

# **GOAL III**

**DEVELOP CELL  
REPLACEMENT THERAPY**

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**The *Special Statutory Funding Program for Type 1 Diabetes Research* has facilitated the study of beta cell biology, immune modulation, and islet transplantation. These efforts are helping scientists improve existing strategies, as well as identify new strategies, to replace the insulin-producing beta cells that are destroyed by the immune system in type 1 diabetes.**

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The *Special Statutory Funding Program for Type 1 Diabetes Research* is focusing on strategies to replace the beta cells of the pancreas that are destroyed in type 1 diabetes by an immune system attack against the body's tissues (autoimmunity). One therapeutic strategy that has shown promise is islet transplantation. Islet transplantation is a procedure in which insulin-producing cells are taken from a deceased human donor and transferred into an adult patient, most commonly in the liver. Once implanted, these islets begin to make and release insulin in response to the body's needs. Currently, only patients who have severely unmanageable blood glucose levels and thus are at great health risk, or patients who have undergone a kidney transplant, are eligible for this experimental therapy due to the toxicity associated with the required immunosuppressive medicines.

Although the improvements in success rates with the therapy have brought hope for a cure, formidable obstacles impede widespread application of this approach. First, the procedure is limited by the inadequate supply of donor pancreata. Research supported by the *Special Funds* is addressing this shortage in a variety of ways. Collaborative research consortia have been established to optimize transplant procedures, to improve islet handling and distribution mechanisms, to create and study animal disease models, to understand beta cell development and function, and to investigate the potential use of porcine islets as an alternative to human islets. Together, these consortia constitute a multifaceted approach to addressing the limitation in islet supply. Another major obstacle to islet transplantation is the need for lifelong immunosuppression. Drug intervention, which can have serious and adverse side effects, is required to prevent rejection of the transplanted islets by the immune system, as well as to prevent a recurrence of the underlying autoimmunity that initiated the disease. The *Special Funds* are used to foster research devoted to elucidating methods to prevent islet rejection and the recurrence of autoimmunity.

The *Special Funding Program* also supports research on alternative strategies to restore beta cell mass and function. For example, research in beta cell regeneration is determining if adult beta cells could be coaxed to form more beta cells (replication), or if other resident cell types could be directed toward a beta cell fate (neogenesis). Collaborative study groups are determining each step in the developmental pathway of beta cell development so that beta cells could be grown in a laboratory or beta cell growth could be stimulated in people with diabetes. New noninvasive, *in vivo* imaging technologies could allow scientists to actually "see" people's beta cells, which would permit researchers to monitor disease progression, response to therapy, or the survival of islets after transplant. The *Special Funds* have played a pivotal role in advancing research on replacing the beta cells that have been destroyed in type 1 diabetes and have laid the foundation for promising research in years to come.

## HIGHLIGHTS OF SCIENTIFIC PROGRESS

**W**hile numerous significant advances have emerged since the beginning of the Special Funding Program, many of the research efforts to develop cell replacement therapies are still in progress, and the full impact of these projects will not be realized for several years. The advances made possible by the Special Funding Program thus far are therefore only the beginning of the scientific gains that can be expected in the future.

### **Completion of First Multicenter Trial of Islet**

**Transplantation:** Nine sites participating in the Immune Tolerance Network (ITN; see Goal II ) successfully replicated the “Edmonton Protocol” for islet transplantation. As reported in March 2006, 1 year after transplant, 44 percent of the patients achieved insulin independence with good glycemic control; 14 percent achieved insulin independence with a single donor islet infusion. Insulin independence declined over time in study participants. Importantly, even among patients who still required insulin injections, the presence of functioning transplanted islets led to an absence of severe hypoglycemic events due to hypoglycemia unawareness. The results of this study extend the demonstration that islet transplantation may become an alternative to whole pancreas transplantation. They also highlight the continued need for safer, more tolerable anti-rejection therapies.

### **Strategies To Promote Islet Survival and Function**

**After Transplant:** Toxicity of immunosuppressive drugs and rejection and loss of transplanted islets are major barriers to human islet transplantation. Researchers in the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) have made significant progress in identifying strategies to overcome these barriers in non-human primate models, and their research is being translated to human studies. For example, a 14-day tolerance induction protocol, which consisted of anti-CD3 conjugated with immunotoxin (to deplete T cells) and 15-deoxyspergualin (to arrest proinflammatory cytokine production and maturation of dendritic cells), was sufficient to protect the transplanted islets from rejection by the immune system and achieve long-term and stable beta cell function with only short-term immunosup-

pressive therapy. In addition, researchers in this Study Group demonstrated that in a steroid-free immunosuppressive protocol, a modified blocking protein known as LEA29Y prolonged islet survival in a non-human primate model. This promising study provided the basis for a successful phase II kidney transplantation clinical trial, which in turn has led to the development of a soon-to-enroll pilot study to be conducted by the NIH Clinical Islet Transplantation Consortium. An additional kidney transplantation clinical trial using LEA29Y in a steroid-free protocol is in development through the ITN (see Goal II). Furthermore, research conducted by the NHPCSG demonstrated significantly prolonged transplanted islet cell survival using a combination of IL-2/IL-15 fusion proteins with a steroid-free protocol. A clinical trial is approved for development by the ITN.

### **Achievement of Insulin Independence Using Islets from a Single Donor:**

The improved success rates of islet transplantation have largely been achieved using islets isolated from 2-3 donor pancreata. Recently, success has been realized using single donors. Researchers tested a single donor procedure on eight type 1 diabetes patients and found that all patients achieved insulin independence and freedom from hypoglycemia. Five patients remained insulin-independent for more than 1 year. An important factor in the observed success was improved isolation procedures resulting in increased islet viability and survival. Thus, improved islet isolation procedures in the future could help to overcome the current barrier posed by the shortage of islets available for transplantation.

**Improving Islet Isolation and Distribution:** Pilot clinical trials have demonstrated that insulin independence and

long-term islet graft function could be obtained, not only with islets processed and transplanted at the same institution, but also with islets processed at regional NIH funded Islet Cell Resource Centers (ICRs) and shipped for transplantation at remote institutions across the U.S. This success has validated the concept that regional centers could be used for effective islet cell processing and distribution. Furthermore, the establishment of the ICRs has enabled an infrastructure that permits collaborative optimization of pancreas shipping devices, preservation media, islet isolation technology, and interim storage through comparative assessments. The collaboration has also led to the identification of salient roadblocks to large-scale islet production and transplantation. The ICRs provide resources, structure, and a coordinated community of investigators focused on enhancing the quality of isolated islets, promoting basic islet research, and enabling additional facilities to perform the procedures. The ICRs work closely with the Collaborative Islet Transplant Registry (CITR) to collate and disseminate data on islet procurement and production, as well as on clinical outcomes following transplantation in North America. This joint effort facilitates comparative analyses that will eventually define the safest and most effective clinical protocols.

**Immune Monitoring for Early Diagnosis of Rejection and Tolerance:** There are many clinical and biological markers that can be used to determine if a solid organ graft is being rejected. In contrast, there is no biochemical marker for islet rejection that enables detection of islet loss early enough following transplantation to permit effective intervention and rescue. At the time of documented hyperglycemia and need for return to exogenous insulin administration, significant islet loss has already occurred. This observation is similar to the situation that occurs at the onset of type 1 diabetes, as described in the previous chapters. Scientists have recently demonstrated elevated expression of several key genes in the

peripheral blood associated with inflammation—an event that precedes clinical evidence of islet loss after transplant. Gene expression profiles may serve as molecular signatures that foretell impending graft rejection. In addition, these profiles may also provide predictive guideposts for withdrawal of immunosuppression. Early detection of destructive processes will guide the development of effective intervention strategies to reverse immune activation after islet transplantation, before islet cell destruction occurs.

**Imaging the Pancreatic Islet:** Since 1999, there has been significant progress toward directly visualizing the pancreatic beta cells, transplanted islets, and the inflammation of type 1 diabetes using imaging technologies, particularly positron emission tomography (PET) and magnetic resonance imaging (MRI) (see Goal VI). Isolated human islets have been labeled with non-toxic imaging agents that allow them to be seen after transplantation into animals. Targeting molecules that can carry imaging agents directly to proteins on the beta cell surface are being developed to permit counting the number of beta cells in people. The visualization of early beta cell loss would enable imaging to be used as a noninvasive tool to allow one to follow the progression of type 1 diabetes and help scientists monitor survival of transplanted islets. When the pancreas is under attack by the immune system, its blood vessels become “leaky”; this process can be visualized by an imaging molecule that moves from the blood into the inflamed tissue. The ability to actually see inflammatory events in the pancreas prior to the onset of diabetes may help determine the appropriate times for clinical intervention. These tools may also help identify early signs of islet graft rejection after engraftment in the liver. Imaging techniques will ultimately be invaluable for assessing islet survival or loss *in vivo* after transplantation and may also permit scientists to quantitatively follow beta cell replication or neogenesis as therapies to stimulate these processes are developed.

**New Technology To Study Developmental Biology of the Endocrine Pancreas:** Scientists in the Beta Cell Biology Consortium (BCBC) have created mouse models that allow researchers to visually track the expression of transcription factors (proteins that regulate gene expression) that characterize pancreatic progenitor cells at various stages of progression toward mature beta cells. Using these genetically engineered mice, researchers can isolate pancreatic beta cells using an experimental technique called “fluorescence activated cell sorting (FACS).” This advanced technology yields pure populations of mouse pancreatic beta cells at different stages of development. These cell populations can then be used to gain further insights into which genes regulate beta cell development and function. Importantly, through this approach, researchers will be able to identify appropriate cell surface markers on pancreatic progenitor cells. Pursuit of this research avenue could pave the way to the isolation and prospective purification of human progenitor cell populations that will mature into insulin-producing beta cells.

**Role of Master Control Genes in Regulating Formation of Pancreatic Beta Cells:** Researchers have identified important transcription factors that have essential roles in either the formation or function of the pancreas, pancreatic islets, or pancreatic beta cells. Some of the transcriptional regulators expressed in pancreatic beta cells during development, when mutated, have been found to cause rare forms of diabetes mellitus termed *Maturity Onset Diabetes of the Young (MODY)*. Identification of many of these transcription factors was the result of years of systematic studies of the insulin promoter, the part of the insulin gene that regulates its expression. This research pinpointed specific regulatory DNA sequences within the promoter and the transcription factor proteins that bind to them. The initial identification and molecular characterization of key transcription factors that preceded the *Special Funding Program* provided a starting point for understanding the complex gene regulatory networks that exist within both the pancreatic progenitor cells and the mature beta cells and opened the door for work supported by the *Special Funding Program*. With new tools such as the PancChip (see sidebar in Goal I), additional key genes have been more easily identified. These studies can help researchers identify the necessary steps to turn progenitor/stem cells into insulin-producing beta cells.

## EVALUATION OF MAJOR RESEARCH CONSORTIA, NETWORKS, AND RESOURCES RELATED TO THE DEVELOPMENT OF CELL REPLACEMENT THERAPIES

**W**ith the increase in Special Funds that became available in FY 2001, unique, innovative, and collaborative research consortia, clinical trials networks, and resources for the diabetes research community were launched. This section evaluates the progress of these ongoing efforts thus far and describes the impact that the efforts have already had—and have the potential to have—on type 1 diabetes patients.

### Beta Cell Biology Consortium (BCBC)

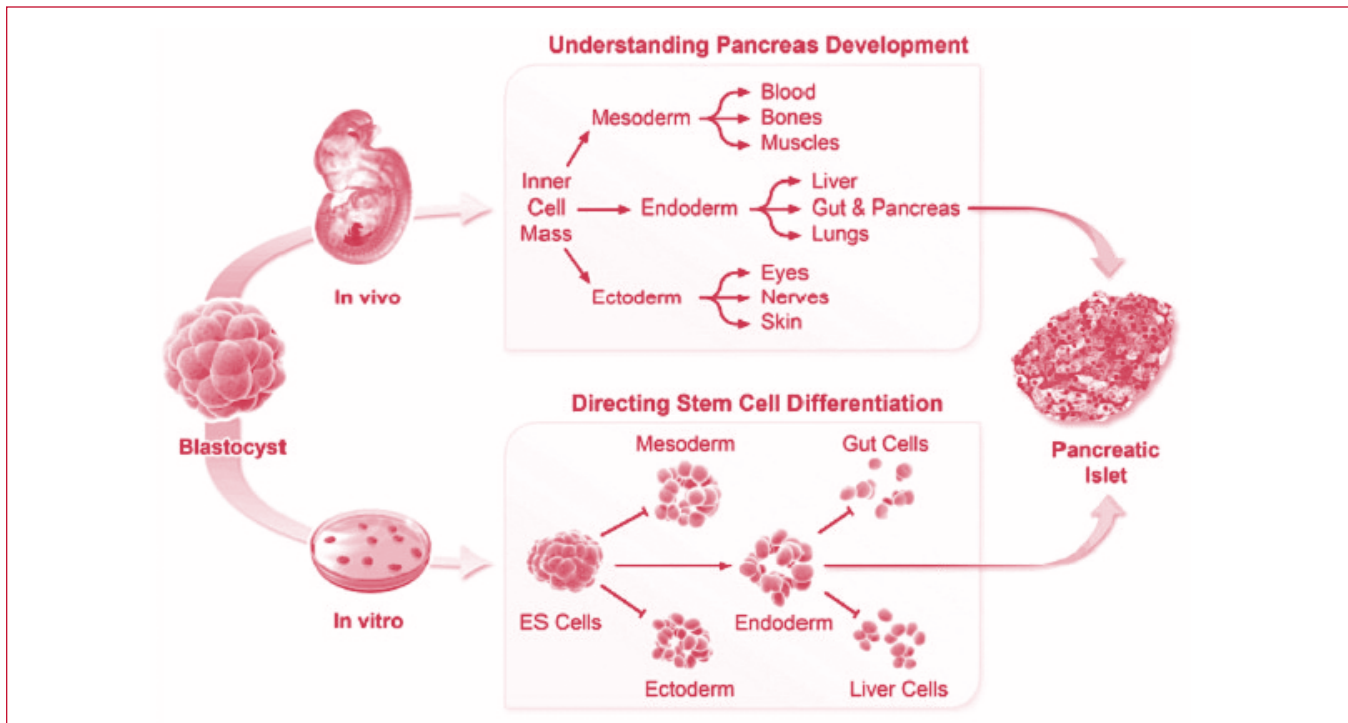
The BCBC is an international Consortium of investigators pursuing key challenges of enormous relevance to development of therapies for type 1 diabetes by: (1) understanding how endogenous beta cells are made through the study of pancreatic development, with the hope of making pancreatic islets in culture; (2) exploring the potential of animal and/or human stem cells (embryonic\* or adult) as a source for making pancreatic islets; and (3) determining the basic mechanisms underlying beta cell regeneration in the adult as a basis for producing new cellular therapies for diabetes. The BCBC is responsible for collaboratively generating necessary reagents, mouse strains, antibodies, assays, protocols, and technologies that are beyond the scope of any single research effort and that would facilitate research on the development of novel cellular therapies for diabetes.

#### Highlights of Progress

The progress that BCBC has made as of March 1, 2006, includes:

- Generated and characterized 29 polyclonal antibodies and 25 monoclonal antibodies against markers expressed at different stages of stem cell to beta cell maturation, and made them available to the broad scientific community.
- Created for distribution to the scientific community four PancChips (microarrays) that enable researchers to study genes expressed in the pancreas/islets of both humans and mice, as well as over 36,000 gene promoter regions in mice.
- Generated new mouse embryonic stem (ES) cell lines and strains to enable researchers to study pancreatic/islet cell development in animal systems. These mouse resources will be made available to the broad scientific community through a BCBC web-based mouse database.
- Initiated EPConDB, a searchable database, containing information about genes expressed in the cells of the pancreas, including 12 mouse and 7 human libraries.
- Attracted new talent to beta cell biology through the Pilot and Feasibility Program in 2002-2005, funding seven new investigators.
- Attracted new talent to beta cell biology research through the Seeding Collaborative Research Program in 2004. This mechanism permitted investigators outside the BCBC to collect preliminary data and form collaborative research teams prior to applying for full-scale grants during the BCBC re-competition.

\*The NIH supports research on human embryonic stem cells within federal guidelines.



Embryonic stem (ES) cells hold significant potential for deriving differentiated cell types, including insulin-producing beta cells. Knowledge of genes and signals controlling pancreatic development in the whole animal can enable test tube recapitulation of specific embryonic programs in stem or progenitor cells to produce functioning insulin-producing cells for replacement therapy in type 1 diabetes. (Image courtesy of Dr. J.P. Cartiailler, Beta Cell Biology Consortium.)

### Anticipated Outcomes

BCBC research will increase understanding of the developmental pathways required to produce a fully functioning pancreatic islet; the nature of stem/progenitor cells during normal pancreatic development and in the adult pancreatic islet; and the mechanisms of beta cell regeneration in the adult animal and human islet. Furthering basic research on beta cells will enhance efforts to produce an abundant supply of beta cells for transplantation. A major restriction of islet transplantation is the inadequacy of tissue supply, which is currently limited to donor pancreatic tissue. Research that uncovers methods for restoring insulin production by regenerating beta cells, or by producing beta cells generated from stem/progenitor cells, could lessen or obviate the reliance on donor pancreatic tissue as a source of transplantable cells. The potential outcomes of BCBC research could also permit scientists to grow islets in

the laboratory for use in future research or clinical efforts. This knowledge could help scientists recreate an environment in the transplant patient that would optimize the success of the grafted islets, as well as make the treatment more widely available.

The BCBC provides an infrastructure that is conducive to tackling these critical issues that can revolutionize type 1 diabetes research and, ultimately, the treatment of type 1 diabetes patients. BCBC researchers work collaboratively and are encouraged to share data and information on a regular basis through a coordinating center that organizes retreats, meetings, conference calls, and a comprehensive website. This rapid and efficient communication ensures that all members are aware of the “latest” research findings, and that they

can tailor their own research endeavors to build upon that knowledge. Furthermore, research through this Consortium and in the broader scientific community is also accelerated by having core facilities that produce key laboratory reagents (e.g., mouse models, antibodies, microarrays). This easy access to resources means that more time is spent performing real experiments, rather than preparing reagents needed to do the experiments. The *Special Funding Program* has facilitated the establishment of this multifaceted, interdisciplinary, collaborative, team-science approach to bring together leading experts in beta cell biology to address fundamental questions about this important area of science, which is key to combating type 1 diabetes.

### External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance from an External Advisory Board (EAB) focused on the BCBC, leading scientific and lay experts were asked to evaluate the progress of the BCBC at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ This Consortium works extremely well: it should be used as a model for establishing other consortia, and it should continue to be supported and, if possible, expanded.
- ▶ The Consortium's progress has been very good. Successes include the development of the Mouse PancChip 5.0 and the Human PancChip 1.0.
- ▶ The Consortium has many strengths: it is a solid organization; the coordinating center effectively manages the program; and the participating investigators direct their own research programs.

### Actions Taken in Response to Expert Panel Recommendations

The BCBC took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

### Recommendation: Continue To Expand the BCBC

- ▶ Two Requests for Applications (RFAs) were released requesting new and re-competing projects for the BCBC. A limited competition RFA was released for renewal of the BCBC Coordinating Center.
- ▶ In 2005, the BCBC was expanded in scope to include research projects focused on beta cell regeneration. The BCBC currently includes 29 participating laboratories—10 cooperative agreements (8 U01 and 2 U19 projects) and 2 NIDDK intramural projects.

### Recommendation: Pursue More Collaborative and Discovery-Based Research

- ▶ In 2006, the BCBC initiated a new program, Collaborative Bridging Projects (CBPs), designed to enhance team science among BCBC members as well as to jump-start collaborations with outstanding researchers not affiliated with the BCBC. This program supports high-impact, discovery-based research, which would exploit emerging technology and develop novel tools and resources for the beta cell biology community.

### Recommendation: Define Overarching Goals for Pursuing Studies on Stem Cells, Consistent with Federal Funding Policies

- ▶ The BCBC initiated a new CBP that is focused on making human islets from human ES cells in a step-wise manner in culture, beginning with the efficient generation of pancreatic endoderm. Only NIH-approved human ES cell lines are being used for this project. In parallel projects, other BCBC affiliated laboratories have focused on generating human beta cells from adult human progenitor cells in culture.



## Ongoing Evaluation

The BCBC External Advisory Board met in conjunction with the BCBC Steering Committee meetings in May 2003 and May 2004. The purpose of these joint meetings was to critically review the scientific progress of current BCBC U19 (Cooperative Agreement) projects. The EAB made recommendations to the NIDDK concerning these projects, and letters summarizing the EAB's recommendations were sent to BCBC principal investigators. Participating laboratories in the second phase of the BCBC were selected based on peer review of applications to join or continue in the BCBC in 2005. The EAB attended the BCBC Kick-off Retreat in August 2005, the purpose of which was to initiate new CBPs and strategic planning for the BCBC. The EAB made additional recommendations to NIDDK staff. In addition, an *ad hoc* Advisory Meeting for the Beta Cell Working Group (composed of representatives from the NIDDK and the NCRR) was held on February 10, 2004, to solicit recommendations from scientists external to the NIH for future directions in beta cell biology research. A report from this meeting is available on the NIDDK website: [www.T1Diabetes.nih.gov/BCWG%20Translational%20Research%20Report%20final.doc](http://www.T1Diabetes.nih.gov/BCWG%20Translational%20Research%20Report%20final.doc)

## Coordination with Other Research Efforts

The BCBC coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaborative efforts, please see Appendix 2.

### Sharing Samples, Data, and Resources with the Research Community:

- ▶ The BCBC developed a comprehensive website ([www.betacell.org/](http://www.betacell.org/)) with information on mouse models,

antibodies, microarrays, and data available to the scientific community.

- ▶ Collections of data and bioinformatics analytical tools developed by the BCBC are made available through the EPConDB database ([www.betacell.org/resources/data/epcondb/](http://www.betacell.org/resources/data/epcondb/)). This database has been linked to other relevant databases, such as the NIDDK-sponsored Diabetes Genome Anatomy Project database and the JDRF-sponsored T1Dbase.

### Coordinating Research Efforts on Human Islets:

- ▶ BCBC investigators obtain human islets through the ICRs for use in basic science research.
- ▶ Data collected from BCBC investigators using ICR samples are collected within the informatics coordination center of the ICR Consortium.

### Collaboration Among Mouse Resources:

- ▶ Mouse strains developed by BCBC investigators are available through mouse repositories (Type 1 Diabetes Mouse Repository [T1DR] and Mutant Mouse Regional Resource Centers [MMRRC]), which provide greater access to the scientific community to these resources.
- ▶ The BCBC mouse database was designed to directly interface with T1DR and MMRRC to foster data sharing.

### BCBC Administrative History

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Component	NIDDK
Website	<a href="http://www.betacell.org">www.betacell.org</a>

The BCBC is comprised of a diverse group of 29 laboratories in the United States, Europe, and Israel. The BCBC Coordinating Center at Vanderbilt University oversees all collaborative scientific endeavors of the BCBC, including scientific cores, reagent databases, Steering Committee meetings, investigator retreats, the Pilot and Feasibility Program, the Seeding Collaborative Research Program, and the Collaborative Bridging Projects.

## **Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG)**

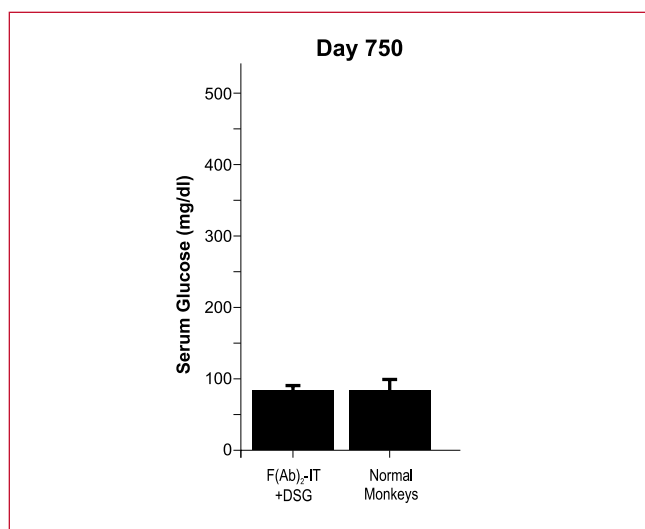
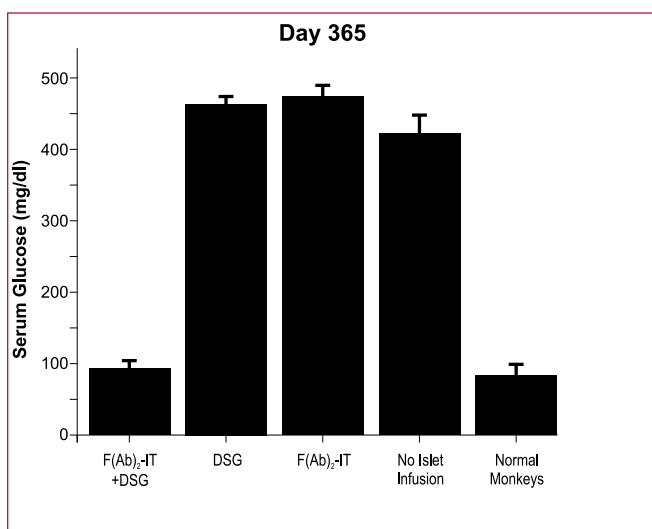
The NHPCSG is a multi-institution Consortium collaboratively evaluating the safety and efficacy of novel therapies to induce tolerance in non-human primate (NHP) models of islet, kidney, heart, and lung transplantation. The program also supports research into the underlying molecular mechanisms of immune tolerance and fosters the development of surrogate markers for the induction, maintenance, and loss of tolerance. Two specific pathogen-free NHP breeding colonies provide a shared resource of high-quality NHPs for these research studies. An Opportunities Pool was also established to support innovative pilot projects, capitalize on emerging research opportunities, and share resources to further the goals of the NHPCSG. Pre-clinical research conducted by this Group will help scientists move promising therapeutic agents from the laboratory into clinical trials.

### **Highlights of Progress**

The progress that NHPCSG has made as of March 1, 2006, includes:

- First to demonstrate long-term and sustained beta cell function without continuous immunosuppressive therapy following islet transplantation in a drug-induced diabetic NHP model. The researchers discontinued treating the primates with immunosuppressive therapy 14 days after the transplant. The 14-day tolerance induction protocol, which consisted of anti-CD3 conjugated with immunotoxin (to deplete T cells) and 15-deoxyspergualin (to arrest proinflammatory cytokine production and maturation of dendritic cells) was sufficient to protect the transplanted islets from rejection by the immune system, as well as from loss of functional islet mass. Toxicity of immunosuppressive drugs is a major barrier in human islet transplantation. Therefore, if the results of this study and others show similar benefits in humans, then islet transplantation may be a therapy option for greater numbers of type 1 diabetes patients.
- Demonstrated that in a steroid-free immunosuppressive protocol, a modified blocking protein known as LEA29Y prolonged islet survival in a primate model. This promising study provided the basis for a phase II kidney transplantation clinical trial. The trial has demonstrated excellent results and has led to the development of a soon-to-enroll pilot study to be conducted by the NIH Clinical Islet Transplantation Consortium. An additional kidney transplantation clinical trial using LEA29Y in a steroid-free protocol is in development through the ITN (see Goal II).
- Demonstrated significantly prolonged transplanted islet cell survival using a combination of IL-2/IL-15 fusion proteins with a steroid-free protocol. A clinical trial is approved for development by the ITN once Good Manufacturing Practice (GMP) reagents are available. The Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID; see Goal VI) program is undertaking production of reagents for pharmacokinetic, toxicology, and efficiency studies prior to clinical trial development.
- Demonstrated that elevation of cytotoxic lymphocyte (CL) gene expression preceded the rejection of transplanted islets in NHPs. These findings also extended to clinical studies in humans in which increased CL gene expression preceded clinical evidence of graft rejection. These results may help identify early stages of islet graft rejection and provide signal markers for intervention to save the graft.
- Evaluating over 15 different protocols to establish immune tolerance and/or islet graft acceptance.
- Established two specific pathogen-free NHP breeding colonies to provide high-quality primates for type 1 diabetes research studies.

- Performing pedigree analysis and histocompatibility gene typing of key primate colony breeders and offspring to facilitate establishment of selective breeding groups. Understanding the degree of MHC disparity between the transplant donor and recipient is crucial for interpretation of transplant outcomes. This gene typing program will greatly enhance the value of the colony for future transplantation studies.



Long-term tolerance of donor islets without the need for continuous immunosuppressive therapy in a non-human primate model of drug-induced diabetes: One and two years after receiving an islet transplant, drug-induced diabetic animals treated with a 14-day tolerance induction protocol and receiving no subsequent immunosuppression maintained normal glucose levels after a mixed meal challenge. The tolerance-inducing short-term immunosuppressive protocol consisted of a modified antibody, anti-CD3 conjugated with immunotoxin (F(Ab)<sub>2</sub>-IT), and an immunosuppressive drug, 15-deoxyspergualin (DSG). Drug-induced diabetic control animals that received an islet transplant but were treated with only one of the components of the immunosuppressive protocol, or that received the complete immunosuppressive protocol without an islet transplant, had much higher glucose levels than normal animals. (Study from the Laboratory of J. Thomas at the University of Alabama at Birmingham. Figures adapted with permission from Blackwell Publishing from Contreras, JL et al. *Am J Transplant*. 3: 128-138, 2003.)

### Anticipated Outcomes

Model systems in which to study type 1 diabetes are essential for translation of basic research into clinical practice. The NHPCSG uses primate models for the study of islet, kidney, heart, and lung transplantation. NHP transplantation studies are critical to the design of scientifically sound and ethically acceptable clinical trials, and to the development and evaluation of novel therapeutics to induce immune tolerance due, in part, to the close approximation of the NHP immune system and physiology to that of humans. However, there are also limitations in the use of NHP models, particularly because the

animals do not develop type 1 diabetes. Therefore, the animals are not susceptible to recurrent autoimmunity after islet transplantation—a major obstacle that must be overcome in humans. Nonetheless, NHPCSG studies have led to clinically relevant discoveries. Most notably, researchers have demonstrated the ability of transplanted islets to survive in NHPs without the requirement for long-term immunosuppression. By working together, sharing reagents and protocols, and directing the primate colony breeding program, researchers have contributed significant findings to the field of islet transplantation; many of these findings are already being translated

to clinical trials. This success demonstrates the importance of using pre-clinical large animal model systems to make real improvements in the health of patients. Future NHP studies using novel therapeutic agents may enable control of the immune response in humans, resulting in long-term islet cell transplant survival, with limited, short-term immunosuppressive therapy. These primate models serve the crucial role of bridging the gap between basic research and clinical progress in type 1 diabetes patients.

### External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of the NHPCSG at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ Research supported by this program is essential to making progress in the field of cell-based transplantation therapy.
- ▶ The NHPCSG is meeting and exceeding its goals and making tremendous progress.
- ▶ A strength of the program is the experience and talent of the participating investigators.
- ▶ An important aspect of the program is the establishment of specific pathogen-free NHP breeding colonies.

### Actions Taken in Response to Expert Panel

#### Recommendations

NHPCSG took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

#### Recommendation: Increase/Enhance New Interactions, Training, and Collaborations Within and Outside the NHPCSG Through Venues Such as Retreats, Workshops, and Research

- ▶ A workshop was held at Emory University on September 20-21, 2005, to exchange information about immune

analyses and research techniques in NHPs. A primary objective of the workshop was to actively engage graduate students and fellows in sharing techniques and protocols.

- ▶ Techniques and immune assay protocols from the NHPCSG laboratories were collated and placed on a public website, providing access to all NHP investigators ([www.transplant.emory.edu/nhp](http://www.transplant.emory.edu/nhp)).
- ▶ Meetings of the NHPCSG Steering Committee are held 1-2 times per year. The meetings provide a venue for sharing ideas, evaluating progress, and enhancing ongoing collaboration.
- ▶ An Opportunities Pool funding program within the Consortium provides additional opportunities for collaborations within and outside the NHPCSG and allows for timely research studies in response to the emergence of promising new therapeutics.
- ▶ Subcommittees of the Steering Committee have periodic conference calls and meetings. For example, a subcommittee for the rhesus macaque colony provides recommendations to NIAID regarding breeding strategies to enhance the utility of the colony.

#### Recommendation: Continue Support of the NHPCSG Program

- ▶ The islet and kidney model grants within the NHPCSG program expire in FY 2007. The NIAID and NIDDK will renew these components of the program in FY 2007, by issuing a competitive renewal RFA.

### Ongoing Evaluation

The NHPCSG Steering Committee (SC) serves as the governing body and is composed of the Principal Investigators (PIs) for each grant and an additional PI from multi-project grants. Program Directors of the NIAID and the NIDDK all serve as voting members of the SC. Investigators present details of progress and issues that arise in their research at the annual meeting. In addition, research agendas, collaborations, and

resource sharing are established and implemented by the SC, as well as coordination with clinical trials networks. The NIAID Program Officer coordinates several subcommittees of the SC geared toward maximizing the resources and within group collaborations. Annual review by program staff is performed to ensure that appropriate progress has been made prior to release of funds. Finally, the SC establishes guidelines for the setting of milestones, priorities, and review/evaluation procedures for projects funded with the Opportunities Pool funds. The SC provides funding recommendations to the NIAID and the NIDDK for Opportunities Pool projects.

The NHPCSG chair of the Steering Committee provided an update of progress to the NIAID Advisory Council (NIAID Division of Allergy, Immunology, and Transplantation Subcommittee) during the open session of the January 30, 2006, meeting. Council members concurred that the NHPCSG has made excellent progress and has made many valuable contributions to transplantation immune tolerance research.

### Coordination with Other Research Efforts

The NHPCSG coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaboration efforts, please see Appendix 2.

### Coordinating Research Studies:

- ▶ Cross-representation of investigators between NHPCSG and the Clinical Islet Transplantation (CIT) Consortium will facilitate collaborative design of pre-clinical testing of novel therapeutics in NHPs.
- ▶ ITN priorities for pre-clinical testing of new therapeutics are considered in evaluating NHPCSG Opportunities Pool applications. Several ITN high-priority strategies are currently funded as pilot projects.
- ▶ The CIT, ITN, and NHPCSG are interested in analyzing similar reagents for use as immune modulators for the treatment of type 1 diabetes or for islet transplantation.
- ▶ The NHPCSG and the ITN share information about scientific priorities and interests for research planning.
- ▶ There are many common research interests between the NHPCSG and the Immunobiology of Xenotransplantation Cooperative Research Program. There is cross representation both at the PI and program director levels. Plans are in place for sharing of reagents, techniques, and protocols that may be relevant to the two programs.

### NHPCSG Administrative History

Date Initiative Started	1999
Date <i>Special Program</i> Funding Started	2002
Date NHPCSG Expanded to Include Heart and Lung Transplantation Models	2005
Participating Components	NIAID, NIDDK

The NHPCSG is a multi-institution Consortium consisting of 11 research cooperative agreements, including 4 multi-project awards.

## Immunobiology of Xenotransplantation Cooperative Research Program

This multi-institution cooperative research program focuses on the development and evaluation of pre-clinical, porcine to non-human primate models of xenotransplantation (solid organ, tissue, or cell transplantation between species). Although the feasibility of human islet transplantation has been established, one barrier to the widespread use of this treatment strategy is the shortage of available islets. The pig source of islets is abundant and suitable for specific pathogen-free manufacturing practices. Therefore, it is important for the research community to evaluate the clinical complexities that accompany the use of these xenogeneic tissues in the transplant setting. This research program supports pre-clinical research to address immunological and physiological issues critical to the engraftment, survival, and function of xenografts. The goals of this program are: to delineate the cellular and molecular mechanisms of xenograft rejection and the induction of tolerance; to develop effective strategies to improve xenograft survival; and to characterize the physiological compatibility/limitations of xenografts. The long-term goal of this program is to develop novel and efficacious strategies for broad clinical application of xenotransplantation.

### Highlights of Progress

The progress that researchers have made include:

- Evaluated whether transplanted adult or neonatal porcine islets could restore glucose control in drug-induced diabetic non-human primate recipients. Similar immune suppressive protocols designed to achieve immune tolerance were used. The adult and neonatal porcine islets had an extended but not indefinite survival and both were able to restore glucose control in the diabetic recipients without transmission of porcine pathogens. Although further refinements to these protocols are indicated, the results provide encouragement that xenotransplantation may ultimately provide a useful therapeutic strategy to alleviate the inadequate islet supply.

### Anticipated Outcomes

Xenotransplantation offers a potential solution to the severe shortage of human organs, tissues, and cells to treat patients with end-stage organ diseases. Currently, the swine is the primary species of interest as a source of donor organs, tissues, and cells for xenotransplantation due to its favorable reproductive capacity as well as anatomical and physiological similarities to humans. However, xenotransplantation poses significant challenges, including the immune response of the recipient against the xenograft; the physiological limitations of organs or tissues functioning in a xenogeneic environment; and potential transmission of xenogeneic infectious agents, such as porcine endogenous retrovirus (PERV), from the graft to the recipient. Recently, researchers have generated several

lines of genetically modified pigs to address some of these obstacles in porcine to NHP xenotransplantation models. By working together and sharing reagents, resources, and protocols, researchers in this program will facilitate understanding of the mechanisms of xenograft rejection and the induction of tolerance and development of effective strategies to improve xenograft survival. As prolonged xenograft survival is achieved in NHP models, researchers may also address the physiological compatibility and potential limitations of xenografts after transplantation. Future porcine to NHP xenotransplantation studies using novel agents and resources may enable control of the immune responses, resulting in long-term xenograft survival with limited immunosuppressive

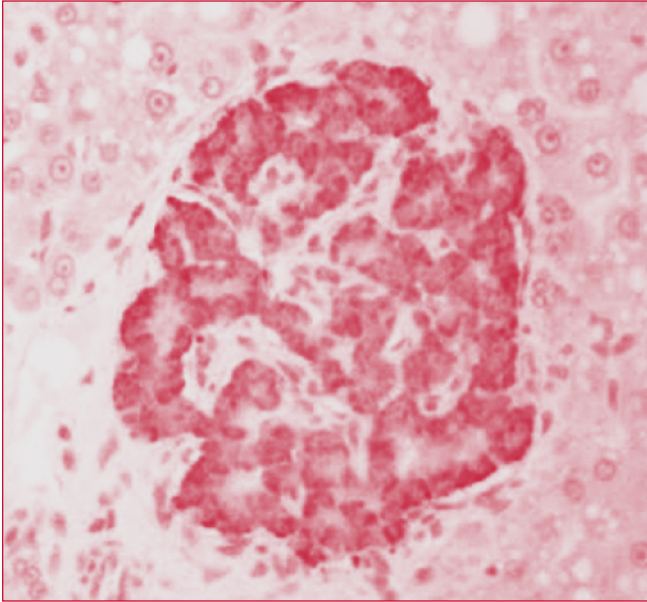


Image of porcine (pig) islets stained red for insulin in the liver of a non-human primate recipient on day 187 after transplantation while receiving maintenance immunosuppression. The research conducted by the Immunobiology of Xenotransplantation Consortium includes investigations of porcine islets as a possible source of islets for transplantation. (Image courtesy of Dr. Bernhard Hering and reprinted by permission from Macmillan Publishers Ltd: Nature Medicine. 12: 301-303, 2006.)

therapy. These primate models can serve a key role in bridging the gap between basic research and potential clinical application of xenotransplantation.

### Ongoing Evaluation

The SC serves as the governing body and is composed of the PIs for each grant and an additional PI from the multi-project grant. The NIAID and NIDDK Program Directors serve as voting members of the SC. Investigators present details of progress and issues that arise in their research at the annual meeting. In addition, research agendas, collaborations, and resource sharing are established and implemented by the SC. Annual review by program staff is performed to ensure that appropriate progress has been made prior to release of funds.

### Coordination with Other Research Efforts

There are many common research interests shared between the Xenotransplantation Research Program and the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG). There is cross representation between programs, both at the principal investigator and Program Director levels. Plans are in place for development of a website to facilitate sharing of reagents, techniques, and protocols that may be relevant to the two programs.

### Immunobiology of Xenotransplantation Cooperative Research Program Administrative History

Date Initiative Started	2005
Date <i>Special Program</i> Funding Started	2005
Participating Components	NIAID, NIDDK
The Program is a multi-institution Consortium consisting of five research cooperative agreements, including one multi-project award.	



## Clinical Islet Transplantation (CIT) Consortium

This Consortium is conducting studies to improve the safety and long-term success of methods for islet transplantation in patients with type 1 diabetes. The CIT is developing and implementing a program of clinical and mechanistic studies in islet transplantation, with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Studies will include a congressionally-mandated clinical trial of islet transplantation in Medicare recipients. Research pursued through this Consortium is expected to make significant improvements in the field of islet transplantation. The members of the Consortium will share data, results, and resources with the broad scientific community so that improvements are extended beyond the participating centers.

### Highlights of Progress

The progress that CIT has made as of March 1, 2006, includes:

- Developed six clinical trials, with associated immunologic, metabolic, and mechanistic studies, of islet transplantation in individuals with normal kidney function and having type 1 diabetes with severe hypoglycemic events despite intensive medical management. One of these trials is a multicenter clinical trial using manufacturing techniques and an immunosuppression regimen that were developed to represent the current standard, based on the results of single and multi-center experiences. The results of this trial will be the basis for consideration by the FDA of licensure of an islet product. The remaining five pilot trials will test new, innovative approaches to immunosuppression in islet recipients. All six trials will use identical inclusion and exclusion criteria and manufacturing specifications.
- Designed a phase III clinical trial that includes Medicare beneficiaries, as mandated by the Medicare Prescription Drug Improvement and Modernization Act of 2003 (Public Law 108-173). The target population consists of individuals with type 1 diabetes who have previously undergone kidney transplantation for diabetic nephropathy and are thus already receiving immunosuppressive therapy to prevent rejection of the donor kidney. These individuals will be randomized to either islet transplantation or intensive insulin medical management. This trial has required close collaboration among the NIDDK, NIAID, and CMS. Patient recruitment is expected to begin in 2006.
- Reached agreement with the FDA regarding a strategy for licensure of an islet product based upon the two phase III trials described above. These trials will use a “standard” anti-rejection regimen for both islet-alone and islet-after-kidney transplant protocols.

### Anticipated Outcomes

Because the CIT is recently established, the benefits of this major research endeavor will only be realized in the future. Islet transplantation is a promising therapy that can yield long-lasting, beneficial results for individuals with difficult-to-manage type 1 diabetes, but limitations of the current state-of-the-art must be overcome so more patients can benefit. Significant progress has been made in expanding the knowledge of islet cell biology and the processes associated with

transplantation and immune rejection, and in pre-clinical studies evaluating new approaches to immunomodulation in conjunction with islet transplantation in animal models. The CIT has created a means by which to rigorously study these new approaches to islet transplantation in the patient population most likely to benefit, using a well-coordinated, collaborative approach. The Consortium is addressing significant hurdles that exist for bringing islet transplantation procedures



into widespread clinical practice and that currently limit its experimental use to patients who have “brittle” diabetes or who have already undergone a kidney transplant. Current research is aimed at achieving long-lasting control of blood glucose, without the use of injected insulin, after a single islet transplant. Additional advances in islet transplantation that may be realized as a result of the work of this Consortium include minimizing the toxic effects of anti-rejection drugs; improving techniques for isolating and transplanting islets; and identifying methods to prevent graft rejection without the need for global immunosuppression. These types of improvements can ultimately lead to more widespread use of this treatment strategy for individuals with type 1 diabetes.

### External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the newly-established CIT at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ This group has a high potential for success.
- ▶ The mechanistic studies being performed by the Consortium are very important and should be supported.
- ▶ The Consortium should be involved in research training to increase the number of people and institutions that could perform islet transplants. It is important that the future successes of the CIT not be limited to the five funded centers.

### Actions Taken in Response to Expert Panel Recommendations

CIT took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

### Recommendation: Continue To Support Mechanistic Studies

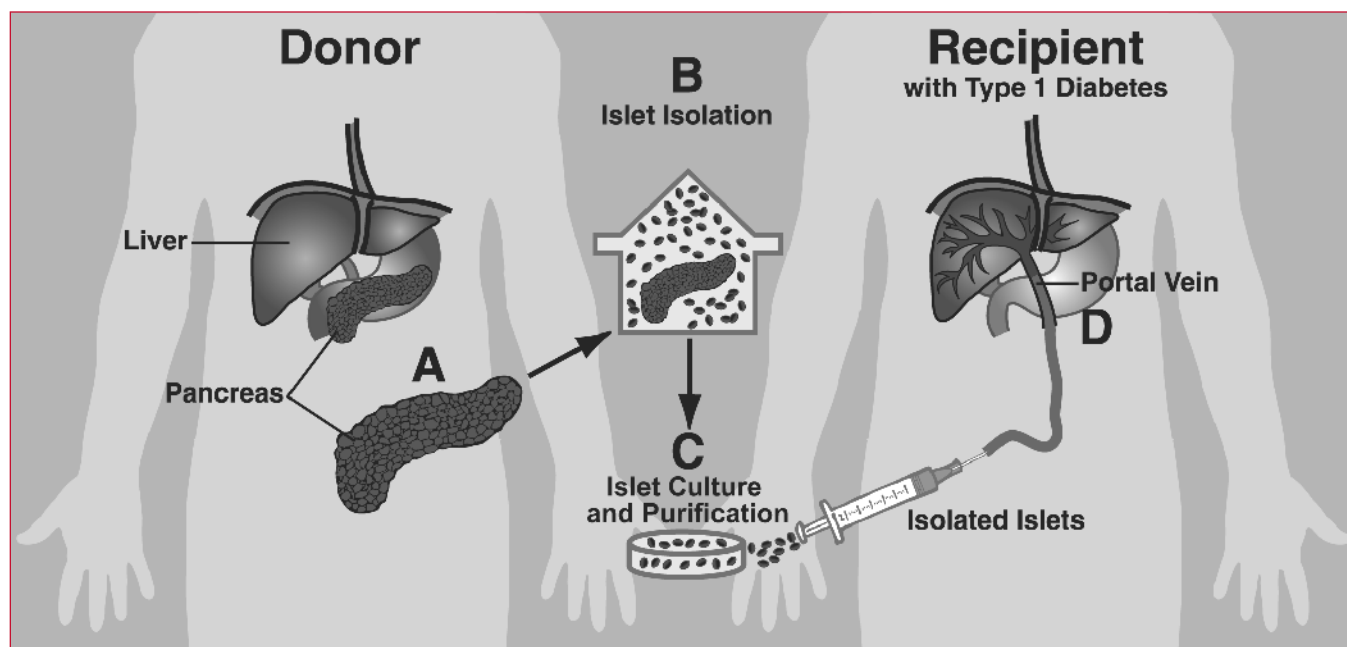
- ▶ The ongoing clinical trials are accompanied by a comprehensive program of mechanistic studies that address the physiology, immunology, and psychological effects of islet transplantation.

### Recommendation: Encourage Collaboration Between CIT and the Islet Cell Resource Centers (ICRs)

- ▶ An active collaboration between CIT, the ICRs, and CITR has been established. One important goal of this collaboration is the harmonization of the data dictionaries for the databases of the three organizations to reduce the time involved in data entry at the participating sites, and to facilitate data sharing. The first joint steering committee meeting between CIT and the ICRs was held in January 2006.

### Ongoing Evaluation

This program is jointly managed by the NIDDK and the NIAID. The Steering Committee is responsible for the overall Consortium operations; their first meeting was held in October 2004. The Committee is composed of the chair, the PIs of the five clinical centers and the data coordinating center, the chair of the Mechanistic Studies Subcommittee, and representatives from the NIDDK and NIAID. Several subcommittees have been formed that report to the Steering Committee. These subcommittees include: Mechanistic Studies; current Good Manufacturing Practices; Performance, Annual Report, Publications and Presentations; Organ Procurement Organization and Organ Recovery; and the Kidney plus Islet Transplantation Subcommittees. The clinical protocols are reviewed by the NIDDK Islet Transplantation Data Safety and Monitoring Board, which is composed of outside experts in diabetes, clinical trial design, ethics, transplantation, and biostatistics.



Islet transplantation is an experimental procedure in which islets are isolated (B) and cultured and purified (C) from a donor pancreas (A) before infusion into the portal vein of the recipient's liver (D). If the transplant is successful, the new islets begin producing insulin in response to the recipient's blood glucose levels, thereby eliminating or reducing the patient's need for insulin administration, and providing protection from hypoglycemia. The Clinical Islet Transplantation (CIT) Consortium is conducting clinical trials to improve the safety and long-term success of this procedure.

### Coordination with Other Research Efforts

The CIT coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*, particularly those involved in islet transplantation. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaboration efforts, please see Appendix 2.

#### Sharing Data Across Multiple Consortia Studying Islet Transplantation:

- ▶ Data sharing agreements have been developed among CIT, CITER, and the ICRs. These agreements include use of shared data dictionaries and source verification of data by CIT clinical site monitors, with corrections transmitted to all participants. Monthly teleconferences

ensure communication about maintaining up-to-date information. This effort will minimize redundancy in data collection and will enhance its dissemination.

- ▶ On-site data review of transplantation centers is performed by the CITER and is provided to the ICRs. The data includes determination of islet quality and collection of transplant outcome information.
- ▶ Investigators who use ICR resources must agree to place their clinical study data in the CITER.
- ▶ The CITER is planning to list all active islet transplantation protocols on their website. The CIT will be using this information as part of its informed consent process for enrollees.

#### Coordinating Research Studies:

- ▶ Cross-representation of investigators between the NHPCSG and CIT will facilitate collaborative design of

pre-clinical studies and pre-clinical testing of therapeutics in non-human primates.

- ▶ The CIT, ITN, and NHPCSG are interested in analyzing similar reagents for use as immune modulators for the treatment of type 1 diabetes or for islet transplantation.
- ▶ The CIT and ITN are sharing expertise and coordinating efforts in the planning of immunologic assays in CIT trials. ITN core labs will be used for selected assays in CIT trials.
- ▶ The T1D-RAID program is supporting the manufacture of reagents for use in CIT trials.

- ▶ Clinical grade islets are provided by the ICRs for trials conducted within the CIT.

#### **CIT Administrative History**

Date Initiative Started	2004
Date <i>Special Program</i> Funding Started	2004
Participating Components	NIDDK, NIAID
Website	<a href="http://www.isletstudy.org">www.isletstudy.org</a>

The CIT is composed of five clinical centers in the United States, Canada, and Sweden, and one data coordinating center.

## Islet Cell Resource Centers (ICRs)

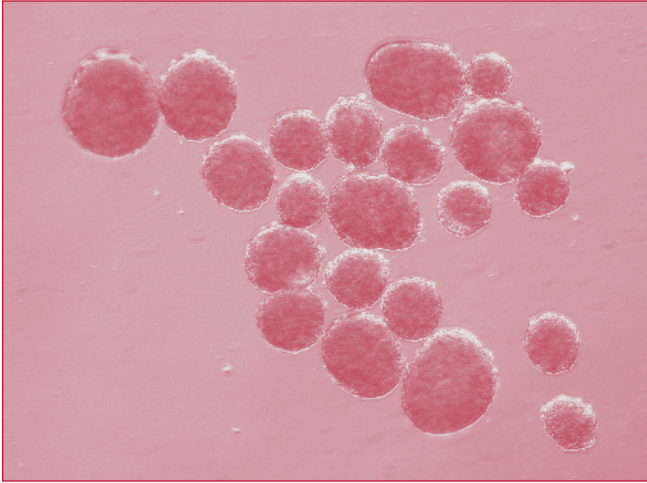
The ICRs represent some of the most critically important resources needed to establish the efficacy and safety of islet transplantation as a treatment for type 1 diabetes. Their mission has three components: (1) to purify clinical-grade pancreatic islets from whole pancreata and distribute them for clinical transplantation; (2) to provide pancreatic islets for basic research studies; and (3) to perform research and development to improve isolation techniques, islet quality, the shipping and storage of islets, and assays for characterizing purified islets.

Islet transplantation research requires multidisciplinary isolation laboratories that meet or exceed FDA guidelines for good manufacturing practice (GMP). The staff must include experts in clinical research and basic science and have specific expertise in the procurement of islets from cadaver pancreata. The ICRs distribute clinical-grade human islets throughout the United States to transplant centers that enroll patients in approved experimental protocols. They also facilitate national distribution of clinical grade islets to approved investigators who use them in basic research protocols. In addition, the ICRs conduct their own research designed to improve the procedures used to isolate, stabilize, store, and ship pancreatic islets and develop tests to be used on islets to characterize their viability, quality, and potency, and to determine their clinical effectiveness after transplantation. The ICRs provide infrastructure, resources, and a community of investigators coordinated to focus on improving the results of islet transplantation by promoting basic islet research, enhancing the quality of isolated islets at the site where they are used, and developing new technologies for islet manipulation and characterization.

### Highlights of Progress

The progress that ICRs have made as of March 1, 2006, includes:

- Provided 153 clinical grade batches of islets for transplantation in 78 patients.
- Distributed 26 million islet equivalents for research to 273 investigators.
- Demonstrated that the oxygen-carrier, perfluorocarbon, stabilizes cadaver pancreata during transportation.
- Developed specialized containers for the shipment of purified islets to improve islet viability and quality. Improvements in shipping have broadened the availability of pancreatic islets for patients in transplantation studies and for investigators performing basic research.
- Made progress toward defining assays that are clinically practical and predictive of clinical outcome. The ICR researchers have shown that the total number of viable beta cells contained within the islet transplant is more predictive of subsequent clinical success than simply the number of islets transplanted. Investigations are currently under way to compare methods of potency analysis, stabilization, and shipping methods in order to provide further improvement and cross-center standardization of techniques. The goal of the current studies is to provide national standards for the purification, preservation, shipment, and assessment of islets used in clinical transplantation and basic research.
- The ICRs support controlled studies for the assessment of a possible clinical benefit to be derived from the transplantation of purified pancreatic islets into selected eligible patients with type 1 diabetes.



Human pancreatic islets. The Islet Cell Resource Centers (ICRs) distribute islets to researchers for use in clinical islet transplantation in patients with severe diabetes and for basic research studies. (Image courtesy of Dr. Camillo Ricordi and Mr. Over Cabrera, University of Miami, Diabetes Research Institute-ICR.)

### Anticipated Outcomes

The regional ICRs have been successful in the support of national demands for clinical islets. Using a centrally located, objectively monitored priority list, the centers have distributed islets throughout the United States. As a result, institutional access to islets for transplantation and basic research has increased since the ICRs were created, thus accelerating the pace of discovery. Furthermore, the ICRs create a collaborative infrastructure that fosters refinement of preservation and cell culture solutions, optimization of shipping devices for both pancreas and islets, and advances in laboratory technologies to isolate islets. The collaborations help to meet the challenges inherent in the provision of viable islets with an optimal chance for survival after transplantation. During pancreatic transport and islet purification, preservation, and shipping, the islets are at risk of suffering irreversible damage that reduces their effectiveness as transplanted tissue. Research designed to improve islet viability and survival after transplant is expected to improve function and management

of diabetes after transplant, with a consequent improvement in the recipient's quality of life and health status. However, cadaver islets are foreign tissue for the recipients. Thus, to maximize transplant survival, recipients require an optimized program of immunosuppressive therapy in addition to optimally prepared donor islets. Increased islet survival could lower the number of islets required per patient for successful transplantation, reduce from two to one the number of transplants currently required, reduce the risks and costs associated with transplantation, and extend the availability of islet transplant to a greater number of people with diabetes. In addition, research is under way to improve the laboratory assessment of islet potency and viability, to refine the purification procedures, and to detect viable islets within the recipient by use of noninvasive methods.

### External Evaluation by Expert Panel

The ICR Steering Committee (SC), composed of a group of internal and external scientists and health care administrators, provides continuous evaluation and guidance to the ICRs. They review procedures and outcomes, adverse events, protocols for scientific studies, and policy matters. In addition, the NIH convened an *ad hoc* planning and evaluation meeting in January 2005, at which, among other topics, leading scientific and lay experts discussed the progress of the ICRs (see Appendix 3). Comments from the panel review included:

- ▶ There are many strengths to this program, and its scientific goals are critical.
- ▶ An interesting concept being addressed by the ICRs is having certain centers in the U.S. isolate and then ship islets to transplant programs around the country. There are many details (such as shipping conditions) that have to be studied for this approach to be successful.
- ▶ The ICRs have helped to pair clinical transplantation centers with islet isolation centers.

- ▶ There is a high potential to fine-tune some of the technical goals of this program to enhance the outcomes. These types of technology-based studies may be performed by small businesses.
- ▶ Appropriate external scientific oversight is important to achieve the program's goals.

### **Actions Taken in Response to Expert Panel**

#### **Recommendations**

ICRs took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

#### **Recommendation: Study Islet Shipping Procedures and Conditions**

- ▶ Efforts are ongoing to evaluate three islet shipping containers that have been designed by ICR scientists and one small business.
- ▶ A Small Business Innovation Research (SBIR) grant is supporting applied research in this area and the beta prototypes will be tested in conjunction with ICR investigators.

#### **Recommendation: Assure Appropriate External Oversight of ICRs**

- ▶ The PIs of each ICR, the Administrative and Bioinformatics Coordinating Center (ABCC), the NCRR, NIDDK, and JDRE, as well as a select group of experts and administrators, form the membership of the ICR SC, which provides oversight to the ICRs. A representative from the FDA is also a member of the Steering Committee.
- ▶ The Chairman of the ICR SC is independent of the ICRs and must not be associated with any of the affiliated institutions. In addition, the SC includes members from transplantation centers from Canada, the Nordic Network, and the Australian Transplant Consortium. Inclusion of non-U.S. experts in islet preparation is intended to

extend the experience of the group and provide objective, cutting-edge analysis of the ICRs' progress in islet purification, stabilization, and transport.

- ▶ The ABCC obtains feedback concerning islet quality from users of the pancreatic islets supplied by the ICRs.
- ▶ Based on recommendations from an *ad hoc* external advisory committee, milestones for continued participation in the ICRs were established. Based on these recommendations, 3 of 10 ICR centers failed to demonstrate the required activity and proficiency in their transplant programs and were discontinued.

#### **Recommendation: Reconfigure the ICR Program and Focus Resources More Efficiently**

- ▶ The NIDDK, NCRR, and the coordinating center regularly evaluate the use of program resources.
- ▶ In response to an RFA, the NCRR conducted a peer-reviewed competition in March 2006.
- ▶ Following peer review, a total of seven ICR centers were recommended for support; the group included three new centers and four previously supported centers.

#### **Recommendation: Increase Research To Improve Quality of Islets Delivered to the Scientific Community**

- ▶ Significant NIH grant funding is directed toward this goal (through the R01, P01, and SBIR/Small Business Technology Transfer [STTR] mechanisms).
- ▶ ICRs share new developments with the community through their comprehensive website, review of clinical and basic science research proposals, and frequent publications.
- ▶ In 2006, a competitive Opportunities Pool funding program was established within the Consortium. This mechanism provides additional opportunities for collaborations within and outside the ICRs and allows for timely research studies in response to the emergence of promising new technologies.

**Recommendation: Undertake “Systematic” Approaches To Understand the Variables Involved in Islet Isolation, Purification, Storage, Shipment, and Characterization**

- ▶ An islet workshop meeting on July 11, 2005, at the City of Hope addressed these issues. Of note, participants discussed data derived from the recent Oxygen Consumption Rate (OCR) assays to evaluate this procedure as a test to predict islet potency. The ICRs funded the OCR study carried out at several ICRs to address this question. This workshop was open to the entire transplantation community in addition to the ICRs.

**Recommendation: Organize a Meeting of the ICRs, Basic Scientists, and Islet Transplant Centers**

- ▶ The ICR SC held an open meeting on January 30-31, 2006, in Miami. Participants discussed strategies for facilitating the goals of the newly initiated CIT. They reached a consensus regarding how the ICRs would share information and work in a supportive manner with the CIT members and CITR. The ICR SC planned a second meeting for Fall 2006 to revisit this topic with addition of the new ICR members.

**Ongoing Evaluation**

As described above, the SC consists of the Chairman, the Director of the ABCC, seven ICR directors, two outside experts, and representatives from the NCRR, NIDDK, JDRF, and FDA. This committee meets semiannually to review clinical protocols and requests for clinical grade islets; present data relevant to improving islet isolation, purification, culture, shipping, and storage; discuss issues relevant to the field of islet transplantation; and provide overall direction to the ICR Consortium. A subcommittee of three SC members provides monthly reviews of requests for islets that will be used in basic research.

**Coordination with Other Research Efforts**

The ICRs coordinate their efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaboration efforts, please see Appendix 2.

Enabling Clinical and Basic Research Studies:

- ▶ The ICRs provide clinical grade islets for trials conducted within CIT.
- ▶ The ICRs provide islets for multicenter clinical studies using the Edmonton Protocol in the ITN.
- ▶ T1D-RAID supports the manufacture of reagents that will be tested for their effects on improving the survival and function of islets in culture.
- ▶ Investigators from the following consortia supported by the *Special Funding Program* receive islets used for clinical assays and for basic research through the ICR basic science human islet distribution program:
  - The Search for Diabetes in Youth Study (SEARCH);
  - ITN;
  - Autoimmune Disease Prevention Centers;
  - Genetics of Kidneys in Diabetes Study (GoKinD); and
  - BCBC.

Sharing Data Across Multiple Research Consortia Studying Islets:

- ▶ Investigators who use ICR resources must agree to place their clinical study data in the CITR.
- ▶ The CITR performs on-site data review of transplantation centers and provides the results to the ICRs. The data include determination of islet quality and collection of transplant outcome information.

- ▶ The CIT, CITER, and ICRs have developed data sharing agreements. These agreements include use of shared data dictionaries and source verification of data by CIT clinical site monitors with corrections transmitted to all participants. Monthly teleconferences ensure communication about maintaining up-to-date information. This effort will minimize redundancy in data collection and enhance its dissemination.
- ▶ Data collected from BCBC investigators using ICR samples are collected within the informatics coordination center of the ICR Consortium.

Improving Characterization of Islet Quality:

- ▶ ICR and BCBC investigators share reagents and expertise to develop improved methods of characterizing islet quality and viability.

**ICRs Administrative History**

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Components	NCRR, NIDDK
Website	<a href="http://icr.coh.org">http://icr.coh.org</a>

There are currently 7 ICRs. The Administrative and Bioinformatics Coordinating Center (ABCC) coordinates the activities of the ICRs and the Steering Committee, including the administrative, supervisory, and collaborative arrangements required to achieve the goals of the program.



## **Collaborative Islet Transplant Registry (CITR)**

The CITR expedites progress and promotes safety in islet transplantation through the collection, analysis, and communication of comprehensive and current data on all islet transplants performed in North America. The CITR collects both retrospective and prospective data from participating islet transplant programs. All islet transplants performed since January 1, 1999, are expected to be captured by the CITR, as well as future islet transplants performed through 2013. The CITR prepares an annual report with data on recipient and donor characteristics; pancreas procurement and islet processing; immunosuppressive medications; function of the donated islets; patients' lab results; and adverse events. This information is widely disseminated throughout the islet transplant community, diabetes community, and the general public. The data collected and analyzed by the CITR will help to define the overall risks and benefits of islet transplantation as a treatment option for type 1 diabetes patients.

### **Highlights of Progress**

The progress that CITR has made as of March 1, 2006, includes:

- Publication of annual reports in September 2004 and September 2005.
- Determined that episodes of dangerously low blood glucose (hypoglycemia), encountered in most patients prior to transplantation, were nearly absent after islet transplantation. The data were obtained from an analysis of 138 poorly controlled type 1 diabetes patients who had the procedure at 19 medical centers in the United States and Canada.
- Reported that, 1 year after the last islet infusion, 58 percent of recipients no longer had to inject insulin to maintain normal glucose levels, a successful clinical outcome.
- Reported that, 1 year after islet infusion, those individuals still requiring insulin injections had a 69 percent reduction in insulin requirements.
- Current database includes information on over 245 islet recipients, 408 infusion procedures, and 465 donor pancreata.

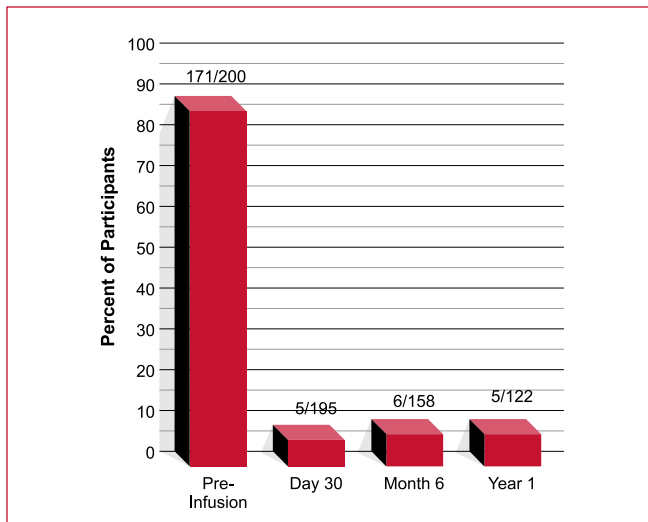
### **Anticipated Outcomes**

Important components of clinical studies are careful monitoring and reporting of findings. The CITR collects data on patients who have undergone islet transplantation procedures and produces reports that document study parameters and clinical outcomes. This monitoring system enables researchers to track the progress of successful patients as well as to follow patients who experienced graft failure. Importantly, long-term data regarding islet transplantation outcomes are collected for analyses. The 2005 Annual Report indicated that, from a study group containing 105 islet transplant patients, 58 percent were free of insulin injections at 1 year following the transplant. However, some patients require additional islet transplants, and successful outcomes are not uniformly observed. Track-

ing these patients is essential to determine the factors that contribute to graft function and longevity. These analyses will provide the basis for determining long-term benefits and therapies that are the most successful. Because islet transplantation is a complex, multifaceted process, and because it is conducted at numerous centers with funding from the NIH, voluntary organizations, and local institutions, the CITR is needed as a structure for making valuable assessments that will provide guidance for continued improvements.

### **Ongoing Evaluation**

To ensure continued and ongoing evaluation of the CITR's data collection process and procedures, the CITR is both peer



Data collected and analyzed by the Collaborative Islet Transplant Registry (CITR) show that there is a dramatic decrease in the number of severe hypoglycemic events following islet transplantation. Data show that 171 out of 200 recipients reported having one or more severe hypoglycemic episodes that required assistance in the year prior to their first islet infusion. During the first 6 months following the first infusion, only 6 recipients reported a severe event and only 5 recipients reported a severe event during months 6-12.

reviewed and reviewed by a Scientific Advisory Committee (SAC). The SAC was established by the Coordinating Center, in consultation with the NIDDK. Current voting members include representatives from the University of Minnesota, University of Miami, University of Alberta, University of Giessen (Germany), United Network for Organ Sharing, VA Puget Sound Health Care Systems, UCLA Immunogenetics Center, and the Nordic Network (Sweden). *Ad hoc* members include representatives from the FDA, CMS, Health Resources and Services Administration, Canadian Organ Replacement Register, JDRF, NCRR, NIAID, and NIDDK.

Participating investigators and transplant coordinators/data managers serve on the following CITR Committees that review its functions, procedures, and status on a minimum quarterly basis:

- ▶ The Compliance Committee monitors participant and

islet transplant program compliance, identifies barriers to consistent compliance with participant registration and follow-up, and suggests mechanisms to improve compliance. The Committee also reviews the results of each on-site data audit and recommends appropriate action based on the results of the audit.

- ▶ The Data Monitoring Committee is responsible for monitoring changes in the standard practice of islet transplantation (which includes islet isolation, purification, transplant technique, immunosuppression medications, and metabolic tests) and for recommending appropriate modifications to the CITR data collection tools.
- ▶ The Transplant Coordinators/Data Managers Committee provides logistical information to the SAC regarding the working of the CITR from the Coordinators' perspective.
- ▶ The Publications and Presentations Committee is responsible for reviewing all proposals for primary and secondary analyses and publications.

### Coordination with Other Research Efforts

The CITR coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*. Collaboration, coordination, and resource sharing serve to synergize research efforts and accelerate research progress. Examples of coordination with other consortia are given below. For a full description of ongoing collaboration efforts, please see Appendix 2.

Sharing Data Across Multiple Research Consortia Studying Islets:

- ▶ The CITR provides all data collection forms, data dictionaries, and codelists to all type 1 diabetes consortia and networks studying islets and islet transplantation.
- ▶ Data sharing agreements have been developed among the CIT, CITR, and ICRs. These agreements include use of shared data dictionaries and source verification of data by

CIT clinical site monitors, with corrections transmitted to all participants. Monthly teleconferences ensure communication about maintaining up-to-date information. This effort will minimize redundancy in data collection and will enhance its dissemination.

- ▶ Investigators who use ICR resources must agree to place their clinical study data in the CITR.
- ▶ Onsite data review of transplantation centers is performed by the CITR and provided to the ICRs. The data include determination of islet quality and collection of transplant outcome information.
- ▶ Meeting minutes of special interest committees such as the CITR Metabolic Monitoring Committee and the Health Related Quality of Life Committee are shared with all type 1 diabetes consortia and networks studying islets. Members from these groups are invited to participate on these committees.

- ▶ The CITR is planning to list all active islet transplantation protocols on their website. The CIT will be using this information as part of its informed consent process for enrollees.
- ▶ The CITR archives data from ITN islet transplantation trials.

**CITR Administrative History**

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Component	NIDDK
Website	<a href="http://www.citregistry.org">www.citregistry.org</a>

The CITR currently consists of one Coordinating Center (The EMMES Corporation, Rockville, MD) and 23 islet transplant programs. An additional 11 islet programs are in the CITR application process.

## EVALUATION OF INVESTIGATOR-INITIATED RESEARCH

**I**n addition to the research consortia previously described, the Special Funding Program supported investigator-initiated research projects addressing particular challenges and opportunities identified by the NIH with the aid of scientific experts at workshops and advisory meetings. Often these recommendations were disseminated to the research community in a Request for Applications (RFA) or Request for Proposals (RFP). (For a list of initiatives supported by the Special Funding Program, please see Appendix 1.) The NIDDK conducted a Grantee Survey (see Appendix 5) to evaluate the impact of the Special Funding Program on investigators with research project grants principally supported by the Special Funds. The survey was used as a tool to assess the research accomplishments (e.g., publications, resulting patents, impact on patients' health), research collaborations, and impact that the Special Program had on careers of investigators supported by it. Data from this survey are found in the "Assessment" chapter.

### Impact of Special Funding Program on Extramural Grantees

Principal investigators who received grants related to developing cell replacement therapy responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- ▶ "This funding source was of critical importance in allowing me to establish my own laboratory and begin an independent career in research and specifically, research related to type 1 diabetes. It also allowed me to integrate into the scientific community giving me the opportunity to contribute as a reviewer, presenter, and author of scientific research at a national and international level."
- ▶ "This grant has advanced my research program in several fundamental ways: (1) It has elevated my recognition at [my] institution in a time of administrative turmoil and resulted in retention and incorporation of my laboratory into a new department. (2) It has helped me focus my research program to one clinically relevant area, and we now have multiple projects with diabetes relevance. (3) It has allowed us to pursue an innovative technology that might not have been funded under the regular mechanisms, which tend to favor low-risk research."
- ▶ "As a young investigator, this grant has opened a world of opportunity for me. With this funding, I was able to establish my laboratory. I am at a highly competitive university that does not give out start-up funds to many new research scientists. This grant has afforded me the opportunity to hire a technician to help with the massive workload and the time to generate data for a larger (R01) grant. Simply put, this grant was the beginning of my career and the first opportunity to prove myself as a scientist."
- ▶ "This funding program has been invaluable. It stimulated additional funding/investment in long term programs/infrastructure by third party agencies, and facilitated new collaborations that we hope will provide critical insight. The pilot nature of our R21 funding puts the pressure on to focus and use these funds to demonstrate that we are genuinely on our way to providing new insights. If not funded by the NIH, this work would likely have gone unfunded!"
- ▶ "This grant was my first NIH grant. As a direct result of receiving this award, I was promoted to an Assistant Professor, my first independent position. This award allowed me to continue to focus my research in the field of transplantation tolerance and immune regulation."

▶ “This grant was very helpful in establishing a clinical research track to my career. My lab had previously been focusing on more basic research, and this grant allowed me to expand more fully into the translational research clinical arena. We have also become established as a

clinical laboratory to help develop assays to monitor the immunologic endpoints or changes, which are critical to gaining an understanding of how these types of therapies work.”

## ADVANCING ISLET TRANSPLANTATION

Beta cells of the pancreatic islets sense glucose levels in the blood and respond by releasing insulin into the circulation when these levels exceed a physiologically optimal range. Glucose levels then fall as insulin promotes glucose uptake by tissues throughout the body. When beta cells are destroyed by the autoimmune attack of type 1 diabetes, the body loses its only natural source of insulin. Lack of insulin causes blood glucose levels to spiral out of control, which can lead to many of the devastating complications of type 1 diabetes. Researchers have recently shown, in limited preliminary studies, that individuals with type 1 diabetes who receive transplanted islets can remain free of insulin injections for extended periods of time. While these results represent a major clinical advance, several challenges remain before this technique can be implemented in a large-scale fashion. Methods for acquisition and delivery of islets must be optimized. Better tolerated clinical treatments to combat the body's tendency to destroy the transplanted islets that have fewer side effects than the currently used therapies must be developed. An adequate supply of islets for all transplant patients must be created based on new understanding of how beta cells are formed and maintained. Research supported by the *Special Funding Program* is tackling these and other critically important areas, resulting in significant progress in advancing the field of islet transplantation.

### What Is Islet Transplantation?

Although research advances have improved the management of type 1 diabetes, patients often have difficulty controlling their disease. No matter how vigilant patients are, they cannot achieve the exquisite regulation of blood glucose levels that is provided by a healthy pancreas. Replacing the insulin-producing pancreatic beta cells that have been destroyed by the disease can help the body assume its normal role of precisely regulating blood glucose levels. In current methods of islet transplantation, insulin-producing

beta cells are taken from a donor human pancreas and transferred, or "grafted," into an adult patient, most commonly in the liver. Once implanted, these grafts begin to make and release insulin in response to the body's needs. The goal is to transplant a sufficient quantity of insulin-producing cells to keep the blood glucose level as close to normal as possible—with little or no reliance on external insulin administration. Researchers have confirmed that many islet transplant recipients are able to maintain near normal blood glucose levels. They also have observed, however, that success of the transplantation process varies greatly and wanes over time, underscoring the need for further research on methods of obtaining and processing islets for transplantation, and for maintaining functioning transplanted islets.

### Overcoming Barriers: Research To Make Islet Transplantation a Viable Therapeutic Strategy for Type 1 Diabetes

The complexity of the barriers associated with islet transplantation requires a broad-reaching scientific approach. Multiple avenues of research are needed to overcome the distinct challenges associated with the therapy. The *Special Funding Program* supports a range of consortia and investigator-initiated research designed to address the limitations of islet transplantation. Together, the pursuit of these research avenues is helping to overcome barriers to the maturation of islet transplantation as a viable therapeutic option.

### Limitations in Supply of Islets for Transplantation

Limitations in the islet supply create a major roadblock for the expansion of the islet transplant technique. Prior to the transplant procedure, the fragile islets must be collected and handled carefully so as to preserve their health and function. Improper handling of cells renders them of little use to the patient. Healthy donor cells must be implanted into the patient in an environment that continues to promote good health

and function. Many of the complex details of what constitutes this type of environment are not yet completely defined. The Islet Cell Resources Centers (ICRs), supported by the *Special Funding Program*, were established to act as regional centers designed to provide quality human islets to researchers engaged in islet transplantation procedures. The ICRs carefully collect fragile donor islets and distribute them for use in both basic science studies and clinical transplantation research. Significant progress has been made improving the collection and handling techniques for these delicate cells, thus improving both the quantity and quality of islets available. The greater the survival of transplanted cells, the lower the number of cells required, and thus the greater the number of patients who can undergo this life-altering treatment. Pilot clinical trials have demonstrated that insulin independence and long-term islet graft function can be obtained not only with islets processed and transplanted at the same institution, but also with islets processed at ICRs and shipped for transplantation at remote institutions across the United States. This success has validated the concept that regional centers could be utilized for islet cell processing and distribution.

Unfortunately, donor pancreata do not meet the demand for islets nationwide. One approach to overcome this barrier is to find alternative sources of islets. The *Special Funding Program* is vigorously supporting research toward this goal. For example, the Beta Cell Biology Consortium (BCBC) was created to facilitate interdisciplinary approaches to study the development and function of beta cells. BCBC researchers have accumulated considerable knowledge regarding the basic biology of pancreatic beta cells, both in terms of how these cells function and how they are affected in type 1 diabetes. They have developed methods to study the genes that are uniquely active in beta cells, and the proteins those genes produce. Through their efforts, knowledge is expanding about how stem/progenitor cells differentiate into insulin-producing beta cells. Furthermore, BCBC researchers are investigating beta cell regeneration, building on studies suggesting that it may be possible to regenerate

beta cells or boost residual beta cell function to coax the small number of insulin-producing cells that might remain in individuals with type 1 diabetes to multiply and once again produce insulin. Research into these novel methods and techniques could lessen or obviate the reliance on donor pancreatic tissue as a source of transplantable cells.

The use of non-human organs for transplantation, known as xenotransplantation, also offers a potential means of addressing the severe shortage of human organs, tissues, and cells to treat patients with end-stage organ diseases. Currently, the swine is the primary species of interest for xenotransplantation due to its favorable reproductive capacity and the anatomical and physiological similarities to humans. Recently, researchers have successfully transplanted insulin-producing islets from pigs into monkeys, a result that represents a promising intermediate advance. The Immunobiology of Xenotransplantation Cooperative Research Program, supported by the *Special Funding Program*, is focusing research efforts to overcome the challenges of xenotransplantation, which include the immune response of the recipient against the xenograft, the physiological limitations of organs or tissues functioning in a xenogeneic environment, and potential transmission of xenogeneic infectious agents from the graft to the recipient. Knowledge of the cellular mechanisms of xenograft rejection will ultimately facilitate the development of novel and effective transplant strategies.

### **Preventing Immune System Destruction of Transplanted Islets**

Following transplantation, patients must follow a lifelong medication regimen to prevent the immune system from attacking and destroying the transplanted cells, as well as to prevent the autoimmunity that caused type 1 diabetes in the first place (recurrent autoimmunity). These drugs can have immediate and longer term serious and adverse side effects, can reduce the body's ability to fight infections, and also may weaken or kill the grafted cells. Immune modulation and prevention of autoimmunity are key hurdles

to overcome before islet transplantation can become a widespread clinical technique. Through support from the *Special Funding Program*, researchers are gaining a deeper understanding of the concept of graft rejection and how to identify early signs of rejection, at a point when intervention is possible. They have developed new, less toxic agents, such as biomaterials, to block the immune attack on the transplanted islets. These agents are close to being tested in islet transplant recipients. In addition, advances in imaging techniques allow researchers to monitor the transplanted beta cells and detect recurring autoimmunity or rejection earlier. Early detection of autoimmunity, rejection, and beta cell loss could permit researchers to intervene to protect the functioning beta cells.

With the *Special Funding Program*, research supported by the Immune Tolerance Network (ITN) attempts to overcome the challenges associated with autoimmunity. The ITN evaluates therapies to reduce autoimmunity and other adverse immune responses by inducing, maintaining, and monitoring tolerance in humans for islet transplantation (as well as other types of transplants and autoimmune diseases; see main text for detailed information on the ITN). The goal of immune tolerance research supported by the ITN is to identify strategies to reprogram the immune system to prevent or inhibit disease-causing or aberrant immune responses without dampening the body's normal disease-fighting immune mechanisms. Research supported through this Network could uncover novel ways to prevent the damaging immune responses that destroy transplanted islets. The ITN works closely with the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) to move novel approaches from testing in non-human primates to human patients.

### **Propelling Clinical Research in Islet Transplantation**

The Clinical Islet Transplantation Consortium (CIT) was created to study and refine islet transplantation technology. Through both clinical trials and mechanistic studies, the

Consortium aims to improve methods of isolating islets, improve techniques for administering those transplanted islets, and develop approaches to minimize the toxic effects of immunosuppressive drugs required following transplantation. This Consortium is coordinating its efforts with other consortia. For example, data from CIT trials will be archived with the Collaborative Islet Transplant Registry (CITR), which tracks and reports information resulting from all islet transplants in North America. This information helps define the risks and benefits of islet transplantation. In addition to data collection, other coordination efforts are essential. The NHPCSG performs pre-clinical studies on newly developed therapies and techniques, thus paving the way for clinical studies, while the ICRs provide the high-quality islets for clinical transplantation research. Coordination efforts streamline discoveries, resulting in rapid clinical translation of basic research.

### **What Lies Ahead?**

The *Special Statutory Funding Program for Type 1 Diabetes Research* has laid the foundation for, and contributed to, major advances in the field of islet transplantation. At the same time that pivotal trials of state-of-the-art methods of islet transplantation in humans are being launched, ongoing basic and pre-clinical efforts continue to capitalize on recent progress, to improve all aspects of the procedure, and to move closer to a universal cell-based therapy for type 1 diabetes. Collaborative research consortia created under the *Special Funding Program* have played a central role in advancing islet transplantation while opening a range of new scientific avenues. With these efforts, the *Special Program* has helped to move the field closer to a cure for type 1 diabetes.



### Islet Transplantation Brings New Hope to a Patient with Type 1 Diabetes

Karla Edge was diagnosed with type 1 diabetes in 1967, at age 6. As a child, her disease was relatively free of complications. However, at age 13, she started having life-threatening hypoglycemic episodes. By the time she reached middle age, the episodes had become much more frequent and severe, to the point that she was experiencing several episodes a week.

“My blood sugar was so out of control that I couldn’t go anywhere by myself,” says Karla. Her husband, Mike, as well as other family members and friends, felt the need to call her at all hours of the day to make sure she was okay. Her two young daughters, Talia and Tatum, worried constantly about their mother. “It was all so very scary. I felt like I was knocking on death’s door,” says Karla.

#### Living with Type 1 Diabetes

Type 1 diabetes results when the body’s immune system destroys the pancreatic insulin-producing beta cells that control blood sugar levels. As a result, people with type 1 diabetes fight a constant battle to keep their levels from going too low or too high. Yet, even those who manage their diabetes well—by controlling their dietary intake and taking daily injections of insulin—are at high risk for a wide range of complications, including heart disease, stroke, blindness, kidney disease, and nerve damage.

Fortunately, Karla has no organ complications whatsoever as a result of her diabetes, and, “My eyesight is perfect,” she says proudly. However, she developed high blood pressure during her first pregnancy, but manages to keep it under control with medication. What she wasn’t able to keep under control, no matter how hard she tried, were her blood sugar levels.



Karla Edge

#### A Roller Coaster Ride

When she was 18 years old, Karla went into convulsions as a result of her low blood sugar. She was taken to the hospital in an ambulance. By the time she arrived in the emergency room, her blood sugar count had dropped to 10 mg/dL. A normal blood glucose level is approximately 100 mg/dL. Karla was told that she was lucky. Just the week before, another young woman had come into the hospital with a blood sugar count of 16 mg/dL and had died.

Since that time, Karla’s life has been a roller coaster ride. She was fine as long as her blood sugar was in the normal range. But when it suddenly dropped, she would become disoriented, start slurring her words, and her eyes would dilate. “I looked crazed,” she says. Karla often had to rely on close friends to give her glucose tablets to bring her blood sugar back up and to make sure she got home all right. The disease was taking an emotional toll on her family, as well. She recalls a time when she was standing in a department store checkout line with her then 6-year-old daughter. “My daughter looked up at me and knew I was in trouble. She

urgently told the person standing next to us, 'Please, my mom is a diabetic and she needs help.'"

Her diabetes affected her working life, as well. Karla worked as a data entry operator and was often late for work as a result of her hypoglycemic episodes. Her boss didn't understand the severity of Karla's condition and wasn't sympathetic to her being late or staying home from work. Over the years, the disease's impact on Karla's body—plus the emotional stress at work—had become so intense that her primary care physician strongly recommended that Karla retire early from her job, which she did at age 42.

It was about that time that Karla's sister, Kathy, read a newspaper article about an experimental treatment for type 1 diabetes, called islet transplantation, offered by the Diabetes Research Institute (DRI) in Miami, Florida. Karla immediately contacted the DRI, filled out an application, and was told she was a perfect candidate for the procedure. Although she had to wait nearly 3 years before undergoing her islet transplant, she says that it was well worth the wait.

### **Undergoing a Life-Changing Islet Transplant**

In September 2005, Karla underwent a new procedure for islet transplantation, called the Edmonton Protocol. Originally developed by researchers at the University of Alberta in Edmonton, Canada, the protocol uses a novel, steroid-free combination of three drugs that appears to prevent rejection, as well as halt autoimmune destruction of transplanted islets. Islet transplantation replaces the islets that have been destroyed by type 1 diabetes with islets from a donor cadaveric pancreas. The donor islets are infused through a catheter (small tube) into the portal vein of the liver. In a successful transplant, the new islets start producing insulin—eliminating or reducing the need for patients to take insulin. In effect, islet transplantation could be considered a real "cure" for the disease.

Karla's transplant was performed on September 19, 2005. She went into the procedure at about 2:00 p.m. and was given a local anesthetic, which meant she was awake throughout the entire procedure. She reports having felt very little pain or discomfort from the procedure itself and was back in her hospital room by 4:30 p.m. and released from the hospital the next day. Because the transplanted islets started working immediately, her physician reduced her insulin dosage that first day. Within 2 weeks, Karla was totally insulin-free. "It was the first time since I was 6 years old that my body produced enough insulin naturally to keep me alive," she says. "I'm very grateful to Dr. Rodolfo Alejandro, Director of Clinical Islet Transplantation at the DRI, as well as Drs. Tatiana Froud and David Baidal for their kindness and expertise," says Karla.

### **A New Beginning**

After undergoing the islet transplant, Karla felt that her future had arrived. At the time this profile was written, she was insulin-free and says that the transplant has been a life-changing event for her for the better. "I never knew I could feel so good," says Karla. "It's amazing!" Karla still needs to check her blood sugar before meals and two hours afterwards, as well as at bedtime. "It's always normal," she says with great relief. "It's nothing like it was before, when I had to check it every time I left the house or got in the car to drive somewhere." She also no longer needs to eat on a regimented schedule. Moreover, she can now do volunteer work at her daughters' school without concerns about episodes of severe low blood sugar.

It has been an enormous relief for her family, as well. "Before the procedure, my husband would wake me up in the middle of those nights when I would go into a hypoglycemic convulsion, and he would have to give me an emergency injection of glucagon to prevent me from going into a diabetic coma and perhaps dying. This would happen at least once a month. He says that now he can sleep well at night, without having to worry about me."

As with any transplant, rejection is a major concern. The immune system is programmed to destroy bacteria, viruses, and tissue it recognizes as “foreign,” including transplanted islets. Immunosuppressive drugs are needed to keep the transplanted islets functioning. These drugs, however, come with potentially serious side effects. Fortunately for Karla, her body has handled them well. “Aside from experiencing some nausea when I was in the hospital, I don’t remember the last time I felt sick from the drugs.” Nor, she adds, has she experienced any other side effects.

While the experiences of islet transplant recipients can vary, Karla’s reactions have been very positive. Karla adds: “I remember days, before the procedure, when I felt like I was 120 years old. Now I feel like I’m back in my 20s again. It’s wonderful,” she says joyfully, and then pauses. “No, it’s a miracle!”

### **Future Research: The Quest To Make Islet Transplantation a Viable Treatment Strategy for Patients with Type 1 Diabetes**

The demonstrated success of the Edmonton Protocol has engendered new hope for people with type 1 diabetes. It has also benefited patients such as Karla. However, islet transplantation using the new protocol is still very much in its infancy. For example, people who undergo a transplant may not be able to tolerate the immediate side effects of the immunosuppressive drugs, and the potential long-term side effects are not fully known.

The Collaborative Islet Transplant Registry analyzed outcomes in 138 patients at 19 medical centers in the United States and Canada. Data analysis showed that 58 percent of recipients no longer had to inject insulin 1 year after their last islet infusion; in 19 recipients, the donor islets failed to function. These data show that not every recipient becomes insulin-independent after undergoing this procedure. In addition, because islet transplants are experimental, they are available only to people who meet specifically defined criteria stated in the study protocol. To date, only adults with

severely unmanageable blood sugar levels or who have already undergone a kidney transplant have been eligible.

Further research is needed to overcome the current barriers in the field of islet transplantation. To propel research progress, the NIH is supporting multifaceted research efforts, primarily with support from the *Special Statutory Funding Program for Type 1 Diabetes Research*. Major goals are to increase the number of islets available for transplantation and to reduce or eliminate the need for immunosuppressive drugs after transplant. For example, the NIH launched a major new Clinical Islet Transplantation Consortium, which is conducting multiple islet transplantation trials to improve methods of isolating islets, improving techniques for administering the transplanted islets, and developing approaches to minimize the toxic effects of immunosuppressive drugs. The Islet Cell Resource Centers are a key resource for providing islets to the broad scientific community for use in both clinical islet transplantation and basic research studies. The Non-Human Primate Transplantation Tolerance Cooperative Study Group is evaluating novel methods to induce immune tolerance to transplanted islets in non-human primates to achieve long-term graft survival. This tolerance induction approach would avoid the need for lifelong immunosuppressive therapies. To tackle the shortage of islets, researchers in the Beta Cell Biology Consortium (BCBC) are collaboratively working to understand beta cell development and function, in order to identify ways to grow unlimited numbers of beta cells in the laboratory that can be used to treat patients. Research is also under way in xenotransplantation, which studies the possible use of non-human organs (such as from pigs) for transplantation into humans.

In addition to research on islet transplantation, the NIH also supports research on other methods to replace the insulin-producing beta cells that are destroyed in type 1 diabetes. Recent studies have shown that people with long-standing type 1 diabetes have some remaining functional beta cells. Therefore, research on the mechanisms controlling beta

cell growth and regeneration, such as those being pursued through the BCBC, could lead to novel therapies designed to stimulate beta cell growth in the body. Through islet transplantation, Karla Edge has re-experienced life without the need for daily insulin administration. It is only through

additional research efforts that Karla's life-changing, positive experience may become a reality for many more patients with type 1 diabetes who could potentially benefit from islet transplantation.

## EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

**T**he Special Funding Program has fueled the emergence of a wide range of research opportunities. Opportunities that have largely been made possible by the Special Funding Program have been excerpted below from the Type 1 Diabetes Research Strategic Plan (see Appendix 6).

### Islet Transplantation

Develop Novel Strategies and Infrastructure That Support Advancing Pancreas Procurement and Islet Processing:

- ▶ Study potential donor interventions that minimize the negative effects of brain death and ischemia (low blood supply)/hypoxia (low oxygen) on islet survival and function.
- ▶ Develop improved preservation medium, shipping containers, and monitoring technologies to improve pancreas preservation during transport.
- ▶ Develop improved islet isolation and purification methods and novel methods for tissue processing, beyond the currently available enzyme-blend techniques.
- ▶ Develop new strategies to improve pre-transplant islet culture that will sustain graft survival and function.

Develop Improved Methods To Assess Islet Beta Cell Viability and Function That Predict Early Islet Function After Transplant:

- ▶ Define and implement novel strategies and methods for assessment of beta cell-specific viability and function.
- ▶ Develop predictive tests to determine the suitability of an islet cell product for clinical use (i.e., tests predictive of post-transplant survival and function).

Investigate the Use of Porcine Islets as an Alternate Source of Islets for Transplantation:

- ▶ Develop strategies to overcome hyperacute rejection.
- ▶ Address immunological barriers to xenotransplantation.
- ▶ Pursue regimens for immune tolerance induction to xenografts.

Improve Islet Transplant Procedures:

- ▶ Determine the optimal sites for islet transplantation.
- ▶ Develop novel islet survival strategies.

Develop Novel Methods To Accurately Assess the Post-Transplant Islet Mass:

- ▶ Define and implement post-transplant metabolic testing of the transplant recipients to estimate: (1) functional islet mass that successfully engrafted, and (2) eventual changes in functional islet mass in long-term post-transplants.
- ▶ Develop novel strategies for imaging islet cells post-transplant and/or in the native pancreas (PET, MRI, videoendoscopy, *in vivo* microscopy).

Harness New Understanding of the Immune System To Develop Improved Clinical Monitoring and Immunotherapies:

- ▶ Identify markers of immune rejection and recurrent autoimmunity.
- ▶ Define effective strategies for immunomodulation of the recipient immune response and for tolerance induction following islet transplantation.
- ▶ Develop effective strategies for T cell regulation.
- ▶ Develop novel strategies for costimulatory blockade and expansion of candidate humanized monoclonal antibodies for costimulatory blockade.
- ▶ Employ tissue engineering strategies to protect transplanted islets from immune cell destruction.

## **Pancreatic Development, Stem Cells, and Regeneration**

Grow a Renewable Supply of Pancreatic Beta Cells That Can Be Transplanted into Patients:

- ▶ Identify and characterize genes that play particularly critical roles in the formation of the pancreas.
- ▶ Develop reagents and protocols for isolating pancreatic endocrine progenitor cells.
- ▶ Identify growth conditions that permit the stepwise differentiation of beta cells from stem cells or precursor cells.
- ▶ Develop animal models to test the engraftment, survival, and metabolic impact of beta cells or islets derived in culture from stem/progenitor cells.
- ▶ Determine if multipotent cells from fetal and adult tissue could be viable sources for beta cell replacement therapy.

Understand How Mature Beta Cells Are Maintained and Replenished in the Adult Pancreas:

- ▶ Determine the mechanism by which beta cell number is restored after beta cell loss.
- ▶ Identify factors and agents for enhancing beta cell division or decreasing cellular apoptosis.

Develop Strategies To Regenerate Beta Cells Through Replication or Neogenesis:

- ▶ Enhance understanding of the regenerative potential of beta cells.
- ▶ Determine whether beta cell replication or neogenesis is a clinically significant process.
- ▶ Develop therapeutic strategies to promote beta cell regeneration.