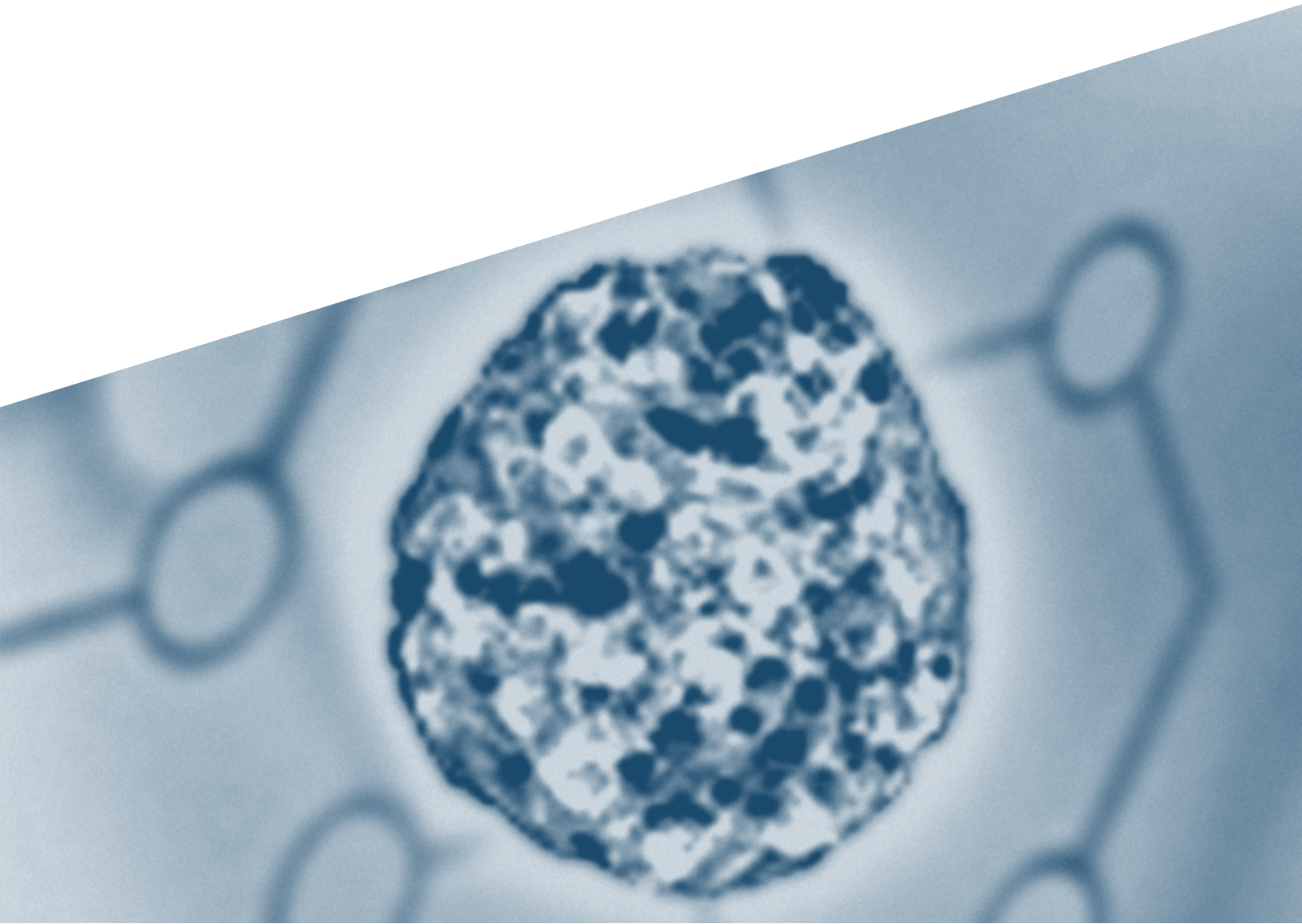
GOAL III

DEVELOP CELL REPLACEMENT THERAPY



Beta cells of the pancreatic islets sense glucose levels in the blood and respond by releasing insulin into the circulation when glucose 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, and prevents tissues from absorbing circulating glucose, which is the primary cellular fuel. Thus, understanding the specialized molecular and cellular functions of beta cells and restoring these functions in individuals with type 1 diabetes are fundamental goals of research on this disease.

Encouraging results from recent trials of islet transplantation have held out the hope of a turning point in the treatment of type 1 diabetes. However, significant barriers remain to widespread implementation of these protocols in the type 1 diabetic population. Importantly, the supply of cadaveric donor islets is sufficient to perform several hundred transplants per year in the U.S. Insulin independence often requires two or more transplant procedures. At current success rates, approximately 250 patients would be insulin independent at 1 year post-transplant, a number far less than the estimated one million type 1 diabetic individuals. Islet transplant therapy could potentially be extended to substantially more patients each year by increasing the number of available pancreata and improving islet isolation and transplantation techniques. Thus, a focus of continuing research is to improve the efficiency of islet transplantation and to develop methods for generating a renewable source of fully differentiated islets or beta cells from progenitor/stem cells or other sources. In addition, less toxic methods of preventing islet rejection and the recurrence of autoimmunity are urgently being sought.

The Special Statutory Funding Program for Type 1 Diabetes Research has had significant, beneficial impacts on research on the development of beta cell replacement therapy, which is essential to finding a cure for type 1 diabetes. At every level of the discovery pathway—understanding the basic biology of the beta cell, testing new treatment approaches in preclinical animal models, and optimizing islet transplantation protocols in patients—the special funds have fostered collaborative, innovative, and high-impact research that has led to important scientific advances and has paved the way for future opportunities. Moreover, the infrastructure to support islet isolation and transplantation procedures that has been established with the special funds will facilitate swift progress in using these promising new therapies to make a real difference in the health of individuals with type 1 diabetes.

Photo
Pancreatic islet.

MAJOR RESEARCH CONSORTIA AND RESOURCES

With the marked increase in special statutory funds that became available in FY 2001, major research consortia, trial networks, resources, and research solicitations were launched in FY 2001 and FY 2002. Brief descriptions of the research efforts and expected outcomes of initiatives supported in whole or in part by the special funds are presented below. More detailed scientific plans are available in Appendix 3.

Beta Cell Biology Consortium (RFA DK01-014)

Loss of the insulin-producing pancreatic beta cell causes type 1 diabetes; understanding how the beta cell develops and functions is, therefore, key to developing cell replacement therapy. The NIDDK-sponsored Beta Cell Biology Consortium (BCBC) is comprised of a diverse group of more than 30 laboratories in the U.S. and Europe. The BCBC focuses on basic developmental research, including islet cell lineage and beta cell regeneration, the isolation and characterization of putative pancreatic progenitor/stem cells, and the establishment of necessary reagents that will serve the beta cell biology research community-at-large. A related effort, the Functional Genomics of the Developing Endocrine Pancreas Consortium, has identified a large number of novel genes expressed in developing and adult pancreas. This project is now being integrated into the BCBC, which began in 2001 and is expected to extend through 2007.

Comprehensive Programs in Beta Cell Biology (RFA DK02-014)

Pancreatic beta cells are found in the islets of Langerhans in close contact with other hormone-producing cells that collectively work to regulate blood glucose levels. Molecular signaling within and among these cells in response to glucose and other metabolites and hormones is thought to be critical to the proper functioning of the beta cell. This initiative supports multidisciplinary research projects to investigate the signaling pathways of adult pancreatic beta cells and signaling networks among the different cell types of the pancreatic islet. Collaboration is encouraged between experts in beta cell biology or diabetes and scientists who could provide expertise in a new field or technology. The focus of the comprehensive programs on beta cell functioning and cell signaling complements the developmental biology interests of the Beta Cell Biology Consortium. The NIDDK awarded seven multi-year grants for collaborative research in September 2002.

Non-Human Primate Immune Tolerance Cooperative Study Group (RFA AI01-006)

Transplantation is now routine therapy for many end-stage organ diseases and 1-year graft survival often approaches 90 percent with standard immunosuppressive therapies. While new immunosuppressive drugs have reduced acute rejection in the first year post-transplant, they have only marginally improved long-term graft survival. Therefore, recent attention has focused on the potential for donor-specific immune tolerance to achieve long-term graft survival without non-specific, life long immunosuppressive therapies that have deleterious and often life-threatening side effects. Although certain tolerogenic regimens have been promising in animal models, these approaches have not been rigorously evaluated in transplantation settings. The Cooperative Study Group, which was established in FY 1999 and renewed in FY 2002, develops and evaluates novel, donor-specific tolerance induction regimens for kidney and islet transplantation to obtain safety and efficacy data before clinical trials are launched. The Study Group, which is supported by the NIAID and NIDDK, will continue at least through 2007.

Immune Tolerance Network (ITN): Islet Transplantation (RFP AI-DAIT-99-30)

A major breakthrough in the search for a cure for type 1 diabetes occurred with the success of the "Edmonton protocol" of islet transplantation that was pioneered at the University of Alberta. This experimental protocol led to insulin independence for a significant number of patients. The Immune Tolerance Network, an international collaboration of more than 70 basic and clinical investigators (*see also Goal II*), is seeking to replicate the success of the Edmonton protocol and is studying new methods to improve islet engraftment, survival, and function. The ITN is co-sponsored by the NIAID, NIDDK, and JDRF, which expect to support its efforts at least through 2005.

NIDDK Intramural Research Program

In 1999, the NIDDK Division of Intramural Research, in collaboration with the Department of Defense, the NIH Clinical Center, and the Diabetes Research Institute of the University of Miami, established an intramural Transplantation and Autoimmunity Branch (TAB). The TAB performs clinical research on new approaches to both islet and kidney transplantation for the treatment of diabetes and its complications. The special statutory funding program partially supported the TAB through the purchase of equipment and the installation of a facility in the NIH Clinical Center to harvest pancreatic islets for research and human transplantation purposes. The TAB was the site of the first U.S. islet transplantation using the Edmonton protocol. The NIDDK intramural program also supports research on the endocrine pancreas, primarily to understand the process by which progenitor cells differentiate into mature pancreatic islet cells, and to apply this knowledge to the treatment of patients with type 1 diabetes.

Islet Cell Resource Centers (RFA RR01-002)

Recent trials of a new islet transplantation protocol have shown that some transplant patients have achieved insulin independence, at least in the short term. A major problem in implementing additional trials of this protocol is the need for islet isolation laboratories that meet very strict sterility and procedural requirements to ensure the quality of isolated islets and the subsequent safety of islet recipients. Ten geographically-dispersed Islet Cell Resource Centers (ICRs) were established in FY 2001 to provide pancreatic islets to eligible investigators throughout the country for use in clinical protocols for transplanting human islets into patients with type 1 diabetes. In addition, the centers are investigating procedures to maximize the number, quality, and clinical functionality of the islets. The ICRs are co-sponsored by the NCRR and NIDDK and are expected to extend for at least 5 years.

Islet/Beta Cell Transplant Registry (RFP DK00-002)

Numerous clinical trials of islet transplantation are under way to determine how best to harvest pancreata, isolate and administer islets, and modulate the immune system to prevent destruction of the transplant. The Collaborative Islet Transplant Registry (CITR) will expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in the U.S. and Canada. The CITR was established in September 2001 by the NIDDK and its efforts are expected to continue for at least 5 years.

HIGHLIGHTS OF SCIENTIFIC DISCOVERIES

Many significant scientific advances have emerged from investigator-initiated research that began in the early years of the special statutory funding program. Highlights of these discoveries are provided here. More extensive discussion of initiatives and their research progress can be found in Appendix 3. Some grants or programs supported by the early initiatives are still in progress and the full impact of these projects on developing cell replacement therapies for type 1 diabetes may not be realized for several years. It is premature to assess accomplishments of the newly formed consortia or investigator-initiated research grants awarded in FY 2001 or FY 2002.

New Genomics Data and Resources

- More than 20 cDNA libraries enriched for genes from mouse and human pancreas have been created and over 160,000 DNA sequences have been obtained and deposited in public databases. These genes, including many that are newly-discovered and apparently unique to the pancreas, provide opportunities for the research community to explore potential new signaling pathways, develop new targets for therapeutic intervention, and characterize gene expression patterns in the developing endocrine pancreas and during disease progression.

- The first microarray cDNA chip specific to the pancreas has been developed. The clone set used to generate this mouse pancreas gene chip, the "PancChip," has been distributed to NIDDK-funded biotechnology centers for access by diabetes researchers. This chip will permit scientists to monitor expression patterns of thousands of genes in response to nutritional, pharmaceutical, and hormonal manipulations and during the progression of type 1 diabetes. A similar microarray chip containing human pancreatic gene sequences is in preparation.

Advances in Islet Transplantation

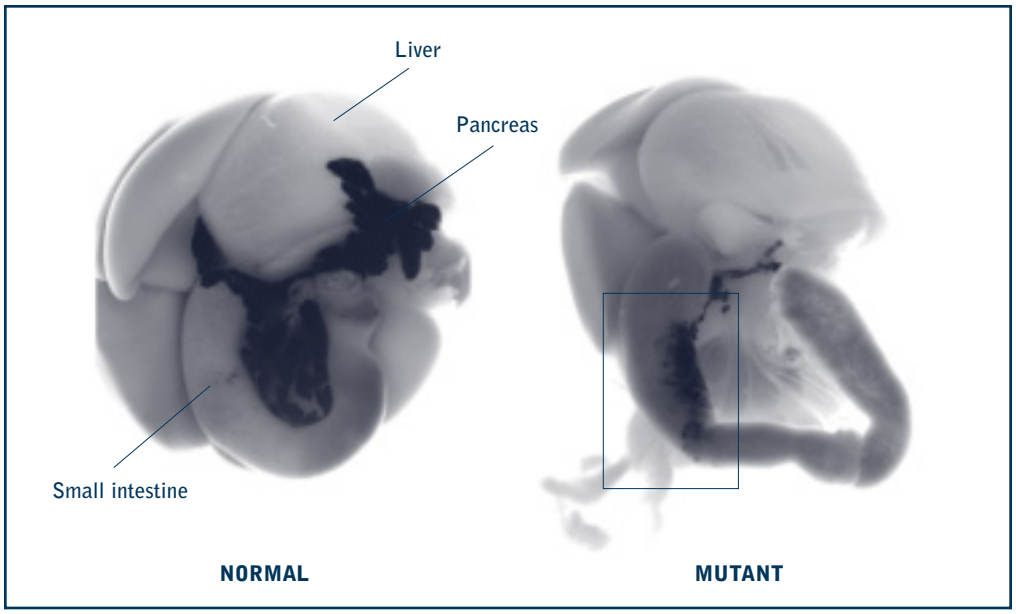
- In a non-human primate model, diabetes has been reversed using islet transplantation with the induction of tolerance. In this study all immunosuppression, consisting of two novel immunosuppressives, was discontinued after day 14 post-transplant. The recipients have remained insulin independent for greater than 1 year after transplantation. The preliminary success of this tolerance procedure in a non-human primate model raises the hope of developing a similar approach in humans, which would greatly decrease the risks associated with the current requirement for life-long immunosuppression.

- In a macaque model of diabetes, hematopoietic stem cells derived from the bone marrow of an islet donor improved the survival of transplanted islets when injected into transplant recipients. Thus, these stem cells have the potential to serve as a potent tolerogenic agent. In preliminary experiments, five of seven animals that received matched islets and stem cells retained the function of transplanted islets significantly longer than transplant recipients that were not also given donor stem cells. These findings may help in the design of future transplantation protocols for human patients.

Progress Towards Generating Renewable Sources of Beta Cells

- Scientists have discovered multipotent adult progenitor cells (MAPCs) in human, mouse, and rat bone marrow that appear to have properties of stem cells. Researchers established culture conditions that permit isolated MAPCs to differentiate into a broad repertoire of specialized cell types. Similarly, when mouse MAPCs are injected into a host animal, these cells become part of multiple tissues, including the liver, lung, intestine, and blood. By revealing the remarkable differentiation potential of MAPCs, these studies open new opportunities for stem and progenitor research on cell-based therapy for a variety of diseases, including type 1 diabetes.

- Identifying factors that control the fate of pancreatic cell types during development could lead to methods for coercing stem cells to selectively differentiate into insulin-producing beta cells. Researchers showed that a protein called "Ptf1a" is expressed in early pancreas progenitor cells and helps determine the fate of all pancreatic cells, including the beta cells. When the gene that encodes Ptf1a is removed from the mouse genome, cells that would normally have differentiated into pancreatic cells become intestinal cells instead. This research suggests that Ptf1a is an important trigger of pancreatic development that could, with more study, be harnessed as a tool for generating beta cells from undifferentiated embryonic or adult stem cells.

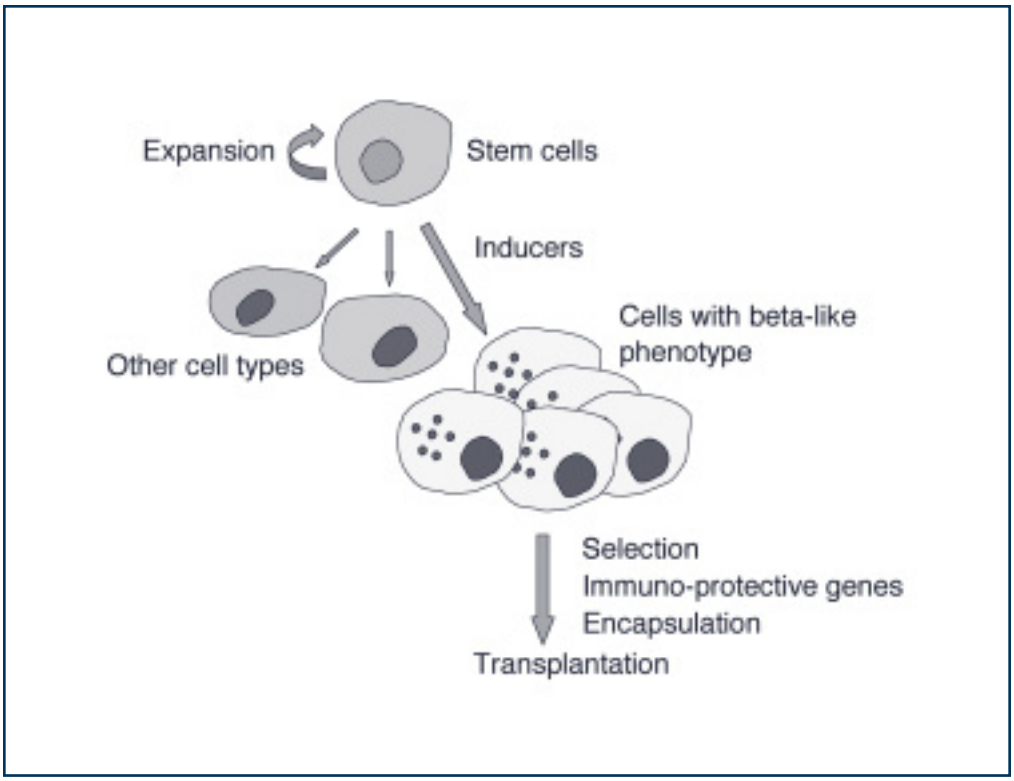


Mutant mice lacking the *Ptf1a* gene fail to develop a pancreas. Instead, cells that would have normally differentiated into pancreatic tissue become part of the small intestine (*boxed region in mutant tissue*). Understanding the mechanisms that control pancreatic development and beta cell differentiation will help researchers to devise new therapies to replace the insulin-producing beta cells that are lost in type 1 diabetes. This research was supported in part by the Special Statutory Funding Program for Type 1 Diabetes Research.

(Photo Credit: Dr. Christopher V.E. Wright, Vanderbilt University)

Stem cells have the potential to provide a renewable source of replacement beta cells for the treatment of type 1 diabetes. Researchers must first learn how to selectively induce stem cells to differentiate into insulin-producing cells. Knowledge of the basic cell biology of both stem cells and pancreatic beta cells derived from the Beta Cell Biology Consortium will enhance our ability to develop novel cell replacement strategies for the treatment of type 1 diabetes.

(Credit: Reprinted from Trends in Molecular Medicine, Vol. 8, S. Efrat, Cell Replacement Therapy for Type 1 Diabetes, pp 334-340, Copyright (2002), with permission from Elsevier.)



- Advances in stem cell biology have the potential to generate new supplies of beta cells from undifferentiated precursors. Researchers have now identified specific tissues and molecules that control whether early pancreatic progenitor cells differentiate into cells of the exocrine pancreas that make digestive enzymes, or into the endocrine islets, including insulin-producing beta cells.

- Human beta cell lines lose differentiated function when grown in culture, but regain glucose-responsive insulin secretion if stimulated by transcription factor PDX-1 downstream pathways, cell-cell contact, and the glucagon-like peptide (GLP-1) receptor. Cells treated with these factors retained the ability to secrete insulin in response to glucose upon transplantation into immune-deficient mice. This study introduces new approaches that could help in the generation of an unlimited supply of beta cells for islet transplantation.

- The promise of recent advances in beta cell replacement therapy for type 1 diabetes is limited by the relative scarcity of human islets available for transplantation. A primary research goal is to develop methods for culturing isolated islets in vitro to expand their numbers before transplantation. Researchers found that cellular senescence—the irreversible arrest of cell division—is the mechanism responsible for limiting the potential expansion of human beta cells in culture. Thus, senescence represents a major problem that will have to be overcome before expanded human islets can be used for transplantation.

Potential Therapeutic Targets for Preventing or Treating Type 1 Diabetes

- Anti-CD154, an antibody that targets a molecular tag on the surface of T cells, prevents rejection of transplanted islets and the recurrence of autoimmunity in a rat model of type 1 diabetes. This finding suggests a potential target for the development of new therapeutic agents for type 1 diabetes in humans.

- Chemical signals, called "cytokines," released by T cells and other immune system components, contribute to beta cell loss in type 1 diabetes. Researchers developed a set of cytokine-resistant and cytokine-sensitive cell lines that can be used to define genes that enhance beta cell survival. Using these lines, a protein involved in gene expression, STAT-1 alpha, was shown to protect cells from the damaging effects of multiple cytokines. Thus, STAT-1 alpha could provide a means of protecting beta cells or islets against cytokine-induced destruction in type 1 diabetes or islet transplantation.

- Cytokines such as interleukin-1 (IL-1) are important triggers of damage to beta cells during the development of type 1 diabetes. Investigators found that levels of an enzyme called 12-lipoxygenase (12-LO) are increased and its activity is turned on by IL-1. This enzyme causes the formation of certain fat molecules that directly damage the beta cells. Importantly, mice are protected from the development of diabetes when the gene for 12-LO is deleted from their genomes. These findings provide the rationale for developing new therapeutic agents to block 12-LO activity and, thereby, prevent or treat type 1 diabetes in humans.

- Treatment with an antibody to CD45, a protein tag on the surface of T cells, prolongs islet transplant survival in mice by up-regulating the expression of another surface marker, CTLA-4. CTLA-4 inhibits T cell activation and acts as a "brake" on the immune response against foreign islet tissue. Understanding the mechanism by which anti-CD45 works will open up an entirely new approach to immunosuppression for preventing rejection of transplanted islets and, potentially, for blocking the autoimmune process underlying type 1 diabetes.

- Targeted beta cell expression of an over-active form of the potassium ATP channel, which is part of the insulin secretion pathway, causes severe diabetes in newborn mice. This finding indicates that normal potassium ATP channel activity is important for maintaining proper glucose levels and that defects in the channel may have a potential causative role in the development of diabetes.

New Animal Models for the Study of Cell Replacement Therapies

- A chemically-induced model of type 1 diabetes, along with islet isolation and transplantation protocols, were established in macaques. This non-human primate model of diabetes and islet transplantation will serve as an excellent resource for preclinical trials of new tolerance induction and immunosuppression therapies.

- Investigators established a primate (monkey) model of islet transplantation to test strategies for the induction of tolerance. These efforts demonstrated that monkey islet transplantation can be performed with technical success, that standard immunosuppression is not sufficient to achieve prolonged graft survival, but that methods to induce tolerance can achieve prolonged islet graft survival without ongoing immunosuppression.

EXTERNAL EVALUATION

This section provides commentary from leading scientific experts within the diabetes research community who assessed the accomplishments of the special statutory funding program and from researchers who participated in the use of the special funds. A complete description of the evaluation process and the use of evaluative data regarding the special funding program is available in the Assessment chapter and Appendix 2.

Advisory Panel

A panel of scientific and lay experts on type 1 diabetes research convened at the NIH in May 2002 to review the use of the special statutory funds. Comments from the advisory panel regarding initiatives for cell replacement therapy established by the special funding program include:

- The advisors applauded the NIH's efforts to implement collaborative, "big science" programs in beta cell biology. They emphasized the dramatic advances in this field that have been made possible by the infusion of the special statutory funds and support from the NIH.

- The panel observed that the substantial infrastructure established in recent years by the NIH and the JDRF has positioned the field to capitalize on new developments in basic research, especially from cell biology and immunobiology. They stressed the importance of sustaining momentum, so that this infrastructure can be maintained and so that real gains can be made in reversing type 1 diabetes in patients.

- A major breakthrough in the treatment of type 1 diabetes has been the Edmonton protocol of islet transplantation. This procedure has permitted some patients with poorly controlled diabetes to achieve insulin independence. The advisors advocated continued investment in basic beta cell biology research to support the development of adequate supplies of isolated beta cells, and research to optimize transplantation techniques and methods of immunomodulation.

- The panel members were encouraged by significant progress in the production of functional islet cells from both adult and embryonic stem cells and they emphasized continued investment in cellular therapy as a high priority.

- The advisory panel was impressed with the breadth of cooperative programs and resource development that have been made possible through the special funds. The group reiterated the need to strengthen mechanisms for cross-talk and data sharing among the various research consortia and networks, as well as with the general research community.

Extramural Grantees

Principal investigators who received grants or grant supplements related to the development of beta cell replacement therapies responded to a survey asking, in part, about the value of this grant or funding source. Representative remarks include:

- "Creating [multiple] endocrine pancreas libraries from various developmental stages in mouse and man, and then sequencing over 100,000 genes, is a task far more consuming and expensive than could be funded by normal R01 mechanisms. Funding this project allowed us to create a valuable resource for the entire diabetes research community."

- "Sequencing the human genome provided us with knowledge of virtually all genes expressed in man. The Endocrine Pancreas Consortium now has provided us with knowledge of virtually every

gene expressed by the endocrine pancreas. This information will be used by future generations of researchers to create beta cells for insulin therapy and treatment of diabetes, as well as [to] provide the molecular targets for prevention of type 1 diabetes in impending patients."

- "The type 1 diabetes research funds...have clearly brought new people to the type 1 diabetes field and should allow the development of major advances in prevention, treatment, and eventual 'cure' of the disease."

- "This grant funded a high-risk project aimed at producing an important new research tool for use in the field of islet transplantation. I would not even have attempted to get this project funded through the regular funding processes because it was so different (high-risk and research tool) from what is normally funded by the regular research funding process."

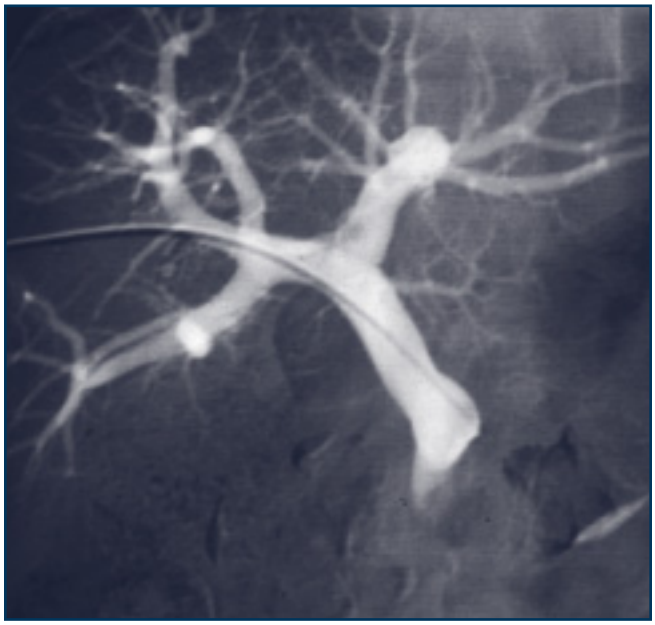
- "Our laboratory has been involved in type 1 diabetes throughout its existence (15 years). However, this grant was important because it allowed us to develop a new direction for the lab—the study of genes that can protect islets from environmental damage. This project has grown into a major initiative in our group."

- "This federal funding enables us to bring the latest innovations in islet cell isolation, processing, shipping, and transplantation to clinical testing in patients with type 1 diabetes. Without this support, advances in the field of cure-focused research would be severely impaired, and the search for a cure postponed indefinitely."

- "This grant was very important because it allowed me to pursue ideas that arose from studies related to other diseases and apply them to diabetes research."

- "The concept that [this molecular] pathway is important in islet cell dysfunction or destruction is a new concept that is now being tested by other groups and investigators. The findings first identified in our NIH grant have therefore led to new ideas that will permit investigators with varied expertise to attack this problem using varied approaches. This will greatly accelerate research in this field to help people with diabetes."

- "This grant has played an instrumental role in my career and, even more rewardingly, may allow my work to directly impact upon clinical care of transplant patients or those with autoimmune diseases like diabetes."



Transhepatic portal venogram. Radiological imaging techniques allow islet transplant surgeons to monitor the insertion of a catheter into the main portal vein of the liver prior to the infusion of purified islets that will restore natural insulin-producing capacity to type 1 diabetes patients. The minimally-invasive nature of islet transplantation significantly reduces surgical risks to the patients compared with whole-pancreas transplantation. The Immune Tolerance Network is studying ways to minimize the risks and optimize the outcomes of islet transplantation.

(Photo Credit: Reprinted with permission from Berney T, Bühler L, Caulfield A, Oberholzer J, Toso C, Alejandro R, Cooper DKC, Ricordi C, Morel P. Transplantation of islets of Langerhans: new developments. Swiss Med Wkly 2001;131:671-680.)

ISLET TRANSPLANTATION – PROGRESS AND CHALLENGES

A major goal of the Special Statutory Funding Program for Type 1 Diabetes Research is to develop cell replacement therapy to restore to patients the natural insulin-producing ability that has been destroyed by their own immune systems. Considerable progress is being made toward realizing this goal—which would represent a "cure" for the disease. Approaches include innovative research on the transplantation of insulin-producing clusters of cells—known as islets—from donor pancreata into patients with difficult to control type 1 diabetes, as well as basic research on the potential of undifferentiated stem cells to be developed into insulin-producing cells for transplantation or tissue regeneration.

Since the discovery of insulin was recognized with the Nobel Prize in 1923, insulin therapy for diabetes has dramatically extended and improved patients' lives. Insulin administration, however, is an imperfect therapy—not a cure—and its successful application requires extreme vigilance. Intensive therapy, which has been shown to effectively prevent diabetic complications like blindness and kidney failure, means that patients must keep their blood glucose levels as close to normal as possible throughout the day. Intensive therapy usually means multiple daily doses of insulin via injection or pump. Further, patients must watch what they eat, account for their exercise, and monitor their blood glucose levels several times each day.

The critical importance of intensive therapy, guided by frequent glucose monitoring, was demonstrated in the landmark Diabetes Control and Complications Trial (DCCT), an NIH-supported, multicenter clinical trial. This trial showed that intensive treatment dramatically reduced the risk of small blood vessel damage in patients with diabetes—the so-called "microvascular" complications, which include eye, kidney, and nerve disease. A follow-up study, known as EDIC, showed that the limited period of improved glucose control during the DCCT yielded benefits that persisted long after the trial ended–with diabetes complication rates dramatically reduced for at least 7 years after the DCCT ended. However, intensive therapy was also associated with an increased risk of dangerously low blood sugar levels (hypoglycemia). The burden and difficulty of trying to maintain optimal blood glucose control with externally-supplied insulin has prompted researchers to redouble their search for a cure—a transplant that would enable people with diabetes to make their own insulin.

One approach is to transplant an entire pancreas from a donor into a diabetic patient. This operation however is technically demanding (it can last 8 hours or more), and exacts a great toll on the patient. For instance, the patient must take drugs after the transplant to prevent rejection, and these medications are both expensive and toxic. Therefore, pancreas transplantation is usually limited to people undergoing a simultaneous kidney transplant. The limitations of whole pancreas transplantation have prompted researchers to seek a means to transplant only the clusters of insulin-producing cells within the pancreas—the islets—as this is viewed as a potentially simpler and safer procedure since major surgery would not be required.

In 1972, an NIH-supported scientist first reported that islet transplantation could cure diabetes in rats. Until recently, the intermediate and long-term success of this procedure, in humans, has been disappointing: of the more than 300 islet transplants performed over a decade, fewer than 10 percent of islet recipients remained insulin-independent for 1 year after the procedure.

Edmonton Protocol Spurs New Efforts

The prospects for islet transplantation research changed abruptly in the summer of 2000, when a group of Canadian researchers led by Dr. James Shapiro from the University of Alberta in Edmonton reported results of a revolutionary new procedure commonly referred to as the "Edmonton protocol." With this approach, the islets, which have been specially purified subsequent to isolation from an organ donor's pancreas, are injected into the portal vein that supplies blood to the liver. The islets then migrate to the liver, where they engraft and naturally produce insulin. If a sufficient number of islets engraft, nearly perfect blood sugar control occurs.

The Edmonton protocol built upon earlier work in islet transplantation and incorporated several improvements to the procedure. For example, a typical human pancreas is believed to contain about one million islets—only about one-third to one-half of which are actually harvested during the isolation procedure. The Edmonton group reasoned that it might be necessary to approximate the number of islets actually found in the pancreas, and consequently infused islets from more than one donor organ for each transplant recipient. In addition, the islets were maintained in purified human albumin and transplanted immediately after isolation. In previous islet transplantation efforts, steroids were generally used following the transplantation procedure to prevent transplant rejection; however, when given in high doses they can be toxic to islets. The Edmonton group used a novel immunosuppressive regimen that did not include steroids, and thus resulted in fewer side effects. The drug combination appears to prevent rejection and halt immune destruction of the islets, and is less damaging to transplanted islets than previous methods of suppressing the immune system. More than 80 percent of the patients who have been transplanted using this new protocol have remained insulin-free for a year compared to about 10 percent in previous islet transplantation trials. As a result, the approach taken in Edmonton is being evaluated in a larger number of patients at several transplant centers in the United States and Europe. However, the drugs used in the Edmonton protocol, while less toxic to transplanted islets, nonetheless have significant side effects. Thus, researchers continue to seek improved methods to halt immune destruction of transplanted islets.

Positive Directions in Islet Transplantation Research

Since 2000, several investigative teams have explored a variety of new approaches to islet transplantation with the goal of replicating or expanding the successful results achieved by the Edmonton research team. These research efforts involve intramural scientists in the Transplantation and Autoimmunity Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) at the NIH Clinical Center; the Immune Tolerance Network; and multiple investigator-initiated research projects.

Transplantation and Autoimmunity Branch and Organ/Tissue Transplant Center at the NIH Clinical Center: Resources provided by the Special Statutory Funding Program for Type 1 Diabetes Research in fiscal year 1998 provided an opportunity to establish within the NIH Clinical Center both the NIDDK Transplantation and Autoimmunity Branch and the Organ/Tissue Transplant Center. These newly created research entities have facilitated the testing of novel therapies to modulate the immune system to prevent transplant rejection—and thus replace harsh immunosuppressive drugs. In 1999, a clinical research program was launched involving new approaches to both kidney transplantation and islet transplantation for the treatment of diabetes. This new

initiative also involved collaboration with the Department of Defense and the Diabetes Research Institute at the University of Miami. This team was the first in the U.S. to perform islet transplants in type 1 diabetes patients based on the Edmonton protocol. The team is now working on ways to improve on the important leap made by the Edmonton group by finding a new way to prevent islet rejection, and to test other approaches for transplanting those cells. The intramural effort utilizes both clinical protocols to evaluate experimental therapies in the clinic, and animal models to develop and test approaches not yet at that stage.

Immune Tolerance Network: Replication of the success of the Edmonton Protocol is a major goal of the ITN–an international consortium of clinical researchers dedicated to developing approaches to induce immune "tolerance" to transplanted tissue, and thus avoid conventional immunosuppressive drugs.

Non-Human Primate Immune Tolerance Cooperative Study Group: To further develop tolerance approaches for islet transplantation in animal models most closely related to humans, the NIH has established a Non-Human Primate Immune Tolerance Cooperative Study Group. Researchers have developed a successful tolerance procedure for islet transplantation in a non-human primate model.

Collaborative Islet Transplantation Registry: Along with continuing refinements and improvements in research on islet transplant procedures and new immunomodulation approaches, it is also critically important to collect and analyze data to ensure the safety and effectiveness of new experimental therapies. This information will help to document the donor islet characteristics, clinical outcomes, secondary complications, and quality-of-life aspects of islet transplantation. To this end, the NIDDK has established the Collaborative Islet Transplantation Registry to collect data on islet transplants performed in the U.S. and Canada.

Shortage of Islets for Transplantation

If the promise of islet transplantation is realized in ongoing studies with larger numbers of patients, a major obstacle to its widespread therapeutic use will be limitations in tissue supply. Importantly, the supply of cadaveric donor islets is sufficient to establish insulin independence in approximately 250 transplant recipients per year in the U.S., a number far less than the estimated one million individuals with type 1 diabetes.

To address the shortfall of islets for potential therapeutic use, the NIH is pursuing research using multiple basic science approaches. These include developing alternative sources

Immune Tolerance Network website

(http://www.immunetolerance.org/)

for islets–such as embryonic, hematopoietic, pancreatic, and hepatic stem cells–in accordance with the established criteria for NIH-supported stem cell research. Additionally, researchers are developing engineered surrogate beta cells that secrete insulin. To foster this area of research, the NIDDK has established the Beta Cell Biology Consortium (described below) to develop new mouse models and research tools to investigate beta cell development and regeneration, and to explore innovative ways of producing differentiated islet cell types from multiple mouse and human stem cell sources. In addition, the Functional Genomics of the Developing Endocrine Pancreas Consortium is generating important genomic and bioinformatics tools from studies of mouse and human pancreatic tissue during development. These consortia are jointly assembling a public database that will permit rapid dissemination of data and should greatly stimulate research in this area.

Beta Cell Biology Consortium website

(http://www.betacell.org/)

Beta Cell Biology Consortium (BCBC): The mission of the BCBC is to facilitate interdisciplinary approaches to advance understanding of pancreatic islet development and function. An understanding of the mechanisms involved in the differentiation of pancreatic endocrine cells is likely to be necessary for the efficient conversion of human stem cells into pancreatic endocrine cells for the treatment of type 1 diabetes by cell replacement therapy. The BCBC recently awarded seven pilot and feasibility grants to allow exploration of innovative new leads for established investigators in stem cell biology and/or developmental biology of the pancreas; and to stimulate investigators from other areas to lend their expertise to research in this area.

Other Efforts to Enhance Islet Availability: In related efforts to enhance islet availability, the National Center for Research Resources established 10 Islet Cell Resource Centers around the country in order to provide clinical-grade islets to the transplant community and to facilitate improvements in the islet isolation procedure. The Special Statutory Funding Program for Type 1 Diabetes Research made this initiative possible. Opportunities now exist to improve islet transplantation techniques by avoiding or reducing dependence on freshly isolated islets—a dependence that can make transplantation logistically difficult. Previously, a very short window of time existed in which to successfully isolate and transplant islets subsequent to harvesting a pancreas. However, researchers have recently reported success at culturing islets in a manner that maintains their viability and function for longer periods, thus providing the ability to ship islets throughout the country. This extended viability offers greater flexibility in using islets and increases their availability to patients who would otherwise not be candidates for transplantation.