of minorities consenting to deceased-organ donation, promote healthy behaviors to reduce the need for organ/tissue transplantation, and lower minority transplant waiting times by 10 percent within 5 years (NIDDK, NCMHD).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
R01 DK050474	Minority Organ and Tissue Transplantation Education Program (MOTTEP): Preventing the Need	Callender, Clive Howard University

THE RANDOMIZED EVALUATION OF MECHANICAL ASSISTANCE FOR THE TREATMENT OF CONGESTIVE HEART FAILURE (REMATCH) is a collaboration among the NHLBI, Columbia University, and Thoratec Corporation. The overall purpose of the study is to evaluate the efficacy, safety, and cost-effectiveness of the HeartMate ventricular assist device compared with intensive medical care to improve survival in patients with end-stage heart failure who are ineligible for transplantation. Recruitment has now been completed (NHLBI).

STEM CELL AND TISSUE ENGINEERING RESEARCH includes the following programs (and sponsors), which focus on stem cell and tissue engineering research and contain individual projects related to transplantation:

- Axonal Damage in Multiple Sclerosis: Strategies for Protection and Repair (NINDS)
- Basic and Applied Stem Cell Research for Arthritis and Musculoskeletal Diseases (NIAMS)
- Basic Research on Mesenchymal Stem Cell Biology (NHLBI)

- Beta Cell Biology Consortium (NIDDK)
- The Biology of Nonhuman Stem Cells in the Environment of the Nervous System (NINDS, NIMH, NIDCD, NIA, NICHD)
- Centers of Excellence in Translational Human Stem Cell Research (NINDS, NHLBI, NIDDK)
- Characterization of Pluripotent Stem Cells (NINDS, NIDCD, NIA, NICHD, NCI, NIDA, NIMH)
- Directed Stem Cell Differentiation for Cell-Based Therapies for Heart, Lung, and Blood, and Aging Diseases (NHLBI)
- Development of the Endocrine Pancreas (NIDDK)
- Development of the Gut, Liver, and Exocrine Pancreas (NIDDK)
- Directed Stem Cell Differentiation for Cell-Based Therapies for Heart, Lung, and Blood, and Aging Diseases (NHLBI, NIA)
- Erythroid Lineage Molecular Toolbox (NIDDK)
- Exploratory Centers of Excellence (NIGMS)
- Human Embryonic Stem Cell Research Resource Infrastructure Development (NCRR, NIA, NICHD, NIDDK, NIAID, NHLBI)
- Innovative and Exploratory Research in Digestive Disease (NIDDK)
- Innovative Concepts and Approaches to Developing Functional Tissues and Organs: Heart, Vascular, Lung, and Blood Applications (NHLBI)
- Integrative Neuroscience Initiative on Alcoholism (NIAAA)
- Interactions Between Stem and Progenitor Cells and the Microenvironment In Vivo (NINDS, NIDA, NIDCD, NIA, NEI, NIBIB, NCI, NIAAA)
- Mesenchymal Stem Cell Biology (NHLBI, NIA)
- New Research Strategies in Osteogenesis Imperfecta (NIAMS, NIA)
- NHLBI Competitive Supplements for Human Embryonic Stem Cell Research (NHLBI)
- Novel Approaches to Enhance Animal Stem Cell Research (NCI, NEI, NHLBI, NIAMS, NIBIB, NICHD, NIDDK, NIEHS, NIMH, NINDS, NIA, NIDCD, NIDA)
- Parkinson's Disease Research Centers of Excellence (NINDS)
- Pilot and Feasibility Program in Diabetes Endocrinology and Metabolism (NIDDK)
- Pilot and Feasibility Program in Hematological Disease (NIDDK)
- Plasticity of Stem Cells in the Nervous System (NINDS, NIA, NIMH, NHLBI)
- Progenitor Cell Genome Anatomy Projects (NIDDK)
- R21 Fast Track Grants for Parkinson's Disease Research (NINDS, NIDCD, NIEHS, NIMH, The Michael J. Fox Foundation for Parkinson's Research, The Parkinson's Disease Foundation/National Parkinson's Foundation, The Parkinson's Alliance)

- Regenerative Dental Medicine (NIDCR)
- Research Opportunities in Tissue Engineering (NIBIB, NIDDK)
- Therapeutic Opportunities in Progressive Stages of Spinal Cord Injury (NINDS)
- Stem Cell Based Therapy and Regenerative Medicine (NHLBI)
- Stem Cell Biology and Cell-Based Therapies for Heart, Lung, Blood, and Sleep Disorders (NHLBI)
- Stem Cell Plasticity in Hematopoietic and Nonhematopoietic Tissue (NHLBI, NIDDK, NINDS)
- Stem Cell Research for Alcohol-Related Disorders (NIAAA)

III. Induce Immune Tolerance to Allografts

HUMAN ISLET TRANSPLANTATION INTO HUMANS supports research to maintain islet allograft survival, methods for islet isolation and preservation, measurement of the alloimmune response to transplanted islets, and monitoring of islet function (NIDDK, NIAID, JDRF).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
R01 DK056962	Immune Modulation and Tolerance Induction to Human Islets	Bretzel, Reinhard G. University of Giessen
R01 DK056963	Tolerance to Islet Allografts In Type 1 Diabetes	Hering, Bernhard J. University of Minnesota
R01 DK056953	Pathways to Tolerance in Human Islet Transplantation	Ricordi, Camillo University of Miami
R01 DK056946	Islet Tolerance Induction Based on Anti-CD154 Antibody	Rossini, Aldo A., Jr. University of Massachusetts Medical School
R01 DK056952	Islet-Kidney Transplantation For Type I Diabetes	Smith, Craig V. City of Hope/Beckman Research Institute
R01 DK056951	Tolerance Induction in Pancreatic Islet Transplantation	Rastellini, Cristiana University of Massachusetts Medical School

IMMUNE TOLERANCE NETWORK (ITN) is a consortium of more than 80 investigators in the United States, Canada, Western Europe, and Australia dedicated to the clinical evaluation of promising tolerance induction therapies in kidney, liver, and islet transplantation for type 1 diabetes; and medical treatments for all autoimmune disorders, and asthma and allergic diseases (NIAID, NIDDK, JDRF).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
N01 AI015406	Collaborative Network for Clinical Research on Immune Tolerance	Bluestone, Jeffrey University of California
N01 AI095382	Statistical and Clinical Coordinating Center	Ewell, Marian The EMMES Corporation
N01 AI40089	Regulatory Management Center	Social & Scientific Systems, Inc.
N01 AI40070	Clinical Site Monitoring Groups	PPD Development LP
N01 AI40090	Drug Distribution Center	EMINENT Services Corp.
N01 AI40075	Coordinating Center for Biostatistics, Data Management, and Pharmacovigilance	PPD Development LP

ITN CLINICAL TRIALS AND MECHANISTIC STUDIES IN TRANSPLANTATION	STATUS
Combined Nonmyeloablative Bone Marrow Transplant Plus Kidney Transplant for Patients With Renal Failure, Due to Complications of Multiple Myeloma	Active
Combined Nonmyeloablative Bone Marrow Transplant Plus Kidney Transplant for Patients With Renal Failure, Using an Investigational T-Cell Depleting Agent	Active
The Use of CAMPATH-1H, Tacrolimus, and Sirolimus Followed by Sirolimus Withdrawal in Renal Transplant Patients	Active
Pilot Study Using Donor Stem Cells and CAMPATH-1H to Induce Renal Transplant Tolerance	Active
LEA29Y in an Immunosuppression Withdrawal Regimen in Recipients of Non-HLA Identical Living Donor Renal Transplants	In development
Development of Antigen-Specific Assays Indicative of Donor-Specific Tolerance in Renal Transplant Recipients	Active
Identification and Mechanistic Investigations of Tolerant Kidney Transplant Patients	Active
Immunosuppression Withdrawal in Liver Transplant Recipients	Active
Immunosuppression Withdrawal in Liver Transplant Recipients with HCV Infection	Active
Immunosuppression Withdrawal for Stable Pediatric Living Donor Liver Transplant Recipients	In development
Islet Transplantation in Type 1 Diabetic Patients Using the Edmonton Protocol of Steroid-Free Immunosuppression	In followup

INNOVATIVE GRANTS ON IMMUNE TOLERANCE supports pilot research projects on the molecular mechanisms and applications of antigen-specific immune tolerance and encourages investigators working in other areas of research to bring novel perspectives and expertise to this field (NIAID, NIDDK, NHLBI).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
R21 HL079445	Selective Depletion of Alloreactive T Cells In BMT	Zimring, James C. Emory University
R21 HL079450	Homeostatic T-Cell Expansion as a Barrier to Tolerance	Turka, Laurence University of Pennsylvania
R21 HL079446	Donor Bone Marrow and Immunoregulation in Lung Transplantation	Pham, Si M. University of Miami
R21 AI059920	Immune Function in Desensitized Allograft Recipients	Schneck, Jonathan P. Johns Hopkins University
R21 AI059996	Vitiligo in Tyrosinase-specific TCR Transgenic Mice	Engelhard, Victor H. University of Virginia

NONHUMAN PRIMATE TRANSPLANTATION TOLERANCE COOPERATIVE STUDY GROUP supports studies to evaluate the safety and efficacy of promising tolerance induction treatment regimens in nonhuman primate models of kidney and islet transplantation. The knowledge gained from this research effort is critical to the translation of successful tolerance induction strategies from small animal models to clinical trials (NIAID, NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 AI051706	Tolerance Induction for Primate Islet Transplantation	Koulmanda, Maria Massachusetts General Hospital
U01 AI051694	Induction of Allograft Tolerance in Nonhuman Primates	Monaco, Anthony Beth Israel Deaconess Medical Center
U01 AI051698	Rhesus Monkey Dendritic Cells for Transplant Tolerance	Thomson, Angus University of Pittsburgh
U01 DK062932	Mixed Chimerism in Haploidentical Nonhuman Primates	Hering, Bernhard University of Minnesota
U01 AI051724	CXCR3 Chemokine Receptor in Nonhuman Primate Allograft	Knechtle, Stuart University of Wisconsin, Madison
U01 AI050987	Novel Approaches To Achieve Allograft Tolerance	Strom, Terry Beth Israel Deaconess Medical Center
U19 DK057958	Preclinical Models of Organ and Cell Transplant Tolerance	Thomas, Judith University of Alabama, Birmingham
	Anti-CD3-Immunotoxin in Hematopoietic Stem Cell Grafting	Hering, Bernhard University of Minnesota
U19 AI051731	Transplant Tolerance in Nonhuman Primates	Larsen, Christian Emory University
U19 AI051728	Stem Cells for Tolerance Induction	Kenyon, Norma University of Miami
U19 AI066705	Thoracic Allograft Tolerance in Nonhuman Primates	Madsen, Joren Massachusetts General Hospital
U01 AI066719	Immunomodulation for Heart Allograft Tolerance	Pierson, Richard University of Maryland

IV Establish or Improve Research Infrastructure and Resources

ASSAYS FOR VIRAL DETECTION IN DONATED ORGANS supports technology development to refine nucleic acid-based techniques that will be feasible for the direct detection of blood-borne viruses in donors of organs for transplantation. The long-term goal is to obtain approval for product license applications (NHBLI).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
N01 HB07148	Refinement of New Assays for Direct Detection of Nucleic	McDonough, Sherrol Gen-Probe, Inc.

COLLABORATIVE ISLET TRANSPLANT REGISTRY supports efforts to collect islet characterization and clinical islet transplantation results on North American islet and beta cell transplants. These registries will serve as research tools for the medical community to answer fundamental questions pertinent to improving host and graft survival following pancreas or islet/beta cell transplantation (NIDDK).

DEVELOPMENT OF IMMUNE-MONITORING REAGENTS AND MAJOR HISTOCOMPATIBILITY TYPING TECHNOLOGIES FOR NONHUMAN PRIMATES supports projects to develop, produce, and distribute new or improved nonhuman primate (NHP) immune-monitoring and immune-modulating reagents that are needed to evaluate NHP immune responses in vaccine and adjuvant development for infectious diseases, transplantation research, and autoimmune and infectious disease models; and develop novel immune-based therapeutics, vaccines, and adjuvants (NIAID).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
N01 AI040101	Development of Immune-Monitoring Reagents and MHC Typing Technologies for Nonhuman Primates (Part I)	Reimann, Keith Beth Israel Deaconess Medical Center
N01 AI040088	Development of Immune-Monitoring Reagents and MHC Typing Technologies for Nonhuman Primates (Part II)	Watkins, David University of Wisconsin
N01 AI040087	Development of Immune-Monitoring Reagents and MHC Typing Technologies for Nonhuman Primates (Part II)	Williams, Thomas University of New Mexico, Albuquerque

ISLET CELL RESOURCE (ICR) CENTERS support studies on the isolation, purification, and characterization of human pancreatic islet cells for transplantation into diabetic patients (NCRR, NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U42 RR016597	Human Islet Isolation Program at Washington University	Mohanakumar, Thalachallour Washington University
U42 RR016598	Human Pancreatic ICR	Hering, Bernard J. University of Minnesota
U42 RR016599	ICR Facility at the University of Denver	Gill, Ronald G. University of Colorado, Denver Health Science Center, Aurora
U42 RR016600	Isolation/Distribution of Human Pancreatic Islets	Naji, Ali University of Pennsylvania
U42 RR016602	Standardization and Procedure of Islet Isolation	Gaber, A. Osama University of Tennessee Health Science Center
U42 RR016603	ICR for Diabetes Research and Treatment	Ricordi, Camillo University of Miami
U42 RR016604	Human Islet Isolations in Seattle	Reems, Jo A. Puget Sound Blood Center
U42 RR016606	Human Pancreatic ICR	Weir, Gordon C. Joslin Diabetes Center
U42 RR016607	ICR Center of Southern California	Riggs, Arthur D. City of Hope National Medical Center
U42 RR016629	New York Regional Islet Isolation Facility	Hardy, Mark A. Columbia University
U42 RR017673	National Islet Cell Consortium Coordinating Center	Niland, Joyce City of Hope National Medical Center

NATIONAL SWINE RESEARCH AND RESOURCE CENTER is a central source for reagents, creation of genetically modified swine, and information and training related to the use of swine models in biomedical research (NCRR, NHLBI, NIAID).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U42 RR018877	National Swine Research and Resource Center	Riley, Lela University of Missouri

PRODUCTION ASSISTANCE FOR CELLULAR THERAPIES develops novel somatic cell therapies to aid investigators by providing support in areas ranging from basic science through animal studies to proof-of-principle and eventual clinical human trials. The cell-processing facilities will provide desirable clinical-grade cell products in compliance with all applicable regulations (NHLBI).

AWARD	FACILITY/CENTER	PRINCIPAL INVESTIGATOR INSTITUTION
N01 HB37163	Somatic Cell Therapy Processing Facility	Gee, Andrian Baylor College of Medicine
N01 HB37164	Somatic Cell Therapy Processing Facility	Wagner, John University of Minnesota
N01 HB37165	Somatic Cell Therapy Processing Facility	Whiteside, Theresa University of Pittsburgh
N01 HB37166	Somatic Cell Therapy Processing Administrative Center	Lindblad, Robert The EMMES Corporation

SPECIFIC PATHOGEN-FREE MACAQUE BREEDING COLONIES produce specific pathogen-free rhesus and cynomolgus macaques for use by the Nonhuman Primate Transplantation Tolerance Cooperative Study Group (NIAID, NIDDK).

AWARD	TITLE	PRINCIPAL INVESTIGATOR INSTITUTION
U01 AI049916	Specific Pathogen-Free Macaque Breeding Program	Westergaard, Greg Alpha Genesis Inc.

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