

EVALUATION REPORT

# Special Statutory Funding Program for Type 1 Diabetes Research



Cover photos (l-r): Children and families affected by type 1 diabetes. Dana Lewis, Tré Hawkins, Hannah Beauregard, Casey Burkhalter and her mother Leslie Burkhalter, and Trevor Weinstock.

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# **EXECUTIVE SUMMARY**

This report was developed in response to Section 330B of the Public Health Service Act, which calls for the preparation of an evaluation report to the Congress on the *Special Statutory Funding Program for Type 1 Diabetes Research* established under that Section.\*

Type 1 diabetes—previously known as juvenile diabetes—is a devastating illness that often strikes in infancy, childhood, or young adulthood. The immune system mounts a misguided attack destroying the insulin-producing beta cells found in clusters called “islets” within the pancreas. Without the hormone insulin, the tissues of the body cannot absorb or use glucose (sugar), the major cellular fuel. If left untreated, this disease results in death from starvation despite high levels of glucose in the bloodstream. The discovery and purification of insulin by a team of medical researchers at the University of Toronto in 1921 quickly led to the realization that insulin was the key to restoring the body’s ability to process glucose. This insight, which was recognized by the award of a Nobel Prize, provided a lifesaving treatment for type 1 diabetes in the form of daily insulin injections and transformed type 1 diabetes from an acutely fatal to a chronic disease.

The treatment regimen for type 1 diabetes requires constant attention and is difficult to maintain even in the best of circumstances. On a daily basis, individuals with type 1 diabetes must check their blood glucose levels multiple times with invasive finger sticks, monitor their food intake and physical activity levels, and administer insulin through injections or a pump. Even the most vigilant patients are at risk for sudden, acute episodes of dangerously low or high blood glucose levels (hypoglycemia or hyperglycemia, respectively), either of which can be life-threatening in extreme cases. The constant burden of this disease greatly affects the quality of life of patients and their family members.

Persistent elevation of blood glucose levels, despite insulin therapy, slowly damages nearly all of the body’s organs. Diabetes substantially increases the risk of blindness, kidney failure, chronic wounds and skin ulcers, nerve pain and other neurological problems, limb amputation, heart disease and clogged arteries, stroke, high blood pressure, periodontal disease, erectile dysfunction, bladder control problems, depression, and pregnancy-related complications. Because of these serious, long-term complications, type 1 diabetes is estimated to shorten the average life span by 15 years.<sup>1</sup>

Type 1 diabetes affects an estimated 5 to 10 percent of the 14.6 million people in the United States diagnosed with diabetes.<sup>†</sup> In type 2 diabetes—which is the major form of diabetes and is closely associated with obesity—the body gradually loses or “resists” its ability to respond effectively to insulin, and the pancreatic beta cells cannot secrete a sufficient amount of additional insulin to overcome this insulin resistance. Because both forms of diabetes involve malfunctions in the body’s system for maintaining appropriate blood glucose levels, and because both also share many of the same complications, research directed toward type 1 diabetes also benefits type 2 diabetes.

Type 1 diabetes can be more serious and costly for patients because it tends to strike earlier in life. For example, while type 2 diabetes increases the risk of heart disease 2- to 4-fold,<sup>2</sup> heart disease risk is increased by up to 10-fold in type 1 diabetes patients compared to the general age-matched population.<sup>3,4</sup> Importantly, the longer a person has complications, the more severe, difficult-to-treat, and costly they can become. Thus, early onset of type 1 diabetes can set the stage for a lifetime of living with and medically managing the disease complications.

\* This report to Congress was supplemented with additional patient profiles and other ancillary material prior to printing.

<sup>†</sup> Another 6.2 million people in the U.S. are estimated to have undiagnosed diabetes—bringing the total number of people with diabetes in the U.S. to 20.8 million. (Source: Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2005. Accessed at: [www.cdc.gov/diabetes/pubs/factsheet05.htm](http://www.cdc.gov/diabetes/pubs/factsheet05.htm))

## OVERVIEW OF THE SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

Special funding for type 1 diabetes research, in the total amount of \$1.14 billion for FY 1998 through FY 2008, was provided to the Secretary of Health and Human Services through Section 330B of the Public Health Service Act. The original enabling legislation was the Balanced Budget Act of 1997 (Public Law 105-33), which was later amended by the FY 2001 Consolidated Appropriations Act (Public Law 106-554) and by the Public Health Service Act amendment relating to

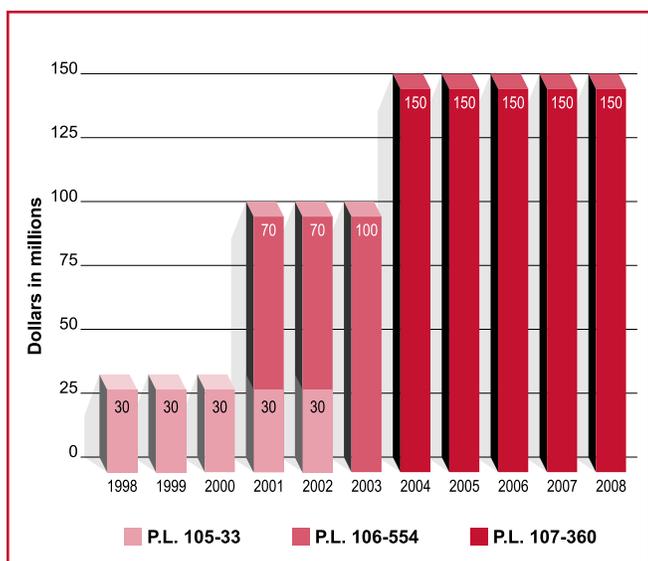


Figure 1: *Special Funding for Type 1 Diabetes Research. Special Program* funding levels per year, FY 1998-2008. The *Program* was established by the Balanced Budget Act of 1997 (Public Law [P.L.] 105-33), and later extended and augmented by the FY 2001 Consolidated Appropriations Act (P.L. 106-554) and by the Public Health Service Act amendment relating to diabetes research (P.L. 107-360).

diabetes research (Public Law 107-360) to extend the *Special Funding Program (Special Program)* in duration and funding levels (Figure 1).

This funding program augments regularly appropriated funds that the Department of Health and Human Services (HHS) receives for diabetes research through the Labor-HHS-Education appropriations subcommittees. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), through authority granted by the Secretary of HHS, has a leadership role in planning, implementing, and evaluating the allocation of these funds in a program that involves multiple Institutes and Centers of the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC).

In the first years (FY 1998-2000), the *Special Program* primarily supported initiatives to solicit research from individual independent investigators on topics of urgent and unmet research challenge. When the *Program* was augmented in FY 2001, the additional funds enabled the creation of unique, innovative, and collaborative research consortia and clinical trials networks. The majority of the funds since 2001 have supported these collaborative research efforts, with a goal of promoting progress in type 1 diabetes research that could not be achieved by a single laboratory. The *Special Funding Program* enabled the initiation of these large-scale, high-impact research efforts at a scientifically optimal scale.



## Highlights of Scientific Accomplishments

**Greatly Improved Prognosis for Americans with Type 1 Diabetes:** New research has provided some very good news for Americans with type 1 diabetes: incidence of certain major complications of the disease is down, and overall life expectancy is up. Scientists examined the rate of premature death and of various complications 20-30 years after diagnosis in people diagnosed in the 1950s through the 1970s. Although the scientists found that the rates of some complications, such as heart disease, have not improved significantly among people with type 1 diabetes, they found that people diagnosed more recently were nevertheless much more likely to live longer, healthier lives than those diagnosed earlier. In particular, kidney failure, diabetic nerve damage, and death are now all less likely to occur during the 20- to 30-year period following a diagnosis of type 1 diabetes than they used to be.

**Hemoglobin A1c (HbA1c) Standardization Improves Care for People with Diabetes:** The landmark Diabetes Control and Complications Trial (DCCT) not only demonstrated the tremendous value of tight blood glucose control in people with type 1 diabetes, but it also established the value of a critical new tool for assessing treatment. Hemoglobin is the protein that carries oxygen in the blood. HbA1c is a modified form of hemoglobin created when sugar molecules are added. The addition of these sugars occurs more easily when blood glucose is high. The DCCT proved that HbA1c tests, which measure the percentage of hemoglobin in the HbA1c form, are an excellent way to assess the quality of blood glucose control over the preceding weeks. However, when the DCCT ended in 1993, such tests were not yet common—there were few laboratories performing them, and those labs did not use a standard, agreed-upon method. With support from the *Special Funding Program*, the CDC launched the HbA1c Standardization Program in 1998 as a key tool to enable translation of tight blood glucose control into common practice. The standardization effort has been a great success and has facilitated vital, lifesaving, and life-improving efforts for people with diabetes, such as the National Diabetes Education Program’s “Control Your Diabetes for Life” campaign.

**New Glucose Monitoring Tools for Controlling Blood Glucose Levels:** With the knowledge that intensive glucose control could prevent or delay the development of diabetes complications, a high priority for research supported by the *Special Funding Program* has been the development of new tools that improve patients’ ability to control their blood glucose levels. The *Special Funding Program* and the NIH supported the development of recently approved continuous glucose monitors, which reveal the dynamic changes in blood glucose levels by assessing glucose levels hundreds of times per day and displaying trends so patients can see if their levels are rising or falling. Alarms warn the patient if blood glucose becomes too high or too low. This revolutionary technology can make it easier for patients to accurately determine how much insulin or food they need to keep blood glucose at healthy levels and can enhance their ability to achieve the tight control necessary to prevent disease complications.

**Long-Term Benefit of Near-Term Blood Glucose Control:** Although the DCCT proved that aggressive control of blood glucose can dramatically lower the rates of some of the complications of type 1 diabetes during the period of intensive control, the longer-term benefits had not been studied. The *Special Funding Program* enhanced the long-term continuation of the follow-on Epidemiology of Diabetes Interventions and Complications (EDIC) Study, in which researchers have continued to study the DCCT participants after the blood glucose control intervention period ended, and have been able to perform more

assessments than would otherwise have been possible. After the initial study, overall blood glucose control in the intensive group gradually declined, while that in the conventional treatment (control) group typically improved, until both groups had similar blood glucose control. But surprisingly, the former intensively-treated group continued to have long-term benefits compared to those in the control group, despite similar HbA1c levels during EDIC: an effect termed “metabolic memory.” Thus, physicians and patients now know that it is particularly valuable to control blood glucose levels early in the course of disease. Importantly, EDIC has also expanded the list of benefits of effective blood glucose control. It has shown that close control lowers the risk of heart disease and stroke by about 50 percent in people with type 1 diabetes. This finding is particularly significant because people with type 1 diabetes have a 10-fold increased risk of heart disease compared to the general age-matched population.<sup>3,4</sup>

**Higher Rates of Hypoglycemia Do Not Affect Neurocognitive Function:** Preliminary results from an ancillary study to the EDIC Study have shown that there are no significant differences in neurocognitive function between the former intensive and conventional treatment groups. This finding suggests that the higher rates of hypoglycemia in the intensive treatment group have not affected cognitive function. Because it is important to treat patients as early and as intensively as possible to prevent or delay the development of disease complications, this result is reassuring to patients and parents of children with the disease. Even though the acute effects of bouts of hypoglycemia are very worrisome for parents, these findings suggest that intensive treatment is safe for their child’s brain, ability to think, and ability to do well academically.

**Novel Drugs for Treating Complications:** Research supported by the *Special Funding Program* has fostered the development of novel drugs to treat diabetes complications. For example, NIH supported the development of a therapeutic agent that inhibits a protein called protein kinase C beta (PKC beta). This agent is currently being tested by industry as a treatment for diabetic eye disease. Ongoing work supported by the *Special Funding Program* is also examining the potential of this drug to slow additional diabetes complications. Other examples of promising therapeutic agents for diabetic eye disease are drugs that inhibit excessive angiogenesis (new blood vessel growth) in the eye. Investigators in the Diabetic Retinopathy Clinical Research Network, which is supported by the *Special Funds*, are collaborating with industry on the development of a protocol to evaluate angiogenesis inhibitors for treating diabetic macular edema.

**Creation of a Pipeline for Testing Therapeutic Agents for Complications:** The *Special Funding Program* has enabled the creation of a research pipeline that is propelling progress in drug development. This pipeline facilitates research to: identify promising therapeutic targets and agents in the laboratory, generate animal models that mimic human type 1 diabetes and complications of diabetes, test promising agents in these animal models, promote pre-clinical drug development, and test promising therapies in human patients. A key resource has been the Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID) program, which supports pre-clinical drug development and facilitates translation of agents from the laboratory bench to patients’ bedside (bench to bedside). New drugs have already made their way through this research pipeline and will be tested for effectiveness in treating patients. Additional agents are at earlier stages of this pipeline. For example, researchers are collaboratively participating in an effort to screen approximately 1,000 compounds that are already approved for other uses in humans to determine if they have an effect in laboratory assays relevant to diabetes complications. This approach has

the potential to translate compounds rapidly from the lab into clinical applications. Another new initiative is promoting the development of biomarkers for type 1 diabetes and its complications. The lack of biomarkers is an enormous barrier to research progress. New biomarkers could help physicians more accurately determine an individual's risk of developing diabetes or its complications; monitor disease initiation or progression; and monitor response to interventions. Biomarkers can also be used as surrogate endpoints for clinical trials and may therefore enable researchers to conduct clinical trials more quickly and less expensively than is currently possible. Research to develop and validate novel biomarkers and animal models, coupled with this new pipeline, can further enhance the translation of novel therapies from bench to bedside.

**Advances in Islet Transplantation as a Therapeutic Approach for Type 1 Diabetes Patients:** The *Special Program* supported the first islet transplantation trial in the United States using a procedure referred to as the “Edmonton protocol,” a revolutionary procedure that greatly improves the outcomes for islet transplantation. Through the Immune Tolerance Network (ITN), the *Special Program* also supported the first international, multicenter trial of islet transplantation using the protocol. These studies have confirmed and extended the demonstration that islet transplantation may become an alternative to whole pancreas transplantation for treatment of type 1 diabetes. However, to make islet transplantation a viable therapeutic strategy, barriers still must be overcome, such as the shortage of donor islets and the toxicity associated with the lifelong immunosuppressive medication that patients must receive to keep their bodies from rejecting the transplanted cells. The *Special Funding Program* is supporting multifaceted research efforts to overcome these barriers through the study of islet development and function and identification of ways to reduce or eliminate the need for immunosuppressive therapy following transplantation.

**Setting the Stage for Testing Novel Type 1 Diabetes Prevention Strategies:** Research supported by the *Special Funding Program* has enabled testing of new type 1 diabetes prevention strategies through infrastructure created by the *Program*. Scientists have completed oral and parenteral insulin type 1 diabetes prevention trials (now part of Type 1 Diabetes TrialNet). These trials demonstrated that it is possible to predict with great accuracy the risk of developing type 1 diabetes. Moreover, although oral insulin did not prevent disease onset in the study group as a whole, there was a suggestion of possible efficacy in the subgroup with the highest insulin antibody titers. This knowledge has set the stage for screening and enrolling patients into new type 1 diabetes prevention trials. Furthermore, other research studies have shown that it is feasible to perform screening in newborns to identify those who have certain genetic risk factors for the disease, and ongoing studies supported by the *Special Funding Program* are now testing preventative approaches in newborns. In addition, the *Special Program* stimulated improvements in the ability of researchers to determine the metabolic activity of individuals with or at-risk for type 1 diabetes. These improvements include standardization of the assay to measure C-peptide (a by-product of insulin production that is co-secreted from the beta cell with insulin and is a useful measure of endogenous insulin production) and information on how best to stimulate and characterize residual insulin production in type 1 diabetes patients on insulin therapy. Research has demonstrated that C-peptide levels correlate with improved long-term outcomes, such as preventing or delaying the development of complications and improving glycemic control with less risk of hypoglycemia. Although an effective type 1 diabetes prevention strategy has yet to be identified, the *Special Funding Program* has created conditions that are now permitting promising strategies to be tested.

## Type 1 Diabetes Research Benefits People with Other Diseases

Research supported by the *Special Funding Program* is far-reaching, benefiting not only type 1 diabetes patients, but also people with type 2 diabetes and those with other autoimmune diseases. For example, research to understand insulin-producing beta cells, and to find ways to preserve and restore beta cell function, benefits all diabetes patients. In the same way, all diabetes patients gain from research directed at the disease complications that type 1 and type 2 diabetes share. Type 1 diabetes research also benefits patients with other autoimmune diseases, such as celiac disease. Some genes confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Studies supported by the *Special Funding Program* to identify environmental triggers of type 1 diabetes are also investigating celiac disease, which can ultimately benefit patients suffering from both diseases.

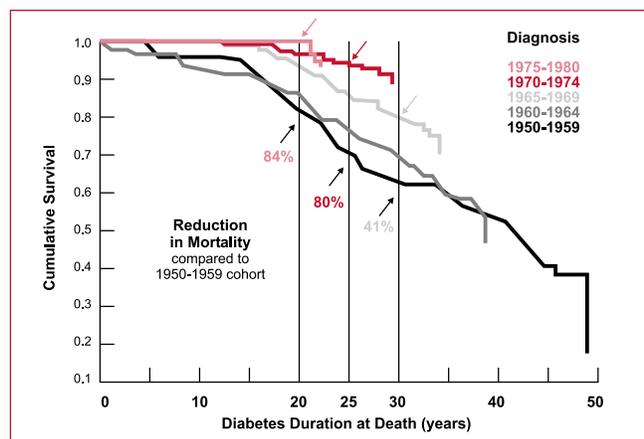


Figure 2: People with Type 1 Diabetes are Now Living Longer, Healthier Lives: Scientists examined the rates of premature death and complications 20-30 years after diagnosis with type 1 diabetes in Western Pennsylvania. Each line shows a survival curve for a group diagnosed over a 5-year interval. Compared to those diagnosed from 1950-1959, those diagnosed from 1975-1980 were 84 percent less likely to die within 20 years of diagnosis. The prognosis continues to improve, with kidney failure, diabetic nerve damage, and death all less likely to occur now than in the past, as research has led to continuous improvements in therapy. (Figure courtesy of the Pittsburgh Epidemiology of Diabetes Complications Study Group. Copyright © 2006 American Diabetes Association. Adapted from *Diabetes*, Vol. 55, 2006; 1463-1469. Reprinted with permission from The American Diabetes Association.)

## How the *Special Funding Program* Contributes to the Pipeline for New Therapies

The *Special Funding Program* supports type 1 diabetes research along a pipeline that facilitates the identification and development of new therapies. Examples of studies supported by the *Special Program* that are feeding into this pipeline are described in the bottom panel.

Identifying Molecular Pathways of Disease Progression	Identifying Therapeutic Agents To Target Molecular Pathways	Pre-clinical Drug Development and Testing	Testing Promising Therapies in People with Type 1 Diabetes
<p>Research to identify genes, environmental triggers, and underlying mechanisms of disease development helps scientists find targets for therapy.</p>	<p>Knowledge about molecular pathways permits identification of drugs or other interventions to act on those pathways and intervene in the disease process.</p>	<p>Before agents can be tested in patients, there are many pre-clinical steps necessary to get agents ready for clinical trials, including testing in animal models.</p>	<p>After pre-clinical development, agents are ready to be tested in human patients to see if they are effective.</p>
<p>In addition to investigator-initiated basic research studying underlying disease mechanisms, the Type 1 Diabetes Genetics Consortium is pinpointing susceptibility genes and The Environmental Determinants of Diabetes in the Young study is following newborns until they are age 15 to study environmental triggers.</p>	<p>A drug screening program is testing a panel of known compounds to determine if they have an effect in laboratory assays relevant to diabetes complications. Studies on the immune system have led to the identification of promising agents targeting the autoimmune destruction of beta cells.</p>	<p>The Type 1 Diabetes—Rapid Access to Intervention Development program promotes translation of research from the bench to the bedside by providing resources for pre-clinical development of agents. The Animal Models of Diabetic Complications Consortium is generating animal models that mimic human complications.</p>	<p>Clinical trials networks, such as Type 1 Diabetes TrialNet and the Immune Tolerance Network, are testing strategies for prevention and early treatment. As new agents are identified for potential prevention or treatment of type 1 diabetes, the standing infrastructure of these networks will be critical for testing promising agents in patients.</p>

## PURSUIT OF SIX MAJOR SCIENTIFIC GOALS

**T**he Special Statutory Funding Program for Type 1 Diabetes Research has been framed around the following six broad scientific goals. The pursuit of research toward attaining each of these goals is propelling progress toward the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. The Special Funding Program supports large-scale, collaborative research efforts that are focused on achieving the overarching goals. These efforts span a continuum from basic research to identify promising therapeutic targets and agents, to pre-clinical studies testing agents in animal models, to clinical trials in type 1 diabetes patients. In addition to these major collaborative efforts, a large portion of the positive impact of Special Funding Program-supported research comes from creative endeavors undertaken by excellent investigators working in small laboratories across the country, selected through a highly competitive, peer-review process.

### Six Overarching Goals of Type 1 Diabetes Research

- Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes
- Goal II: Prevent or Reverse Type 1 Diabetes
- Goal III: Develop Cell Replacement Therapy
- Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes
- Goal V: Prevent or Reduce the Complications of Type 1 Diabetes
- Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

#### **Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes**

A complex interplay of genetic and environmental factors underlies the development of type 1 diabetes. The identification of some key immune system genes has allowed researchers to reliably predict the risk of developing the disease. However, not all genes that play a role in type 1 diabetes are known. In addition, potential environmental triggers are thought to include viruses, dietary factors, environmental toxins, and psychological stress. To date, no single trigger has been conclusively identified. Identification of additional key genes, as well as environmental triggers, will not only help to more accurately predict who will develop the disease, but will also aid in the development of new prevention strategies and may suggest new avenues for treatment.

#### **Goal II: Prevent or Reverse Type 1 Diabetes**

Defining the molecular defects that provoke the immune system to attack and destroy the beta cells is key to predicting, diagnosing, treating, and ultimately preventing this autoimmune process. In addition, research to identify ways to halt or reverse beta cell destruction after disease onset could result in preservation or restoration of patients' insulin-producing capacity. Clinical trials have already suggested that preserving patients' remaining beta cell function can have dramatic, long-term health benefits, and clinical trials with an immunomodulatory agent have shown efficacy in preserving beta cell function in newly diagnosed type 1 diabetes patients.

#### **Goal III: Develop Cell Replacement Therapy**

A real cure for type 1 diabetes could be achieved by replacing the insulin-producing beta cells that have been destroyed by the immune system, and scientists are therefore aggressively pursuing this avenue of research. One possible approach to

replace the insulin-producing beta cells is through a procedure known as islet transplantation. To date, only adult patients with severely unmanageable blood glucose levels, or who have had a kidney transplant and are already on immunosuppressive medications, have been eligible for the procedure due to the toxicity associated with the required immunosuppressive drugs. Research is ongoing to improve upon this experimental procedure so that it may be a viable option for more patients. Furthermore, recent research has shown that many type 1 diabetes patients have some remaining functional beta cells. Therefore, research on the mechanisms controlling islet cell growth and regeneration could lead to novel therapies designed to stimulate beta cell growth *in vivo* and restore a patient's own insulin production.

#### **Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes**

Hypoglycemia (low blood sugar) is a distressing, acute complication of type 1 diabetes. It impairs brain and other bodily functions, including defenses against future hypoglycemia episodes, causing a vicious cycle of recurrent events. The immediate effects of hypoglycemia can include changes in cardiovascular and nervous system function, cognitive impairment, increased risk for unintentional injury, coma, and sometimes death. Furthermore, the potential for acute episodes of hypoglycemia is a severe limitation to the practice of intensive glucose control, which has been proven to prevent other diabetes complications. Newly-developed continuous glucose monitoring devices can reduce the time that patients spend with low blood glucose values and sound alarms to prompt them to take steps to prevent life-threatening episodes of severe hypoglycemia.

#### **Goal V: Prevent or Reduce the Complications of Type 1 Diabetes**

Persistent elevation of blood glucose can lead to life-threatening diabetes complications. Research has dramatically demonstrated that intensive control of blood glucose levels can prevent or delay the onset of complications. However, because of the limitations and difficulties of current therapies for achieving good glucose control, as well as the threat of hypoglycemia, patients rarely achieve recommended glucose levels. NIH-supported research has already led to approved drugs to slow progression of diabetic kidney disease, as well as promising therapies for diabetic eye disease. New insights into the underlying molecular mechanisms of diabetes complications and new tools such as animal models and biomarkers to facilitate testing of therapeutic strategies are imperative for the development of additional new treatments.

#### **Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes**

Research on type 1 diabetes spans a broad range of scientific disciplines, including endocrinology and metabolism; immunology; genetics; epidemiology; clinical trials; neuroscience; behavioral science; cell, developmental, and vascular biology; and the physiology of the heart, eyes, kidneys, urologic tract, and nervous system. Continued research progress depends on attracting and training a workforce of scientists with diverse expertise. In addition, the harnessing of new and emerging technologies sets the stage for innovative discoveries that can bring tremendous benefits to patients.

# PLANNING, IMPLEMENTATION, AND EVALUATION OF THE SPECIAL FUNDING PROGRAM

## Planning Process

To ensure the most scientifically productive use of the *Special Funds*, the NIDDK initiated a collaborative planning process that involves the participation of the relevant Institutes and Centers of the NIH, including the National Cancer Institute (NCI), National Center for Research Resources (NCRR), National Eye Institute (NEI), National Human Genome Research Institute (NHGRI), National Heart, Lung, and Blood Institute (NHLBI), National Institute on Aging (NIA), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of Child Health and Human Development (NICHD), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Environmental Health Sciences (NIEHS), National Institute of Mental Health (NIMH), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), National Library of Medicine (NLM), NIH Office of Dietary Supplements (ODS), and other NIH Institutes and Centers that are represented on the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC); the Centers for Disease Control and Prevention (CDC); the Health Resources and Services Administration (HRSA); the Centers for Medicare & Medicaid Services (CMS); the Agency for Healthcare Research and Quality (AHRQ); and the two major diabetes voluntary organizations: the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA).

Type 1 diabetes is an excellent model for a scientifically targeted and managerially integrated program because it is a systemic disease that is addressed by multiple NIH and HHS components. Type 1 diabetes involves the body's endocrine and metabolic functions (NIDDK) and immune system (NIAID); multi-organ complications affecting the heart and arteries (NHLBI), eyes (NEI), kidneys and urologic tract (NIDDK), nervous system (NINDS, NIMH), and oral cavity

(NIDCR); the special problems of a disease diagnosed primarily in children and adolescents (NICHD); critically important and complex genetic (NHGRI) and environmental (NIEHS) factors; and the need for novel imaging technologies (NIBIB) and specialized research resources, such as islet isolation centers (NCRR). Diabetes complications have intersected with drug development pathways in cancer research (NCI). Thus, the *Special Funding Program* has catalyzed and synergized the efforts of a wide range of NIH and HHS components to combat type 1 diabetes and its complications.

Critical to the planning process is scientific advice the NIH has garnered from type 1 diabetes researchers and the broader research community. Sources of input include a variety of scientific workshops and conferences; the advice of a group of distinguished scientists whom the NIH convened in April 2000, to consider opportunities for allocation of the *Special Funds*; the recommendations of a panel of scientific experts, who met in May 2002, to evaluate the use of the *Special Funds* and to assess opportunities for future research; and a panel of scientific and lay experts who met in January 2005, to perform a mid-course assessment of the large-scale research consortia and networks supported by the *Special Funds* and to make recommendations for future research opportunities.

## Implementation of the Special Funding Program

The *Special Funds* have been expended through a variety of mechanisms in response to recommendations of the trans-HHS planning groups and external *ad hoc* planning and evaluation panels. Large-scale research consortia and clinical trials networks have been launched to support multidisciplinary, collaborative research projects that benefit from the input of scientists with wide-ranging expertise. These consortia, as well as the research resources that they are generating, expand the scope and power of research efforts by making technological developments and tools available to broad segments of



the type 1 diabetes scientific community. Thus, they foster research that would be difficult to achieve in a timely fashion in individual laboratories. The *Special Funding Program* has complemented the efforts of the consortia by also soliciting investigator-initiated research on topics of urgent and unmet need, such as angiogenesis (new blood vessel formation) and beta cell imaging, and other issues of importance to the prevention and cure of type 1 diabetes and its complications, through announcements known as “Requests for Applications” (RFAs).

In addition to directly supporting basic and clinical research and supporting research infrastructure to facilitate other research enterprises, the *Special Funds* have also served to catalyze burgeoning fields of research by bringing together scientists from across disciplines to address specific research challenges. Furthermore, the *Program* has invested in training programs for clinical investigators to ensure a future generation of diabetes researchers. Overall, the *Special Funds* have been deployed in a scientifically focused, but flexible, budgeting process that allows a rapid response to emerging research topics of critical importance.

## Evaluation Process

The public laws providing the *Special Funds* also mandate interim and final evaluation reports on the use of the funds. Initiatives pursued with the Public Law 105-33 funds were described in a 2000 report to the Congress ([www.niddk.nih.gov/federal/initiative.htm](http://www.niddk.nih.gov/federal/initiative.htm)). An interim report that describes research progress and opportunities that resulted from the *Special Funding Program* from FY 1998 through 2003 was published in April 2003 ([www.niddk.nih.gov/federal/planning/type1\\_specialfund/](http://www.niddk.nih.gov/federal/planning/type1_specialfund/)). This final Evaluation Report describes the collaborative, trans-HHS planning process that guides the use of the funds; the progress that has been achieved to date, the expected future accomplishments of the

research programs, and resources that have been established; and emerging research opportunities that have resulted from the *Special Funding Program*.

Critical assessments of the planning and implementation processes, and of the scientific merit of the *Special Statutory Funding Program for Type 1 Diabetes Research*, have been garnered through an evaluation process involving the external diabetes research community, as well as an internal review of archival data. Evaluation metrics include:

- ▶ *Research Accomplishments*: Review of scientific advances and technological developments that have impacted patients or enabled future basic and clinical research.
- ▶ *Professional Assessment*: Scientific judgment of external experts in type 1 diabetes or related fields garnered from specific assessments of the *Special Funding Program* at meetings convened in May 2002 and January 2005.
- ▶ *Stakeholder Input*: Assessment by the *Program's* grantees of the impact of the *Special Funding Program* on their research and careers, as obtained through their responses to surveys administered by the NIH.
- ▶ *Bibliometric Analysis*: Compendium of program-associated publications in peer-reviewed scientific journals and the impact of these publications as determined by a citation analysis.
- ▶ *Grant Portfolio Analysis*: Use of NIH archival databases to determine the *Special Funding Program's* effectiveness in dimensions such as recruitment of new investigators, stimulation of clinical research, and success rate in catalyzing continued research in the field.
- ▶ *Other Metrics of Progress*: Outcome measures, such as patents, research resources, and progress toward patient recruitment goals. These data are primarily obtained from grantee surveys, annual progress reports, or meetings of External Advisory Committees (EACs).

These various assessment measures indicate that the *Special Statutory Funding Program for Type 1 Diabetes Research* has:

- ▶ Produced significant scientific advances with respect to each of the six overarching scientific goals.
- ▶ Yielded robust scientific output with at least 4,755 scientific publications. A citation analysis of 1,552 of these papers found them cited 19,220 times in other publications (prior to January 1, 2006), demonstrating that research supported by the *Special Program* is having far-reaching effects, and accelerating progress in type 1 diabetes research.
- ▶ Led to at least 25 issued patents and over 70 patent applications, many of which have enabled new lines of research or have been further developed by industry for use in medical practice.
- ▶ Attracted new investigators to pursue research on type 1 diabetes: 35 percent of grantees reported that the *Special Funding Program* provided the first independent NIH-supported research grant for which they were the principal investigator.
- ▶ Attracted numerous scientists without previous diabetes research experience to the study of type 1 diabetes: 42 percent of grantees reported that the *Special Funding Program* provided their first grant, from any funding source, related to type 1 diabetes research.
- ▶ Propelled research progress to a point where several human clinical trials are being conducted through the infrastructure created by the *Special Funding Program*.
- ▶ Established key research programs that have been successful in providing new insights into the understanding of type 1 diabetes and its complications.
- ▶ Promoted clinical research and the translation of research from bench to bedside.
- ▶ Developed innovative funding mechanisms to bring together a diverse range of researchers to tackle interdisciplinary problems.

- ▶ Balanced a research portfolio of large-scale, collaborative projects with long time horizons with flexible, short-term projects that provide a rapid response to emerging research challenges of critical importance.

While important findings have already come from research supported by the *Special Program*, it is anticipated that even greater benefits to the health and quality of life of type 1 diabetes patients will accrue in the coming years as the findings from recent, long-term investments come to fruition. Thus, the advances already achieved likely represent the vanguard of the scientific discoveries enabled by the *Special Statutory Funding Program for Type 1 Diabetes Research*.

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# ASSESSMENT OF THE SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

The *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of a unique, extraordinarily collaborative, scientifically comprehensive, and managerially sound research program. This program stands as an effective model for deploying funds that support cross-organizational initiatives of impressive scientific power and synergism. The *Special Funds* have both propelled and enabled researchers to capitalize on remarkable opportunities in diabetes research in ways not typically possible through traditional funding approaches and program-development mechanisms.

## EVALUATION OBJECTIVES

In designating special set-aside funds to “provide for research into the prevention and cure of type 1 diabetes,” the Congress recognized the opportunity to finally overcome this devastating, long-standing disease and its complications. The intent of this congressionally mandated evaluation report is not only to highlight and assess the significant progress made by the *Special Program* toward this goal, but also to describe and analyze the innovative process by which the Department of Health and Human Services (HHS) approached this challenge. The multipronged scientific structure of the *Special Program*, the establishment of large collaborative research consortia and clinical trials networks, the incentives to promote high-risk, pioneering research, and the major investments in translational research, clinical investigator training, scientific infrastructure, and technology and resource development represent a significant departure from traditional mechanisms of funding smaller-scale research in type 1 diabetes. This chapter describes the multiple evaluation approaches used to assess the scientific and clinical outcomes of the research; it also explains the decision processes used in developing the scientific emphases and allocating the resources of the *Special Program*.

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This evaluation has been guided by the following questions:

- ▶ What impact has the *Special Program* made on the field of type 1 diabetes? How has the field progressed in the past 9 years since its inception?
  - ▶ What objective measures can be used to benchmark the progress of the *Special Program*, both scientifically and programmatically?
  - ▶ To what extent has the scientific progress already benefited patients, and what additional anticipated outcomes could affect the lives of patients living with the disease or at risk of developing it?
  - ▶ How appropriate is the scientific focus of the *Special Program* and to what extent has the program been able to adapt to emerging research opportunities and recommendations from external advisors?
  - ▶ To what extent has the planning process for the *Special Program* relied on perspectives of various scientific and lay stakeholders?
  - ▶ How effectively has the *Special Program* been administered by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which was delegated this responsibility by the Secretary, HHS? To what extent do the scientific initiatives and the distribution of resources reflect a coordinated strategic plan?
  - ▶ In which ways could the research supported by the *Special Program* be enhanced?
  - ▶ How are the collaborative research consortia and clinical trial networks perceived by scientists not affiliated with these projects?
  - ▶ Which funding mechanisms have been most effective in stimulating progress?
  - ▶ To what extent has the *Special Program* stimulated high-risk, high-impact research, or diabetes research in new fields that have not previously addressed diabetes?
  - ▶ How successful has the *Special Program* been in cultivating cross-disciplinary interactions and coordination?
  - ▶ How successful has the *Special Program* been in recruiting new investigators to apply their talents to type 1 diabetes research? What impact has it had on their careers?
  - ▶ How effectively have strategies promoted clinical and translational research?
-

## Evaluation Approaches

Multiple approaches were taken to evaluate the planning and implementation processes involved in administration of the *Special Funding Program*, and the scientific accomplishments of initiatives supported by this *Program*. It must be emphasized that achievement in biomedical research is a process that reflects the progressive accumulation of knowledge; the incremental building of scientific knowledge can therefore be a long-term process. Although many promising scientific findings have begun to emerge from research initiated by the *Special Program*, the clinical impact of this program is not yet fully manifest and thus cannot yet be fully assessed.

Type 1 diabetes is a chronic disease often diagnosed in childhood, adolescence, or young adulthood, with complications sometimes appearing decades later. From the *Special Funding Program*, new insights into the biology of this disease and its therapy are continuing to develop. For example, the *Special Program* has initiated long-term prospective clinical studies, including one enrolling newborns who will be followed until they reach age 15; it has also supported infrastructure development to facilitate future research, such as the creation of animal models and the invaluable collections of genetic and tissue samples that are being stored in a repository for later analysis. Thus, many results from the evaluation approaches described in this report represent only a preliminary assessment of the advances that can be expected to flow from the *Special Program*.

The major parameters that guided the evaluation process include:

- ▶ *Research Accomplishments*: Review of scientific advances and technological developments that have had positive impacts on patients or enabled future basic and clinical research.
- ▶ *Professional Assessment*: Scientific judgment of external experts in the type 1 diabetes field garnered from specific assessments of the program at meetings convened in May 2002 and January 2005. Each individual project has ongoing assessment, but these two meetings assessed research supported by the *Special Funding Program* as a whole.
- ▶ *Stakeholder Input*: Assessment by program grantees of the impact of the *Special Program* on their research and careers, as obtained through their responses to surveys administered by the NIH.
- ▶ *Bibliometric Analysis*: Compendium of program-associated publications in peer-reviewed scientific journals and the impact of these publications as determined by a citation analysis.
- ▶ *Grant Portfolio Analysis*: Use of NIH archival databases to determine program effectiveness in terms of dimensions such as recruitment of new investigators, stimulation of clinical research, and success in catalyzing continued research in the field.
- ▶ *Other Metrics of Progress*: Outcome measures including patents, research resources (e.g., microarray chips, antibodies, genetic and tissue samples, Internet-accessible data sets, animal models), and progress toward patient recruitment goals. These data are primarily obtained from grantee surveys, annual progress reports of funded investigators, or meetings of External Advisory Committees (EACs).

### **Cut-off Dates for Data Collection**

In order to prepare this evaluation report to meet the statutory deadline, data collection on research progress was terminated on March 1, 2006. Although there have been notable scientific advances between the cut-off date and the publication of this report, the cut-off date has been maintained, and these ex-

amples have not been included to ensure that data reporting is consistent from project to project. Budget data in this chapter and in Appendix 1 are reported through the end of Fiscal Year (FY) 2005. However, the collection of references for scientific journal publications was limited to articles published prior to January 1, 2006.

## EMPLOYMENT OF AN INNOVATIVE PARADIGM FOR TRANS-HHS, CROSS-DISCIPLINARY, AND TRANSPARENT RESEARCH PLANNING AND MANAGEMENT

As designated by the Secretary, HHS, the NIDDK has coordinated the development of a sound planning, implementation, and evaluation process for the *Special Funding Program*. The allocation of funds has been performed in a scientifically competitive manner in cooperation with multiple Institutes and Centers of the NIH, the Centers for Disease Control and Prevention (CDC), and other components of HHS with expertise in type 1 diabetes. A series of planning meetings—involving these agencies, Institutes and Centers, and members of the diabetes patient-advocacy community—resulted in administrative plans for allocation of the *Special Funds*. These plans, released in 1998 and 2001, established the framework for initiatives and research priorities to be pursued. Notably, the *Special Funding Program* ties a set of HHS-wide research planning and evaluation efforts to the deployment of a specified amount of budgetary resources in a highly effective and efficient research management process.

Type 1 diabetes is an excellent model for a scientifically targeted and managerially integrated program because it is a

systemic disease that is addressed by multiple NIH and HHS components. Type 1 diabetes involves the body's endocrine and metabolic functions (NIDDK) and immune system (NIAID); multi-organ complications affecting the heart and arteries (NHLBI), eyes (NEI), kidneys and urologic tract (NIDDK), nervous system (NINDS, NIMH), and oral cavity (NIDCR); the special problems of a disease diagnosed primarily in children and adolescents (NICHD); critically important and complex genetic (NHGRI) and environmental (NIEHS) factors; and the need for novel imaging technologies (NIBIB) and specialized research resources, such as islet isolation centers (NCRR). Diabetes complications have intersected with drug development pathways in cancer research (NCI). Type 1 diabetes is also of importance to other NIH components such as NIA, NINR, NLM, and ODS, and other HHS agencies, such as the CDC, FDA, HRSA, CMS, and AHRQ. Thus, the *Special Funding Program* has catalyzed and synergized the efforts of a wide range of HHS components to combat type 1 diabetes and its complications.



## PURSUIT OF A SCIENTIFICALLY FOCUSED, BUT FLEXIBLE, BUDGETING PROCESS

**S**ix major, scientific research goals that offer exceptional promise for the treatment and prevention of type 1 diabetes form the basis of the planning and allocation processes of the Special Program. (The annual funding levels for this Program since its inception are shown in Table 1.)

### **Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes**

- ▶ Type 1 diabetes results from complex interactions of inherited genes and unknown environmental triggers. Long-term epidemiological research is required to pinpoint environmental factors for this complex disease. Large-scale collection and analysis of genetic samples are needed to identify the multiple genes involved.

### **Goal II: Prevent or Reverse Type 1 Diabetes**

- ▶ Type 1 diabetes is caused by autoimmune destruction of the pancreatic beta cells. Focused research on the immune system and well-designed clinical studies are critically important to advance understanding of the mechanism of diabetic autoimmunity and to find new means of blocking or reversing this process.

### **Goal III: Develop Cell Replacement Therapy**

- ▶ Replacement or regeneration of the pancreatic beta cells that are lost in type 1 diabetes would relieve patients of the need for insulin therapy, restore proper glucose control, and drastically reduce the risk of long-term complications. Further research on beta cell biology, immune modulation, and islet transplantation protocols could transform these highly experimental, but promising, treatments into a viable cure for type 1 diabetes patients.

### **Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes**

- ▶ Extremely low blood glucose—hypoglycemia—is a serious, acute complication of type 1 diabetes that can be life-threatening in extreme cases. It is the major factor that limits achievement of metabolic control shown to prevent complications. Research on the brain functions needed to recognize and avert hypoglycemia, and on the development of sensors to optimize the daily management of blood glucose levels, could not only significantly improve patients' quality of life, but could also improve control and avert complications.

### **Goal V: Prevent or Reduce the Complications of Type 1 Diabetes**

- ▶ Over time, the high blood glucose levels of diabetes cause extensive damage to many of the body's organ systems. The development of new therapies or behavioral interventions to treat or prevent such complications could substantially reduce the health and financial costs of type 1 diabetes. Importantly, individuals with type 2 diabetes also benefit from research on diabetic complications.

### **Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes**

- ▶ Type 1 diabetes is an extremely complex disease in terms of its origin, daily management, and clinical progression. The pace and scope of type 1 diabetes research would be greatly enhanced by recruiting researchers from a variety of scientific fields who have not yet applied their expertise to the study of diabetes, and by expanding the pool of talented researchers whose main focus is on type 1 diabetes.

**Table 1. Budget of the Special Funding Program by Goal (FY 1998-2005)±**

	1998	1999	2000	2001	2002	2003	2004	2005
Goal I	493,436	2,070,192	4,463,743	22,535,131	16,378,537	19,717,454	34,808,000	45,084,403
Goal II	9,247,235	6,211,806	5,615,924	25,888,609	21,934,292	21,631,424	19,367,709	15,176,867
Goal III	6,379,977	6,293,237	5,881,222	25,204,681	19,346,899	19,701,970	47,148,270	41,716,120
Goal IV	3,470,740	3,672,012	2,579,693	2,674,074	8,993,845	7,643,699	8,389,536	7,680,901
Goal V	10,339,294	11,725,416	11,344,751	19,435,977	21,402,845	15,017,921	16,359,078	17,748,844
Goal VI	0*	0*	0*	4,049,000	11,793,551	16,130,672	23,789,681	22,056,018
Administrative (e.g., conferences, personnel)	69,318	27,337	114,667	212,528	150,031	156,860	137,726	536,847
<b>TOTAL</b>	<b>30,000,000</b>	<b>30,000,000</b>	<b>30,000,000</b>	<b>100,000,000</b>	<b>100,000,000</b>	<b>100,000,000</b>	<b>150,000,000</b>	<b>150,000,000</b>

± Please see Appendix 1 for a detailed budget analysis.

\* Prior to FY 2001, Goal VI was addressed by solicitations for research projects that encouraged the participation of new investigators and the submission of applications for pilot and feasibility awards. These early efforts relative to Goal VI are thus embedded in other goals during the FY 1998-2000 period of the program. Starting in FY 2001, specific initiatives were launched relative to Goal VI.

The professional judgment of scientific and lay expert panels has repeatedly endorsed the structure of these goals as an appropriate and effective framework to manage the *Special Funds* (see Appendix 3). One challenge in managing large-scale science is the time required to accelerate or decelerate research programs in response to availability of funds. The dynamic interdependence of the efforts of NIH program managers and the external scientific and diabetes voluntary communities has helped the scientific priorities develop to reflect the changing needs of research.

Based on this scientific framework, a comprehensive management strategy has been used to promote maximum flexibility, to respond to new scientific opportunities, and to plan and initiate broad, multidisciplinary projects that would not have been undertaken without the *Special Funds*. The *Special Program* has included both short-term and long-term initiatives. Short-term grant supplements and pilot and feasibility grants have enabled the *Special Program* to capitalize quickly on emerging research opportunities of high priority. Longer-term research grants and consortia and research infrastructure initiatives have been pursued to initiate large-scale research projects of critical importance.

The *Special Program* has also established targeted type 1 diabetes-relevant components within initiatives that are supported in part by regularly appropriated funds. This strategy has maximized the NIH and CDC's investment in type 1 diabetes research by building upon and realizing the greatest potential benefits from existing research infrastructure and ongoing clinical trials. Moreover, several initiatives launched with the *Special Funds* have attracted investment from private foundations, industry, or other non-federal government sources with an interest in type 1 diabetes research. The total budget distribution of the *Special Program* by Goal from FY 1998 through FY 2005 is displayed in Figure 3.

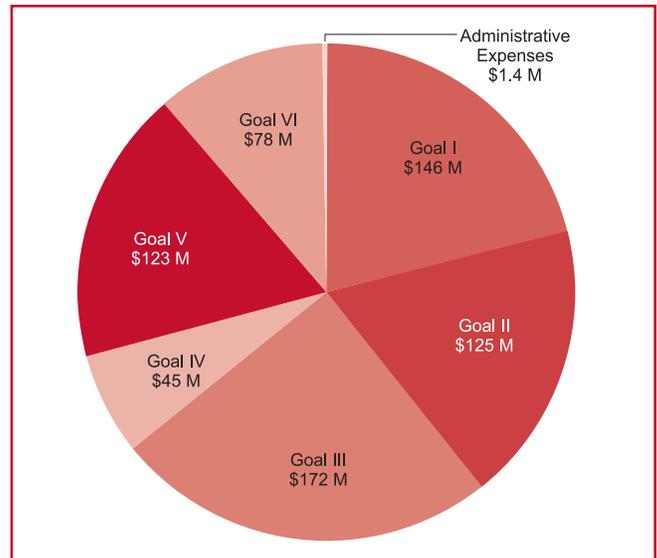


Figure 3: Total budget distribution by Goal, FY 1998-2005.

## ESTABLISHMENT OF LARGE-SCALE, COLLABORATIVE, AND INFRASTRUCTURAL INITIATIVES

In the first years (FY 1998-2000), the *Special Program* primarily supported initiatives soliciting research from independent investigators on topics of urgent and unmet need. When the *Program* was augmented in FY 2001, the additional funds enabled the creation of unique, innovative, and collaborative research consortia and clinical trials networks. The *Special Program* enabled the initiation of these high-impact research efforts at a scientifically optimal scale. The majority of the *Funds* since 2001 has supported these collaborative research efforts, with a goal of promoting progress in type 1 diabetes research that could not be achieved by a single laboratory. The distribution of funds among these different types of research mechanisms is shown in Figure 4.

The collaborative initiatives, which have become a hallmark of the *Special Program*, include genetics consortia, long-term epidemiological efforts, a beta cell biology consortium, animal models consortia, the clinical islet transplantation consortium, and clinical trials networks. Such projects are significantly different in size, scope, duration, and nature from investigator-initiated type 1 diabetes research efforts supported through the *Special Program* or regular NIH appropriations. Most NIH research takes the form of 3- to 5-year hypothesis-driven research grants, either initiated by investigators in the field or submitted in response to NIH research solicitations. Such grants and funding initiatives often involve only a single NIH

funding component and are carried out in a single, academic research laboratory. In contrast, the infrastructural and other large-scale research initiatives of the *Special Program* represent a new paradigm in that overt trans-NIH and NIH-CDC collaborations are integral and essential to their successful operation, and the involvement of multiple research groups is required.

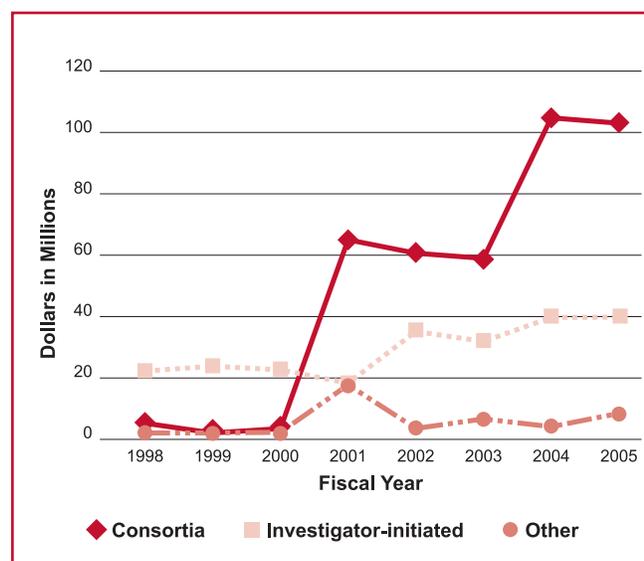


Figure 4: Distribution of funds over the course of the *Special Funding Program*. Data show the funding levels for research consortia (◆; e.g., U mechanism grants), investigator-initiated research efforts (■; e.g., R01 and R21 grants), and other efforts (●; e.g., training grants, contracts) over the course of the *Special Funding Program* from FY 1998 through FY 2005.

## IMPROVING PATIENTS' HEALTH BY PROPELLING RESEARCH PROGRESS ON THE UNDERSTANDING, PREVENTION, TREATMENT, AND CURE OF TYPE 1 DIABETES AND ITS COMPLICATIONS

**I**n the 85 years since the discovery of insulin, diabetes research and the medical treatment of diabetes patients have witnessed many “modern miracles.” Yet, scientific research is both serendipitous and incremental, a process in which advances typically accrue and build upon each other over a relatively extensive time period. In the 9 years since its inception, the Special Funding Program has accelerated this process, uniting government and privately funded medical research with medical providers and biotechnology and pharmaceutical companies to bring about many improvements in the quality of life of people with type 1 diabetes. Examples of scientific advances follow.

### **Greatly Improved Prognosis for Americans with**

**Type 1 Diabetes:** New research has provided some very good news for Americans with type 1 diabetes: incidence of certain major complications of the disease is down, and overall life expectancy is up. Scientists examined the rate of premature death and of various complications 20-30 years after diagnosis in people diagnosed in the 1950s through the 1970s. Although the scientists found that the rates of some complications, such as heart disease, have not improved significantly among people with type 1 diabetes, they found that people diagnosed more recently were nevertheless much more likely to live longer, healthier lives than those diagnosed earlier. In particular, kidney failure, diabetic nerve damage, and death are now all less likely to occur during the 20- to 30-year period following a diagnosis of type 1 diabetes than they used to be.

### **Hemoglobin A1c (HbA1c) Standardization Improves**

**Care for People with Diabetes:** The *Special Funding Program* and the CDC launched the HbA1c Standardization Program in 1998 as a key tool to enable translation of tight blood glucose control proven to reduce complications into common practice. Now, clinical test values obtained in commercial laboratories nationwide are comparable to those in the landmark clinical trial that established the value of the HbA1c measurement. The standardization effort has been a great success, and has facilitated vital, life-saving and life-improving efforts for people with diabetes.

### **New Glucose Monitoring Tools for Controlling Blood**

**Glucose Levels:** The *Special Funding Program* and the NIH supported the development of recently approved continuous glucose monitors, which reveal the dynamic changes in blood glucose levels. Alarms warn the patient if blood glucose becomes too high or too low, thereby reducing the need for invasive finger sticks to monitor blood glucose levels. This revolutionary technology can make it easier for patients to keep blood glucose at healthy levels and can enhance their ability to achieve the tight control necessary to prevent disease complications.

### **Long-Term Benefit of Near-Term Blood Glucose**

**Control:** The *Special Funding Program* enhanced the long-term continuation of the follow-on to the landmark Diabetes Control and Complications Trial (DCCT), called the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Surprisingly, the former intensively-treated group continued to have long-term benefits compared to those in the control group, despite similar HbA1c levels during EDIC—an effect termed “metabolic memory.” Thus, physicians and patients now know that it is particularly valuable to intensively control blood glucose levels early in the course of disease. Importantly, EDIC has also now shown that close control lowers the risk of heart disease and stroke by about 50 percent in people with type 1 diabetes.

**Novel Drugs for Treating Complications:** Elucidation of molecular pathways by which increased blood glucose damages tissues has resulted in the development of novel drugs

to treat diabetes complications. For example, NIH-supported scientists developed a therapeutic agent that inhibits a protein called protein kinase C beta (PKC beta), which is being tested as a treatment for diabetic eye disease. Other examples of promising therapeutic agents for diabetic eye disease being developed with support from the *Special Funding Program* are drugs that inhibit excessive angiogenesis (new blood vessel growth) in the eye.

**Advances in Islet Transplantation as a Therapeutic Approach for Type 1 Diabetes Patients:** The *Special Program* supported the first islet transplantation trial in the United States using a procedure referred to as the “Edmonton protocol.” Through the Immune Tolerance Network (ITN), the *Special Program* also supported the first international, multicenter trial of islet transplantation using the protocol. These studies have confirmed and extended the demonstration that islet transplantation may become an alternative to whole pancreas transplantation for treatment of type 1 diabetes. The *Special Funding Program* is supporting multifaceted research efforts to overcome barriers to making islet transplantation a viable therapy, such as the shortage of available islets and the toxicity associated with the lifelong immunosuppressive medication.

### **Setting the Stage for Testing Novel Type 1 Diabetes**

**Prevention Strategies:** Research supported by the *Special Funding Program* has enabled testing of new type 1 diabetes prevention strategies and demonstrated that it is possible to predict with great accuracy the risk of developing type 1 diabetes. Moreover, while an oral insulin type 1 diabetes prevention trial (now part of Type 1 Diabetes TrialNet [TrialNet]) did not demonstrate protection in the entire study population, it suggested a possible effect in the subgroup with highest antibody titers. This knowledge has set the stage for screening and enrolling patients into new type 1 diabetes prevention trials.

To stimulate continued progress in type 1 diabetes research over the next several years, the *Special Program* has invested in a range of activities from basic research into the cellular and molecular mechanisms causing type 1 diabetes and its complications, to genetic and epidemiological studies that may inform preventing or reversing the disease, to translational and clinical research that is leading to new therapies. The *Special Program* investments in type 1 diabetes research resources will pay dividends in future years as ongoing efforts come to fruition and by facilitating new avenues of research; likewise, the training of clinical investigators will ensure a competent pool of talent to conduct that research.

## SCIENTIFIC PRODUCTIVITY

### Bibliometric Analysis

#### Compendium of *Special Funding Program-Supported Scientific Publications*

Perhaps the most accepted metric for assessing scientific productivity is to look at peer-reviewed publications in scientific and medical journals. Peer-reviewed publication is the forum in which scientists report their discoveries and propound new ideas, and it is one means by which productivity is measured for NIH grant applications, faculty appointments, and tenure decisions. The NIDDK therefore searched for scientific publications associated with grants funded through the *Special Program*, identifying 4,755 articles published from January 1, 1998, and prior to January 1, 2006. However, the final collection of papers analyzed in this evaluation report is almost certainly an under-representation of the actual publication output, because it is impossible to capture all published papers that do not give attribution to the grants that supported the research.

For purposes of the bibliometric analysis, these papers were divided into two pools.

- ▶ *Pool A-1,552 Publications:* Generally speaking, the publications in Pool A are from grants awarded through initiatives, clinical trials, or research consortia made possible through the *Special Funding Program*. With few exceptions, these grants are new since the inception of the Program.
- ▶ *Pool B-3,203 Publications:* The publications in Pool B typically cite pre-existing grants that were augmented through the *Special Funding Program*. Many of the Pool B grants augmented existing research project grants or Diabetes Research Centers grants at academic institutions, allowing innovative pilot projects or development of resources relevant to type 1 diabetes.

Because it was not possible to determine which of the papers in Pool B were made possible by the additional funding, and which were more related to the prior award, more detailed analyses were restricted to the publications in Pool A.

The publications, and a complete definition of Pools A and B, can be found at: [www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm](http://www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm)

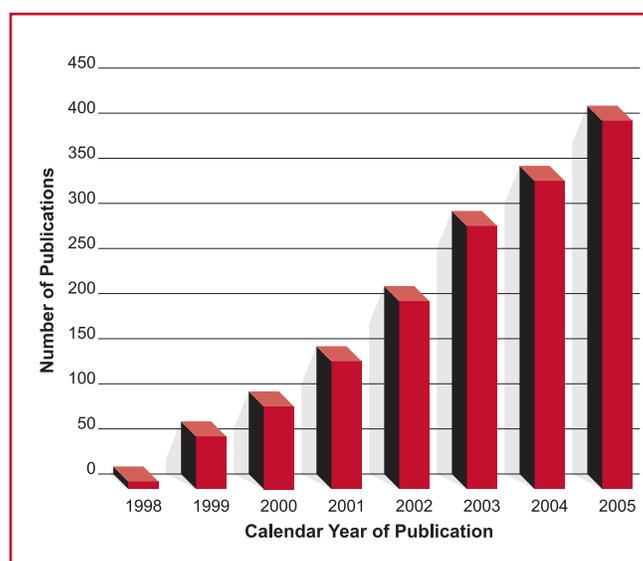


Figure 5: Scientific publications in Pool A supported by the *Special Funds*. This graph represents the number of papers in Pool A published each calendar year. Data only include the identified 1,552 papers published before January 1, 2006, produced from *Special Program* funding.

**Table 2. Citation Analysis for Pool A Scientific Papers**

Year	Total Papers	Papers with Available Citation Data	Maximum Citations	Mean Citations	Median Citations	Total Citations
1998	10	10	227	73	52	730
1999	65	64	157	31	20	1,986
2000	91	84	247	33	20	2,780
2001	144	138	177	24	17	3,329
2002	215	209	355	21	12	4,367
2003	283	270	137	13	9	3,524
2004	334	321	109	6	4	2,082
2005	410	382	22	1	0	422
<b>1998-2005 Total</b>	<b>1,552</b>	<b>1,478</b>	<b>355</b>	<b>13</b>	<b>5</b>	<b>19,220</b>

**Citation Analysis for Pool A Scientific Papers**

The 1,552 papers in Pool A were analyzed to evaluate their impact on the scientific community (Table 2, Figure 5, Figure 6, and Figure 7). One of the most objective methods for assessing the scientific impact of a publication is to analyze how frequently the work has been cited in other scientific publications. Citation data were collected with Internet-based databases; for methodology, please see Appendix 5. The data for each paper are reported in the compendium of publications at the website listed previously. A higher number of citations may indicate that the paper has had a particularly large influence on subsequent work in the field, introducing a new experimental technique, for example. However, it takes time to design and carry out new experiments, so there is typically a lag time of 3 to 5 years after a paper is published before most citations of it appear in the scientific literature. Therefore, papers published in more recent years will likely generate many more citations in the future than are reported here.

Citation data are available for 1,478 of the Pool A research publications (Table 2, column 3). In general, citation data are

missing for the remaining 74 papers because the publications' journals are not listed in the commercial citation database. These 74 references include 22 papers published in the journal *Diabetes Technology and Therapeutics*. It is important to note that a large proportion of articles published on glucose monitors, technology pertaining to the development of an artificial pancreas, and related topics, were published in this journal, including the results of some important clinical trials. Thus, it is not possible to apply the citation analysis method of impact assessment to this area of *Special Funds*-supported research.

Among the 1,478 papers for which citation data are available, the number of citations prior to January 1, 2006, ranged from 0 to 355, with an average (mean) of 13 and a median of 5. As expected, the average number of citations per paper is dramatically higher for the papers published early in the *Program* than for those published later (Figure 6). Also, as expected, the publication output of papers per year has increased annually, as the *Program* has matured (Table 2, Figure 5).



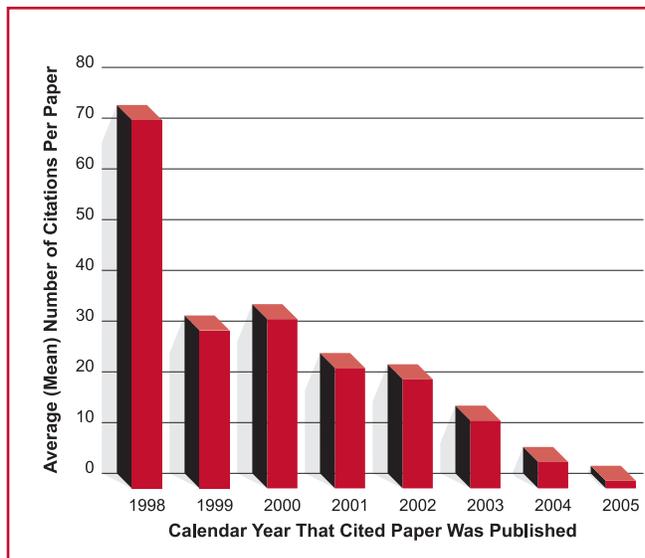


Figure 6: Average number of times Pool A *Special Funds*-supported papers were cited in other scientific publications. Mean citations are grouped by the calendar year during which the cited papers were published. The cited papers are the subset of 1,478 papers in Pool A for which citation data are available. Citations appearing in papers published on January 1, 2006, or later were not included in this analysis. Because there is typically a lag time of 3-5 years after a paper is published before most citation data of it appear in a scientific journal, the average number of citations is lower in more recently published papers.

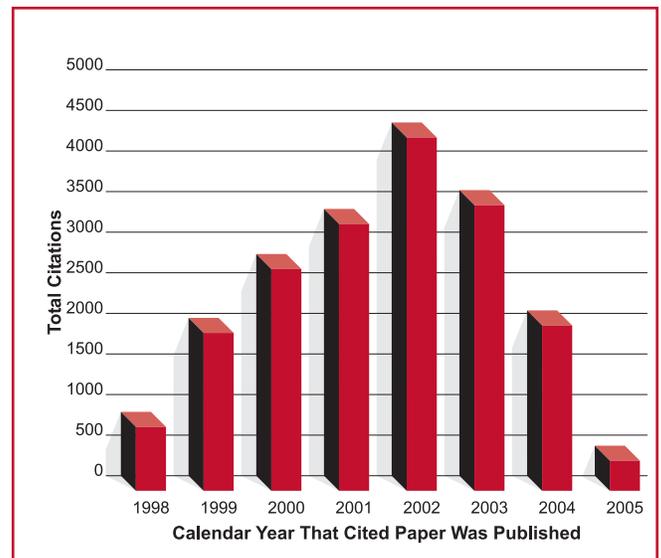


Figure 7: Total citations of Pool A *Special Funds*-supported research publications. Citations are grouped by the calendar year during which the cited papers were published. The cited papers are the subset of 1,478 Pool A papers for which citation data are available. Citations appearing in papers published on January 1, 2006, or later were not included in this analysis.

## Survey of Independent Investigators

To augment the bibliometric analysis and to provide a more complete understanding of the progress from investigator-initiated research projects, the NIDDK conducted an Office of Management and Budget-approved survey. The survey was distributed to researchers who received NIH grants supported by the *Special Funds*, but which were not associated with one of the research consortia or clinical trial networks. Of 334 surveys distributed to grantees, the NIDDK received 274 complete responses (82 percent response rate) from 239 unique investigators (some investigators had more than one grant). Investigators were asked to assess the impact of *Special Program* on their research and careers and also to provide evidence of patent applications, scientific publications, research resources produced and distributed, funding history, and

follow-up funding applications. These data were incorporated into the following sections of this chapter and in the sections on “Evaluation of Investigator-Initiated Research” in the chapters for each scientific goal. For the survey instrument, methodology, and further details on the survey, please refer to Appendix 5.

## Patents and Technology Transfer Agreements

Patents and patent applications represent an objective metric of productivity. Investigators responding to the survey were asked to report patents filed with the U.S. Patent and Trademark Office (USPTO). The issued patents were verified from the searchable database on the USPTO website. Investigators reported 25 U.S. patents that derived from research supported

by the *Special Program*. Issued patents are listed in Appendix 5. Additionally, grantees reported 39 patents that had been filed with the USPTO, but had not yet been issued. A provisional patent is a 1-year intellectual property protection, often used as a preliminary step before filing a non-provisional patent. Survey respondents reported eight provisional patents that had been allowed by the USPTO. In some cases, the technology was patented by the academic institution and licensed to the private sector for further development. In other cases, grantees described technology transfer agreements in which the private sector filed the patents. The breakdown for the total of 72 filed patents is summarized in Table 3.

**Table 3. U.S. Patents\***

Patents issued	25
Patents filed but not yet issued	39
Provisional Patents	8
<b>Total Patents Filed</b>	<b>72</b>

\*Patents reported by investigators in grantee survey. Table does not include patents derived from research supported in consortia, networks, centers, training programs, grants to small businesses, and supplements to ongoing research grants.

## Research Resources

Research resources are research tools, technologies, biological samples, or other scientific materials that are produced or collected to enable scientific experimentation. A focus of the *Special Program* has been to promote development of resources that can be used by the broad scientific community. Therefore, the resources are not only benefiting researchers funded by the *Program*, but the entire type 1 diabetes research enterprise. Fifteen percent of the grants to individual investigators covered in the investigator survey used resources provided by the consortia and networks (41/274 unique grants to 239 investigators). The NIDDK maintains a website ([www.T1Diabetes.nih.gov](http://www.T1Diabetes.nih.gov)) that lists resources that can be shared or purchased at low cost. Additionally, the website provides data and protocols from several of the consortia and

networks. A large majority (81 percent; 77/95) of investigators who were aware of the type 1 diabetes website reported that they found it useful.

Examples of research resources developed by the consortia supported by the *Special Program* include:

- ▶ Animal models
- ▶ Antibodies
- ▶ Assays
- ▶ Data sets
- ▶ DNA sequencing support
- ▶ Human pancreatic islets
- ▶ Microarrays
- ▶ Pre-clinical development of therapeutic agents
- ▶ Samples from clinical research networks (e.g., blood cells, serum, plasma, genetic samples)

Examples of research resources developed by individual investigators, as reported in the survey of *Special Program* grant recipients include:

- ▶ Animal models and new strains of mice
- ▶ Antibodies
- ▶ Assays and reagents for diagnostic tests
- ▶ Bioinformatics databases and resources on the Internet
- ▶ Cell lines
- ▶ Computer-based algorithms to: model blood glucose values; predict genetic risks for developing type 1 diabetes or its complications; and enhance imaging technologies
- ▶ Imaging technology resources
- ▶ Immune monitoring core to analyze cell signaling pathways
- ▶ Glucose sensors
- ▶ Microarrays
- ▶ Tools for genetic engineering and gene therapy (e.g., DNA constructs and vectors)

## PROMOTION OF DIVERSE, INNOVATIVE, AND PATIENT-ORIENTED RESEARCH ON TYPE 1 DIABETES

### Diverse Research Portfolio

Research proposals for support by the *Special Program* are received through a variety of mechanisms, including Requests for Applications (RFAs) for grant and cooperative agreement awards, and requests for administrative supplements for pilot or ancillary studies related to ongoing projects. From FY 1998 through FY 2005, a total of 58 RFAs were issued for the support of focused research of critical importance to the prevention and cure of type 1 diabetes and its complications. RFAs solicit research on a specific scientific topic of high relevance to program goals; they are used to solicit investigator-initiated research, or in some cases to attract applications for participation in a consortium. Solicitations for investigator-initiated research projects asked for creative approaches to solve particularly difficult problems. These solicitations encouraged high-risk, discovery research to overcome obstacles to research progress. Additionally, the *Special Program* provided full or partial support for projects associated with 2 Requests for Proposals (RFPs), 1 Notice, and 20 other initiatives and consortia (see Appendix 1 for a complete list of funding announcements and initiatives). A breakdown of activity in terms of the *Special Program's* funding mechanisms is provided in Table 4.

The *Special Program* funded 534 grants and supplements and 24 contracts through the NIH. Individual investigators predominantly received short-term or long-term research project grants. In some cases, the *Special Program* funded 1-year supplements to ongoing NIH grants for ancillary research. Research consortia and networks were funded either through cooperative agreement mechanisms, which allow NIH program officials to have significant involvement with the external scientists in the framing and achievement of a specified research goal, or with contracts or project grants (R01). The *Special Funds* established resource centers or provided supplements to established research centers to augment their type 1 diabetes research investments. These centers included animal model facilities, non-human primate centers, general clinical research centers, specialized centers, and centers that provided certain resources, such as islets for transplantation or basic research. The *Special Funding Program* also supported nine grants to small businesses—Small Business Innovation Research grants (SBIR) and Small Business Technology Transfer Research grants (STTR)—to promote the development of innovative technologies such as sensors for continuous glucose monitors. Contracts were used for services such

**Table 4. *Special Program* Funding Mechanisms (FY 1998-2005)**

Activity for NIH-supported projects	New Awards	Supplements	Grants + Supplements
Research Project Grants (R01, R21, R24, R29, R33, R37)	354	19	373
Small Business Grants (STTR: R41; SBIR: R43, R44)	9	0	9
Research Programs and Centers (P01, P30, P40, P50, P51, P60, M01)	3	45	48
Cooperative Agreements (U01, U10, U19, U24, U42)	84	6	90
Training Awards (Career: K12, Institutional: T32)	14	0	14
Contracts	23	1	24
<b>Total NIH projects</b>	<b>487</b>	<b>71</b>	<b>558</b>

as coordinating trial networks, maintaining genetic and tissue sample repositories, supporting bioinformatics integration, coordinating patient recruitment for clinical trials, and DNA sequencing. Other programs, such as a major epidemiological study, and efforts to standardize techniques to measure diagnostic biomarkers, are supported by the CDC using the *Special Funds*.

### Innovative and Exploratory Research

The *Special Funding Program* has promoted innovative, cutting-edge research that has the potential to quickly advance the field. The pilot and feasibility grant mechanism, known as an R21 grant, is one means of achieving this goal. In addition to supporting innovative, high-risk/high-impact investigations, R21 grants, which are typically 2-3 years in duration, have helped to ensure budget flexibility in the later years of the *Special Funding Program*. This short-term funding mechanism has helped to free up funds for reallocation as scientific opportunities have emerged. This flexibility allows the program to quickly respond to changes in science, while providing sufficient seed money for investigators to gather data for a full grant application if their hypotheses prove worthy of further pursuit. On the continuum of funding mechanisms, R01 research grants are often based on stronger preliminary evidence and, thus, are considered to be of lower risk and may have a longer funding period, typically 4-5 years. These mechanisms are complementary, and pilot and feasibility grants can often gain the necessary preliminary data to facilitate a successful R01 grant application to the NIH, or funding by a non-profit group or other research organization.

As shown in data on new research grants displayed in Table 5, from FY 1998 through FY 2005, slightly more new R21 grants than R01 grants were awarded through the RFAs issued under the *Special Funding Program*. This level of R21 grant support differs markedly from the NIH-wide pattern; the *Special Funding Program* awarded a much higher percentage of R21 grants in relationship to R01 grants than did NIH as a whole during the same time period. In addition, nearly 92 percent of the responses to the investigator survey (252/274 unique grants to 239 investigators) indicated that these grants supported innovative or high-risk research that the investigators would not otherwise have been able to pursue.

**Table 5. New Research Grants (FY 1998-2005): R01 and R21\***

	R21	R01	Total R21+R01	Percent R21
<b><i>Special Funding Program</i></b>	182	162	344	53 %
<b>NIH-Wide Grant Funding</b>	7,187	32,865	40,052	18 %

\*Totals do not include grant supplements. Source: NIH Office of Extramural Research: [http://grants1.nih.gov/grants/award/success/Success\\_ByActivity.cfm](http://grants1.nih.gov/grants/award/success/Success_ByActivity.cfm)

### NIH Involvement in Research Programs Supported by the *Special Funds*

As noted previously, cooperative agreements (or U mechanism awards) are those in which the NIH is significantly involved with the external scientists in the framing and achievements of the research program. As shown in Table 6, *Special Funding Program* support for cooperative agreements differs markedly from the NIH-wide pattern; the *Special Funding Program* funded a significantly higher percentage of U awards in relationship to R awards than did NIH as a whole during the same time period. This data demonstrates that the *Special Funds* have been deployed so that NIH and the research community work in partnership to develop the research programs and ensure that progress is being made.

**Table 6. New Research Grants (FY 1998-2005): U and R Mechanisms\***

	U Mechanism	R Mechanism	Total U+R	Percent U Mechanism
<b>Special Funding Program</b>	84	363	447	18.8 %
<b>NIH-wide Grant Funding</b>	1,650	47,412	49,062	3.4 %

\*Totals do not include supplements. Source: NIH Office of Extramural Research: [http://grants1.nih.gov/grants/award/success/Success\\_ByActivity.cfm](http://grants1.nih.gov/grants/award/success/Success_ByActivity.cfm)

### Clinical and Translational Research

In addition to encouraging innovative research studies, the *Special Funding Program* has a clear focus on clinically relevant research that can improve the health and well-being of individuals with type 1 diabetes or at risk for developing the disease. This focus is consistent with the statutory language establishing the *Special Program*. The clinical research portfolio (FY 1998-2005) was evaluated by searching the NIH database of funded grants and grant applications for research projects that were coded for human subject research (excluding research coded for human subject research, but that only involved human tissue samples). Of the 439 grants included in the analysis (R and U mechanisms), 162 were categorized as clinical research (37 percent). (For methodology, see Appendix 5). By comparison, 33.7 percent of grants supported by the NIH matched this definition of clinical research (29,688 of 88,097 competing grants using R or U funding mechanisms). Furthermore, 14 of the grants supported by the *Special Funds* involved Phase III clinical trials, the final stage required before a therapy can be approved by the FDA. In each year, between 25 and 55 percent of the new projects had clinical components (Figure 8). The clinical research portfolio was greatly augmented when Congress expanded the *Special Funds* in 2001, enabling the initiation of the clinical trials networks and consortia.

Of the 27 consortia described in this evaluation report, 16 have a clinical focus (59 percent) and an additional 7 support projects to translate basic research into clinical research. Although research project grants tend to have a more basic science focus than the research consortia and clinical trial networks, nearly 42 percent of responses to the grantee survey (116/274 unique grants to 239 investigators) reported that the research required approval from an Institutional Review Board (IRB) that is necessary for research on human subjects, and 78 percent (214/274 grants) described the research as clinically relevant. In addition, 9.5 percent of grants (26/274) used large animals (e.g., pigs, non-human primates), which is often indicative of pre-clinical research.

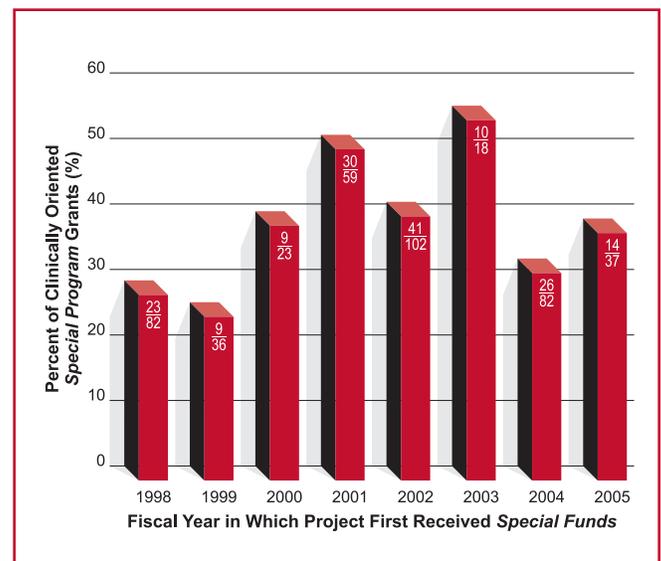


Figure 8: Percent of clinically-oriented grants (R and U mechanisms) supported by the *Special Funding Program* each Fiscal Year. Each bar shows the number of new clinically-oriented grants over the total number of new grants.

The *Special Funding Program* has also engendered significant research that translates basic discoveries to the clinical setting. An innovative series of initiatives initially launched in 2002 promoted “bench to bedside” research in which cutting-edge scientific proposals were given 2 years of exploratory funding for pre-clinical research that could be converted to a longer-term clinical grant if the research proved to be promising and certain benchmarks were achieved. Of the eight projects eligible to convert before March 1, 2006, five were translated into clinical research grants (63 percent). In addition, animal models consortia—such as a consortium that evaluates the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of islet, kidney, heart, and

lung transplantation—expedite the translation of promising therapies into clinical research. To facilitate the pipeline of drug development, the *Special Funding Program* also worked with the NCI to provide a resource for translational research: Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID). The T1D-RAID program provides resources for the manufacture and pre-clinical development of drugs, natural products, and biologics that will be tested in type 1 diabetes clinical trials. The *Special Funding Program* has supported a research continuum from basic to pre-clinical to clinical research, in which promising new therapeutic agents are being identified in the laboratory and subsequently tested in patients.

#### **Key Features of Research Supported by the *Special Statutory Funding Program for Type 1 Diabetes Research***

- Enabled the establishment of large-scale, collaborative research consortia and networks at a scientifically optimal scale of operation.
- R21 and R01 projects supported by the *Special Funds* responded to targeted solicitations to tackle difficult problems and overcome obstacles to research progress.
- Greater percentage of exploratory research (R21) grants and cooperative agreement (U mechanism) grants were supported by *Special Funds* compared to NIH as a whole.
- Innovative funding mechanisms fostered interdisciplinary collaborations and scientific partnerships.
- *Special Funding Program* initiatives attracted investigators who had not previously received NIH funding, as well as scientists who were new to diabetes research.
- Focused on the creation of resources for use by the scientific research community.

## RECRUITMENT AND SUPPORT OF DIABETES RESEARCHERS

**A** high priority of the Special Program is the recruitment and retention of new investigators into diabetes-related research. Understanding the underlying causes of type 1 diabetes and finding new ways to prevent and cure this disease requires the concerted efforts of many investigators with diverse expertise. Relevant fields of scientific inquiry that can contribute to diabetes research include genetics, epidemiology, bioinformatics, genomics and proteomics, immunology, pathogen discovery, cell biology, bioengineering, transplantation surgery, neuroscience, cardiology, nephrology, ophthalmology, radiology, and others.

### New Investigators

The *Special Funding Program* has used several mechanisms to attract new talent to type 1 diabetes research. Institutional clinical investigator training and career development programs for pediatric endocrinologists were established at seven medical institutions. As noted previously, pilot and feasibility grants give new researchers the opportunity to test novel hypotheses that have conceptual promise. This type of award is also useful for established investigators who want to explore a new application or direction for their research. In addition, new research talent has been recruited through initiatives that pair established diabetes investigators with other scientists who can bring a new perspective or technology to the field. These mechanisms can be a magnet for drawing to diabetes research bright, capable investigators with creative research ideas to undertake innovative studies. Through these mechanisms, the *Special Funding Program* attracted investigators who had not previously received NIH funding, as well as scientists who were new to diabetes research.

From FY 1999 through FY 2005, the *Special Program* awarded 258 new research project grants (R01 and R21; this total does not include supplements to ongoing R01 grants). NIH application database records indicated that 61 (24 percent) of these were grants to new NIH investigators. These data are comparable with NIH-wide data for grant applications from new investigators (25 percent) using data from the same NIH database (for methodology, please see Appendix 5). The distribution of grants to new investigators by the *Special Funding Program* each year is summarized in Figure 9. Because of the limitations in available grant application-based data in archival databases, the number of new investigators reported here is likely an under-representation. In fact, a parallel analysis of the NIH-wide portfolio using investigator-based data indicates that an average of 36 percent\* of NIH grants went to new investigators during a comparable time period. These data are consistent with the responses to the survey in which 83 of the 239 unique investigators (35 percent) indicated that the *Special Funding Program* provided the first independent NIH-supported research grant for which they were the Principal Investigator (PI). Thus, the *Special Funding Program* is extending NIH's efforts to invest in human research capital by attracting and supporting new investigators.

\* Of 34,663 competing R01 and R21 grants awarded between FY 1998 and 2004, 12,442 were awarded to new investigators (source data: NIH Office of Extramural Research, [http://grants.nih.gov/grants/new\\_investigators/New\\_Invest\\_by\\_Activity.xls](http://grants.nih.gov/grants/new_investigators/New_Invest_by_Activity.xls) and [http://grants1.nih.gov/grants/award/success/Success\\_ByActivity.cfm](http://grants1.nih.gov/grants/award/success/Success_ByActivity.cfm)).

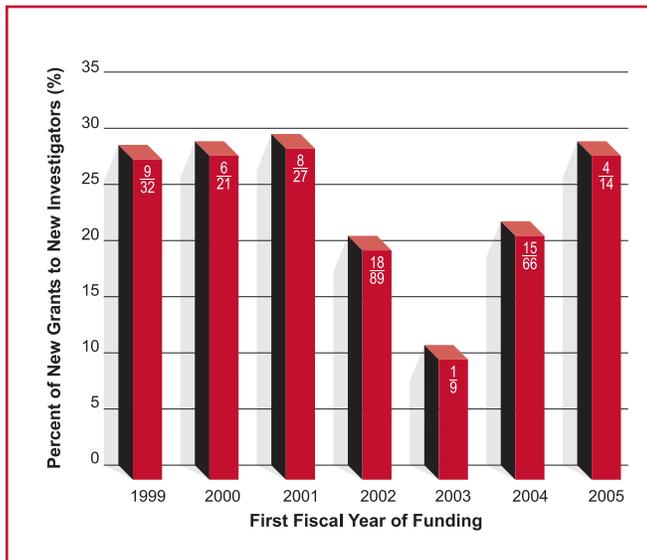


Figure 9: Recruitment of new investigators. Data on *Special Program*-funded investigators collected from NIH grant application database (IMPAC II). NIH grant applications collecting data on new investigators were phased in starting in 1999, so data are not available for 1998 and may be disproportionately lower for 1999.

In addition to attracting new investigators to diabetes research, the *Special Funding Program* sought to attract established investigators who had not previously worked on diabetes. Survey data revealed that the *Special Funding Program* provided their first grant, from any funding source, related to type 1 diabetes research for 100 of 239 unique investigators (42 percent). Of these 100 “new-to-diabetes” respondents, 78 investigators also indicated that they have continued to pursue diabetes research. Thus, the *Special Program* has been highly successful at bringing new scientific talent to bear on research issues in type 1 diabetes. Without this *Program*, it is highly unlikely that these investigators would have ventured into the type 1 diabetes research field or explored new research concepts for the future benefit of patients. Support for the recruitment of new talent to type 1 diabetes research under the *Special Funding Program* is summarized in Table 7.

**Table 7. Recruitment of New Talent to Type 1 Diabetes Research**

<i>Special Program Stimulated:</i>	Source	Fraction	Percent
Investigators receiving first NIH grant	NIH database FY 1999-2005	61/258*	24 %
Investigators receiving first NIH grant	Grantee survey	83/239†	35 %
Investigators receiving first diabetes-related grant	Grantee survey	100/239†	42 %
Subset of investigators who received first diabetes-related grant and then continued in the field	Grantee survey	78/100	78 %
Newly recruited diabetes researchers (fraction of <i>Program</i> grantees who had not previously received any diabetes grant prior to the <i>Program</i> but subsequently continued in diabetes field)	Grantee survey	78/239†	33 %

\*258 investigators were analyzed using the NIH database, which may underestimate new investigator status (see text).

†239 unique investigators responded to the survey representing 274 grants.



## Continuation of NIH Research Funding

One goal of the *Special Funding Program* is to stimulate new lines of successful scientific research in the field of type 1 diabetes. Successful research efforts are often competitively renewed, and R01 research grants continuing along the same line of inquiry will retain the same grant number once they are competitively renewed. From 100 R01 grants initially awarded with *Special Funds* with a project end date before September 30, 2005, there were 54 applications to the NIH for continuation of support with regular NIH funds via recompetition through the peer-review system (Table 8) as of July 2006. Of these, 26 renewal applications had been awarded and funding decisions had not been made for four additional applications (see methodology, Appendix 5). The success rate for continuation of support (48 percent) is slightly higher than the average NIH continuation rate for the funding of competing renewal applications, which was 45.7 percent for FY 2000-2005.\* Moreover, those applications included renewals of long-term projects that had successfully competed in previous renewal applications. Four of the *Special Funding Program*

grants have been successfully renewed twice. Data on continuation of grant activity under the *Special Funding Program* are summarized in Table 8.

Importantly, 59 percent of survey responses (93/158 unique grants that had ended by the time of the survey) reported continued funding for the same line of research. Several additional researchers whose grants were ongoing at the time of the survey had already secured continued support for their research efforts. Some investigators cited NIH support by means other than recompetition of the original grant (e.g., through participation in TrialNet or other research consortia). In addition, several researchers obtained continued funding from non-NIH sources, including: the ADA, American Heart Association, Canadian Diabetes Association, Canadian Institutes of Health Research, Department of Defense, Department of Veterans Affairs, Dutch Diabetes Research Foundation, Endocrine Society, CDC, European Union, Heart and Stroke Foundation (Canada), JDRF, March of Dimes, Michigan Life Science Corridor Funding, National Health and Medical Research Council (Australia), National Institute of Standards and Technology, and the New York State Department of Health. At the time of the survey, additional respondents reported being in the midst of preparing or having recently submitted grants for continued research funding. Together, these data indicate that the *Special Funding Program* has enabled the establishment of a viable research enterprise that continues to make progress toward realizing the scientific goals of the program. Moreover, the research funded by this *Program* has garnered support from a broad array of research funding agencies.

**Table 8. Resubmission Rate of R01 Grants Funded by the *Special Funding Program* Compared to NIH-wide Data (FY 2000-2005)**

R01 <i>Special Funds</i> Grants Eligible for Resubmission	100
Applications Reviewed	54
Applications Pending Funding Decisions	4
Competing Continuations Awarded	26 (48 %)
R01 <i>Special</i> Grants Renewed Twice	4
Survey Responses Indicating Continued Funding in Same Line of Research <sup>†</sup>	59 %
NIH Competing Renewals Awarded	45.7 %

<sup>†</sup>Only grants that had ended by the time of the survey were included in this analysis.

\*The NIH received 32,879 competing R01 applications for continued grant support for FY 2000-2005. Applications that have one or more amendments in the same fiscal year are only counted once (source data: NIH Office of Extramural Research, [http://grants1.nih.gov/grants/award/success/Success\\_ByActivity.cfm](http://grants1.nih.gov/grants/award/success/Success_ByActivity.cfm)).

## BROADLY CONSULTATIVE PLANNING PROCESS FOR PRIORITY SETTING AND RESOURCE DISTRIBUTION

**T**he input of the diabetes research and voluntary communities in all aspects of planning, implementing, and evaluating the use of the Special Funding Program has been critical to its success. Leading scientific and lay experts with expertise relevant to type 1 diabetes and its complications have participated in the priority-setting process for framing special type 1 diabetes research initiatives, helped to evaluate the accomplishments of the program, and identified new opportunities for future research that have emerged from the Special Funding Program.

### Advisory Meetings

#### State-of-the-Science, 1997

In 1997, a trans-NIH conference entitled “Diabetes Mellitus: Challenges and Opportunities” met to discuss the state of research on diabetes and its complications. Symposium participants recommended that diabetes research be intensified in order to close research gaps, take advantage of new technologies, and capitalize on highly promising research leads and advances. The specific conclusions of this group were a critical source of input when the *Special Funding Program* was launched the next year. Moreover, the chairs of four relevant subpanels from the symposium reconvened in 1998 to advise the NIH on the initial deployment of the funds under this *Program*.

Three additional *ad hoc* panels of external scientific experts (described below) have provided input on the implementation of the *Special Funding Program*. Executive summaries from these meetings have been reproduced in Appendix 3.

#### Planning New Initiatives, 2000

In April 2000, scientific advisors helped to prioritize proposed research initiatives for the deployment of a portion of the *Special Funds* that became available after completion of short-term projects launched in FY 1998 and 1999. The deliberations of this group were especially valuable for rapidly identifying high-priority initiatives when the *Special Funding Program* was expanded in duration and funding level in FY 2001.

#### Implementation and Prioritization, 2002

A similar panel of advisors met in May 2002 to review the use of the *Special Funds* at that time and to identify new research objectives and opportunities that arose from the expansion of research efforts on type 1 diabetes through the *Special Funding Program*. The recommendations of this panel constitute a significant guide to the NIH’s ongoing research efforts on type 1 diabetes.

#### Mid-Course Assessment, 2005

In January 2005, a third panel was convened for a 2-day meeting for a mid-course program assessment. The focus of the meeting was to evaluate the progress of 25 major research consortia, trial networks, and infrastructure-development initiatives. The panel also reviewed innovative research ideas proposed by the larger research community and discussed other emerging opportunities for research in type 1 diabetes that were enabled by the *Special Funding Program*. The panel’s specific recommendations for each Consortium are included in the relevant sections within the chapters of this report that address each scientific Goal.

#### 1999 Diabetes Research Working Group Strategic Plan

In 1999, the independent, congressionally established Diabetes Research Working Group (DRWG) issued its strategic research plan for conquering diabetes, including both type 1 and type 2 diabetes. This panel of scientific experts engaged in a year-long, in-depth process to gather input from the diabetes research and voluntary communities. The DRWG’s recommendations of relevance to type 1 diabetes have informed the

planning and implementation of the *Special Funding Program*. These areas of DRWG emphasis include research opportunities identified in the areas of genetics; autoimmunity and the beta cell; clinical research and clinical trials; diabetic complications; special populations, including children; and resource needs.

### **2006 Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan**

Responding to a recommendation from the January 2005 *ad hoc* mid-course assessment of the *Special Funding Program*, the Director, NIDDK, launched the development of a strategic plan for type 1 diabetes research under the auspices of the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC). The 18-month planning process involved creating five scientifically focused working groups to evaluate the state-of-the-science and to propose research objectives for type 1 diabetes research for the next 10 years. Each working group was composed of external scientific experts, members of the DMICC and other NIH officials, representatives from patient advocacy organizations, and lay members. The “Summary and Recommendations” section of the Strategic Plan is reproduced in Appendix 6. The Strategic Plan can also be accessed at: [www.T1Diabetes.nih.gov/plan](http://www.T1Diabetes.nih.gov/plan).

### **Peer Review**

Grants, cooperative agreements, and contracts supported by the *Special Funding Program* have been subject to peer-review mechanisms of the NIH and CDC funding processes. This review system ensures that the funds are expended for scientifically- and technically-meritorious research that is responsive to the goals and priorities of the *Special Funding Program*. A limited number of supplemental research awards were also made to existing peer-reviewed projects.

### **External Advisory Committees**

For most large consortia supported by the *Special Funding Program*, the NIH and CDC have established panels of scientists external to the consortia to provide ongoing oversight. These panels meet regularly to review progress and provide advice on allocation of resources and future directions for the consortia.

### **Solicitation of Innovative Ideas for Research**

To solicit broader input for future research opportunities from the external scientific community as a whole, the NIDDK issued a Request for Information (RFI) in 2004 calling for innovative ideas to advance prevention, treatment, and cure of type 1 diabetes. Over 80 submissions were reviewed by the expert panel during the January 2005 *ad hoc* mid-course assessment meeting. The RFI is further described in Appendix 3.

### **Collaboration with the Diabetes Voluntary Community and Other Non-Federal Funding Sources**

The major diabetes voluntary organizations—the ADA and the JDRF—have been committed and essential partners with HHS in developing the scientific goals and strategies of the *Special Funding Program*. Representatives of these groups have participated in the planning, assessment, and advisory meetings that have aided in the formulation of a scientifically credible and productive plan for the use of the *Special Funds*. Moreover, by co-sponsoring several of the special type 1 diabetes research initiatives, these organizations help the HHS to maximize the resources available for achieving the goals of the *Special Program*.

## COORDINATING TYPE 1 DIABETES RESEARCH EFFORTS

The research efforts supported by the *Special Funding Program* span a wide range of scientific areas. However, many of the large-scale research efforts have elements in common. For example, several research consortia are studying the genetics of type 1 diabetes or of specific complications; there are multiple consortia enrolling newborns in studies and following them to examine different environmental triggers. In order to maximize research progress, the NIH has facilitated coordination among research consortia with both overlapping and distinct interests. The NIH has organized meetings to facilitate broad coordination efforts as well as focused meetings of consortia that share common interests. Coordination helps to prevent duplicative work by promoting the sharing of resources and methodology as well as by facilitating cross-disciplinary research approaches. Furthermore, collaboration between researchers with distinct interests facilitates the pursuit of novel research directions.

In response to recommendations from *ad hoc* panels of external scientific and lay experts to enhance ongoing collaboration and coordination among the research consortia and networks supported by the *Special Funding Program*, the NIDDK

established the Type 1 Diabetes Consortia Coordinating Committee. The Committee spearheaded the development of websites for type 1 diabetes patients ([www.T1Diabetes.nih.gov/patient](http://www.T1Diabetes.nih.gov/patient)) and researchers ([www.T1Diabetes.nih.gov/investigator](http://www.T1Diabetes.nih.gov/investigator)). The website for patients describes clinical research studies recruiting patients and has contact information for the studies if patients are interested in enrolling. The website for investigators includes information on research consortia and clinical trial networks; research resources available to the broad scientific community; and information on research funding opportunities. These websites not only enhance patient recruitment efforts, but provide researchers with access to information, data, and protocols generated by the type 1 diabetes research consortia, thereby facilitating resource sharing and coordination. Additional information on coordination efforts is found in Appendix 2.

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### **NIH Websites Dedicated to Research Supported by the *Special Funding Program***

For Patients: [www.T1Diabetes.nih.gov/patient](http://www.T1Diabetes.nih.gov/patient)

For Scientists: [www.T1Diabetes.nih.gov/investigator](http://www.T1Diabetes.nih.gov/investigator)

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## Organization of the Evaluation Report

The following chapters of this Evaluation Report are framed around the six overarching Goals of type 1 diabetes research. Goal chapters include the following components:

**Introduction and Background:** Scientific background for each Goal, explaining the research challenges in the context of the Goal's medical importance for the lives of patients.

**Evaluation of Major Research Consortia, Networks, and Resources:** An evaluation of major research efforts that are supported under the Goal. These sections were developed so that all the information on a single Consortium is found under that Consortium, rather than cross-referencing other sections of the document. Therefore, information that is relevant to two different consortia will be repeated under each Consortium. This approach, although repetitive, was intentionally used so that complete information could be found in each Consortium's evaluation in a self-contained way.

Consortium evaluations include the following sections:

- *Program Description:* The value added by the Consortium in the context of the overall research portfolio.
- *Highlights of Progress:* Examples of the progress achieved to date.
- *Anticipated Outcomes:* Description of anticipated future progress and the impact that the research effort could have on the health of type 1 diabetes patients.
- *External Evaluation by Expert Panel:* Highlights of input received from an *ad hoc* meeting of external experts who performed a mid-course assessment of the *Special Funding Program* in January 2005.
- *Actions Taken in Response to Expert Panel Recommendations:* Responses to recommendations from the January 2005 *ad hoc* panel.
- *Ongoing Evaluation:* Descriptions of regular oversight mechanisms, such as reviews by external advisory panels.
- *Coordination with Other Research Efforts:* Examples of how the research Consortium or network collaborates and coordinates its efforts with other research efforts to maximize and synergize progress.
- *Administrative History:* Programmatic details, including years of duration and agencies that support the Consortium.

**Evaluation of Investigator-Initiated Research:** An evaluation of research conducted through investigator-initiated research projects supported by the *Special Funding Program*. This section includes:

- *Impact of Special Funding Program on Extramural Grantees:* Self-reported descriptions of the impact that the *Program* had on the careers and research programs of scientists who received a grant under the Goal.

### **Emerging Research Opportunities Resulting from the Special Statutory Funding Program for Type 1 Diabetes**

**Research:** Highlights of future research opportunities that have been fueled by the *Special Funding Program*. The emerging opportunities were identified by scientific and lay experts external to the NIH and the CDC during a recent type 1 diabetes research strategic planning process.

# **GOAL I**

**IDENTIFY THE GENETIC AND  
ENVIRONMENTAL CAUSES OF  
TYPE 1 DIABETES**

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**Type 1 diabetes results from a complex interplay of genetic and environmental factors. To begin to unravel the underlying genetic and environmental causes, the *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of genetics and epidemiologic research consortia and the assembly of appropriate populations of patients for study, which will facilitate investigations by the broad diabetes scientific community.**

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This Goal of the *Special Statutory Funding Program for Type 1 Diabetes Research* is focused on understanding the interplay of genetic and environmental factors that is at the root of the immune system's attack on the body's insulin-producing cells (beta cells found in clusters called "islets" within the pancreas). Until these factors are completely deciphered, it will not be possible to identify with certainty all those who are at risk for the disease and their specific risk profiles. This knowledge is also urgently needed to develop and tailor the most effective clinical strategies for delaying or completely preventing the disease. It would also facilitate research aimed at reversing the disease as soon as possible after onset—before all the precious insulin-producing beta cells are lost and before patients develop damaging complications of the eyes, kidneys, nerves, heart, and other parts of the body.

It has long been known that the likelihood of a person's developing type 1 diabetes is higher the more closely related he or she is to a person with the disease. However, 80 percent of new type 1 diabetes patients do not have close relatives with the disease.<sup>1</sup> Type 1 diabetes is an extremely complex disease believed to involve many genes, which work in concert and can have both large and small effects. Previous research indicated that one of the implicated genetic regions (the major histocompatibility complex, or "MHC") may contribute up to 50 percent of the total genetic risk for type 1 diabetes. Certain variations of the genes in this region can cause a person to have a predisposition to the disease.

The environmental contributors to type 1 diabetes are also likely to be complex, and a variety of triggers have been suggested. The possible triggers include viruses, diet, environmental toxins, and stress. However, no definitive proof of a causative link with any of these factors has yet been found. When the genetic susceptibility is "triggered" by an environmental agent, the body's immune defense system will then turn against itself. When provoked, the normally protective immune system—which fights against bacteria, viruses, and other foreign invaders—will launch an assault on the body's own insulin-producing beta cells. If the factors that trigger this immune assault were known, genetically-susceptible individuals could avoid certain foods or environmental toxins, or be vaccinated against an infectious agent linked to the disease.

Epidemiological research to adequately investigate the underlying genetic and environmental factors that trigger type 1 diabetes in susceptible individuals requires large-scale, long-term, and well-coordinated research efforts. Long-term investment in the research programs described under this Goal will provide the opportunity to follow at-risk individuals for sufficient lengths of time to observe progression to autoimmunity and type 1 diabetes and to correlate the onset of disease with suspected risk factors. These types of studies may have a dramatic and positive impact on disease prevention and treatment strategies. Such studies could not have been undertaken without the *Special Funds*.

## 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 identify the genetic and environmental causes of type 1 diabetes 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.

### **Genetic Factors Associated with Susceptibility to**

**Type 1 Diabetes:** Numerous studies have investigated genetic susceptibility loci, using both case-control and family study designs. Different versions of two human leukocyte antigen (HLA) genes in the MHC class II region have been shown to represent the primary genetic determinants of risk for type 1 diabetes, although other class II genes, as well as class I and class III genes, may contribute to susceptibility. It has been suggested that genes in the MHC may contribute up to 50 percent of the total genetic risk for type 1 diabetes. Recent studies have also revealed that the *PTPN22* and *CTLA4* genes contribute to several autoimmune diseases, including type 1 diabetes. Studies have also shown that the absence of a protein, called AIRE, which results from a rare mutation in people, promotes autoimmunity in several tissues and increases the incidence of type 1 diabetes and other autoimmune diseases.

### **Contribution of INS to Type 1 Diabetes Susceptibility:**

A series of studies has confirmed an association of type 1 diabetes with the insulin gene, *INS*. Recent reports have suggested that insulin may be the critical initiator of the autoimmune destruction of insulin-producing beta cells. Findings in a mouse model of type 1 diabetes, supported by the Autoimmune Disease Prevention Centers (see Goal II), as well as research in humans, now suggest that the insulin molecule itself is an important, potentially disease-initiating autoantigen in type 1 diabetes.

### **Identification of Additional Genetic Regions Linked to Type 1 Diabetes Susceptibility:**

A major barrier to type 1 diabetes gene identification is that previous studies did not include large numbers of sib pair families (families with two or more siblings with type 1 diabetes). The Type 1 Diabetes Genetic Consortium (T1DGC) began collecting data from affected sib pair families and has performed genetic linkage analysis on the subset of the families. Researchers in the T1DGC have demonstrated nine regions in addition to MHC that show some evidence of linkage to type 1 diabetes; three of these regions have a bigger effect on risk than other regions in the chromosome. In addition, the data have clearly excluded other regions. This study represents one of the largest linkage studies ever performed for any common disease.

### **Genes and Genetic Concepts Discovered in Animal Models of Type 1 Diabetes:**

Some type 1 diabetes susceptibility genes, such as *CTLA4*, have first been identified in a non-obese diabetic (NOD) mouse model of type 1 diabetes and then found relevant to the disease in humans. Further identification of disease-susceptibility regions is in progress via a NOD mouse genome sequencing initiative (also supported by the *Special Funding Program*), which compares diabetes-susceptible and diabetes-resistant mouse strains. Findings will be pursued in human genetics consortia, such as the T1DGC.

**Environmental Triggers of Type 1 Diabetes:** Several long-term studies initiated prior to the *Special Funding Program* have suggested that dietary factors, such as timing of introduction of cereal, may affect risk of type 1 diabetes. However, the small size of these studies and variable



findings across studies precluded definite conclusions. In 2004, a carefully designed, long-term international study of sufficient size to test the role of suspected factors and to identify novel triggers was launched. This bold initiative, called The Environmental Determinants of Diabetes in the Young (TEDDY; see Goal II), will follow newborns through age 15 and provide unprecedented data and biosamples for use in identifying the environmental triggers of the disease.

### **Benefits to Children Participating in Long-term**

**Research Studies:** Prior to diagnosis, many patients with undetected type 1 diabetes will develop a condition called diabetic ketoacidosis (DKA) which, if not promptly treated, places them at risk of diabetic coma and death. The severe metabolic disturbance of DKA is not only life-threatening, but also further damages any residual insulin-producing cells. Already, some children who participate in research studies that aim to identify environmental triggers of type 1 diabetes have benefited by avoiding DKA. Researchers can identify those who progress from genetic predisposition to the earliest signs of autoimmunity and educate their families about what to expect in the way of symptoms and how to do blood glucose tests at home. Thus, type 1 diabetes does not blindside their families, and both parents and children are better prepared if and when a child experiences onset of the disease.

### **Defining the Incidence and Prevalence of Type 1**

**Diabetes in the United States:** Rates of type 1 diabetes are known to be increasing in some European countries. However, reliable data on changes over time in the United States, or even how many children in the United States have diabetes, were lacking. This gap in knowledge is being addressed by the Search for Diabetes in Youth Study (SEARCH). The SEARCH preliminary prevalence data indicate that at least 154,000 children/youth in the U.S. have diabetes. Emerging data from the SEARCH study also suggest that the incidence of type 1 diabetes in American children may be higher than an earlier estimate of 13,000 per year. For example, preliminary results show that incidence exceeds 20 per 100,000 per year for non-Hispanic white youth. Now that this important baseline national data on diabetes in children have been collected by SEARCH, the next phase of this study will determine whether the rates of diabetes are changing over time.

## EVALUATION OF MAJOR RESEARCH CONSORTIA, NETWORKS, AND RESOURCES RELATED TO THE IDENTIFICATION OF GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

**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.

### Type 1 Diabetes Genetics Consortium (T1DGC)

The T1DGC is organizing and implementing international efforts to identify genes that determine an individual's risk of developing type 1 diabetes. Teasing apart the multiple gene combinations that predispose someone to this complex disease requires analysis of a very large dataset covering thousands of patients and closely related family members who may or may not have developed the disease. The monumental first phase of the project, expected to continue through 2007, is to recruit families, particularly those with multiple siblings with type 1 diabetes, to join the study and to collect DNA samples for analysis. A Consortium database containing clinical, genetic, and medical history information has been established to facilitate the search for susceptibility genes. In subsequent project phases, the database and centralized DNA repository will serve as a resource accessible to genetics researchers both within and outside the T1DGC.

#### Highlights of Progress

The progress that T1DGC has made as of March 1, 2006, includes:

- Recruited over 1,640 families who have two or more siblings with type 1 diabetes, toward the goal of 2,800 families.
- Performed genome scans on over 1,430 families, toward the goal of 2,800 families.
- Performed analyses of four data sets showing that, in addition to genes in the MHC region, nine other genetic regions may be involved in type 1 diabetes.
- Established an MHC fine-mapping project to study genes in this region involved in susceptibility to type 1 diabetes.
- Established a Rapid Response project to study candidate genes that could contribute to type 1 diabetes.

#### Anticipated Outcomes

The T1DGC is a large-scale, well coordinated effort to identify numerous genes and gene combinations that are important in predicting an individual's risk of developing type 1 diabetes or related autoimmune diseases. The T1DGC is building on the work of the Human Genome Project that spelled out the contents of human genes and the International HapMap Project that is identifying the points at which gene sequences differ from person to person. The T1DGC is resolving which of these genetic differences are significant for type 1 diabetes. Samples stored in NIDDK repositories will be made available to scientists worldwide for application of the latest genetic

technology to study DNA from a large and well-characterized set of affected families. As science progresses to the age of personalized medicine, clinicians may soon be able to determine the optimal treatment strategy for an individual based on his or her genetic background. With new insights into the genetic factors that play a role in type 1 diabetes, researchers may be able to identify with great precision those individuals at risk for the disease, and to develop and test prevention-oriented strategies. It is possible, for example, that certain therapies to delay or reverse the development of type 1 diabetes may be more effective in individuals with specific genetic changes that predispose to type 1 diabetes. Such new genetic knowledge



Human genome map. The lines or bars along the sides of each chromosome represent genetic regions that have been linked to type 1 diabetes. The Type 1 Diabetes Genetics Consortium (T1DGC) is pooling data from 2,800 families to tease out disease genes. (From Smink LJ, et al. *Nucleic Acids Res.* 33 (Database Issue): D544-549, 2005.)

could point the way toward better screening of newborns or to widespread screening of the general population to identify individuals at risk of developing type 1 diabetes. This knowledge would facilitate the design of more specific clinical trials for testing interventions specifically tailored to patients with similar risk profiles. These are just a few examples of the enormously important and predictive and preemptive strides forward that can be envisioned and possibly attained by further understanding the genetic underpinnings of disease development.

### External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance from an External Advisory Board focused on the T1DGC, leading scientific and lay experts were asked to evaluate the progress of the T1DGC at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ Genes that participate in diabetes susceptibility are apparently very common in the population, yet only certain gene combinations confer disease susceptibility. The way to study these interactions is with extremely large databases; hence, the T1DGC provides the best strategy to identify genetic factors and their interactions.

- ▶ The Consortium is committed to making its resources available to the research community and has developed the necessary infrastructure to achieve this objective. The External Advisory Board was pleased with the policies developed by the Consortium that weigh the interests of funded Consortium members who have invested years in collecting material with the interests of the research community at large.
- ▶ Genetic analysis technology is undergoing transition. The Consortium has rapidly and adroitly converted to the more advanced and cost-effective Single Nucleotide Polymorphism (SNP) genotyping approach, and the resulting samples will be available in the NIDDK repository for future technological applications.

### Actions Taken in Response to Expert Panel Recommendations

The T1DGC 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: Enhance Coordination Among Genetics Consortia Supported by the *Special Funding Program***

- ▶ In July 2005, T1DGC participated in a coordination meeting with the other human genetics consortia supported by the *Special Funding Program*—Epidemiology of Diabetes Interventions and Complications (EDIC); Family Investigation of Diabetes and Nephropathy (FIND); and Genetics of Kidneys in Diabetes (GoKinD). In response to recommendations from this meeting, new initiatives are being developed to coordinate future research efforts among these studies. A summary of this meeting is available at: [www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf](http://www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf)

**Recommendation: Improve Coordination of Genetics Research in Mice and Humans**

- ▶ The T1DGC is utilizing T1Dbase (<http://T1DBase.org>) as a web-based tool to coordinate, manage, and interpret human, mouse, and rat genetics data. These data are open access and all software is open source in order to maximize its usage by the broad research community.

**Ongoing Evaluation**

To ensure continued and ongoing evaluation of the study design and the progress of the T1DGC, the NIDDK established an External Advisory Board (EAB). The EAB is composed of investigators with scientific expertise relevant to research conducted by the T1DGC, but who are not members of the Consortium. The EAB meets annually to:

- ▶ Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures; performance of clinical networks, data coordinating center, and core laboratories).

- ▶ Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results.
- ▶ Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

**Coordination with Other Research Efforts**

The T1DGC 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.

**Coordinating Patient Recruitment Efforts:**

- ▶ All 14 Type 1 Diabetes TrialNet clinical centers and 4 Search for Diabetes in Youth (SEARCH) study sites are participating as recruitment centers for the T1DGC North American Network.
- ▶ T1DGC assisted TrialNet in establishing international recruitment sites.

**Enhancing Data Comparison Among Studies:**

- ▶ T1DGC, TrialNet, SEARCH, and The Environmental Determinants of Diabetes in the Young (TEDDY) are all sharing either the same laboratories or laboratory reagents to analyze genetics data. This coordination will permit comparison of genetic data across all four studies, effectively increasing the power of each individual study in learning which genes play a role in disease onset.
- ▶ T1DGC, TrialNet, and TEDDY share the same North American laboratory for measurement of autoantibodies (markers used to predict an individual's risk for developing type 1 diabetes). This coordination will permit direct comparison of results obtained in each study.

- ▶ Researchers in the Diabetes Autoantibody Standardization Program (DASP) provide tools that T1DGC laboratories use to standardize autoantibody data. Data standardization provides confidence that results are independent of the laboratory performing the measurements.

Coordinating Studies of Type 1 Diabetes Genetics:

- ▶ The T1DGC coordinates its research efforts with the other genetics consortia supported by the *Special Funding Program* (EDIC, FIND, and GoKinD) (see “Actions Taken in Response to Expert Panel Recommendations” for a description of coordination efforts).

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

- ▶ The T1DGC has developed a comprehensive public website with information on samples, data, and resources that are available to the scientific research community ([www.t1dgc.org](http://www.t1dgc.org)).

- ▶ The T1DGC is repositing samples and data in all three NIDDK Central Repositories (Biosample, Genetics, and Data Repositories). The Repositories were established to expand the usefulness of NIDDK-supported studies by allowing a broader research community to access these materials beyond the end of the study.

**T1DGC Administrative History**

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NHGRI, and JDRF
Website	<a href="http://www.t1dgc.org">www.t1dgc.org</a>

T1DGC consists of a coordinating center and four clinical recruitment networks in Asia-Pacific, Europe, North America, and the United Kingdom.

## The Environmental Determinants of Diabetes in the Young (TEDDY)

Scientists directing six independent studies of environmental triggers of type 1 diabetes in the U.S. and Europe joined forces to create this international consortium. TEDDY is providing a coordinated, multidisciplinary approach to understanding the infectious agents, dietary factors, or other environmental conditions that trigger type 1 diabetes in genetically susceptible individuals. TEDDY investigators will screen newborns in the general population, as well as those who have a first-degree relative with type 1 diabetes. In this large-scale, long-term epidemiological effort, in which patient follow-up is estimated to continue through 2023, high-risk infants will be followed until they are 15 years of age. The TEDDY study is making progress toward amassing the largest data set and samples on newborns at risk for autoimmunity and type 1 diabetes anywhere in the world. To maximize the return on the investment in TEDDY, samples from the study will be made widely available to researchers worldwide.

### Highlights of Progress

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

- Screened over 62,290 newborns from the general population, toward the goal of 216,000 newborns.
- Recruited over 1,130 newborns from the general population, toward the goal of 5,940 newborns.
- Screened over 1,050 newborns with a first-degree relative with type 1 diabetes, toward the goal of 4,800 newborns.
- Recruited over 120 newborns with a first-degree relative with type 1 diabetes, toward the goal of 1,152 newborns.

### Anticipated Outcomes

Until researchers know what causes type 1 diabetes, it is difficult to develop strategies to prevent it. Previous studies suggested that certain factors, such as early exposure to cereal or cows' milk, might predispose to type 1 diabetes. However, these studies were too small and too short to achieve statistically significant results, and no definitive environmental trigger of the disease has yet been identified. Therefore, TEDDY is a crucially important effort to tease out the environmental factors triggering disease onset. While it is a substantial investment of time and resources to follow individuals for many years, it is only through a long-term, coordinated study such as TEDDY that researchers are likely to answer critically important questions about type 1 diabetes risk and onset. Realization of study goals could have an enormously positive impact on public health efforts regarding disease prevention. For example, if a viral trigger is revealed, a vaccine could possibly be developed to prevent disease onset in genetically susceptible individuals. Alternatively, if a dietary component

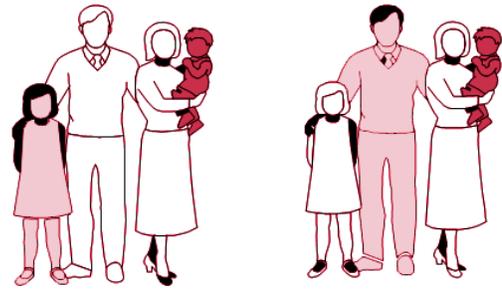
is found to be causative or protective, individuals at risk could take steps to either eliminate or add it to their diets. By pinpointing the constellation of type 1 diabetes disease genes (as is being done in the T1DGC), environmental triggers (as is being done in TEDDY), and their cascading effects on the immune system (see Goal II), researchers may be able to entirely prevent or reverse disease onset. Combating the disease at the “front-end” is especially beneficial because early steps could preclude or arrest the development of disease complications—including kidney failure, blindness, lower limb amputations, heart attacks, and strokes. Research on the genetic and environmental causes of the disease thus offers the real hope of preventing type 1 diabetes.

Importantly, the studies of environmental factors that play a role in type 1 diabetes may also contribute to understanding the development of celiac disease, which is an autoimmune disease primarily affecting the gastrointestinal tract. In the U.S., the prevalence of celiac disease has been estimated to be

## General population cohort 6 centers



## Sibling/offspring cohort 6 centers



While having a relative with type 1 diabetes greatly increases a child's risk for the disease, most of those newly diagnosed with the disease have no family history. To identify the environmental causes of type 1 diabetes, The Environmental Determinants of Diabetes in the Young (TEDDY) is recruiting newborns at increased genetic risk (red shading) from the general population (left panel) without a family history of the disease. TEDDY is also recruiting newborns with a parent or sibling (pink shading) with type 1 diabetes (right panel). (Images courtesy of Dr. Marian Rewers and the Diabetes Autoimmunity Study in the Young.)

approximately one percent of the population.<sup>2</sup> Some genes confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Therefore, ongoing studies to identify environmental triggers of type 1 diabetes are also investigating development of celiac disease. These studies may uncover environmental factors initiating both disorders, benefiting not only type 1 diabetes patients, but also persons suffering from celiac disease and other autoimmune diseases.

### External Evaluation by Expert Panel

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

- ▶ TEDDY is a major project with an important goal. The design and implementation of TEDDY represent the best research approach to that goal.

- ▶ The rigorous design of the TEDDY consortium redresses weaknesses in previous newborn diabetes environmental studies with regard to methodological standardization, sample sizes, research biases, study designs, and follow up.
- ▶ As the consortium began, TEDDY successfully cooperated with on-going newborn studies.
- ▶ The consortium has made significant progress forming reference laboratories, establishing proficiency tests, and developing a protocol manual.

### Actions Taken in Response to Expert Panel Recommendations

TEDDY 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: Publicly Publish the Protocols and Solicit Broad Community Support**

- ▶ The TEDDY study group maintains a website that describes the study protocol, manual of operations, and study forms ([www.teddystudy.org](http://www.teddystudy.org)). This site includes policies, procedures, and other governance documents as well as folders for science and administrative committee support. The site also contains a series of standard reports specific to each geographic region in which the study operates, which can be used by the local sites to enlist broad community support. In addition, the TEDDY study has been presented at various meetings, and the design paper will soon be published.
- ▶ TEDDY study-related materials have been posted on the NIDDK's public website dedicated to research supported by the *Special Funding Program* ([www.T1Diabetes.nih.gov](http://www.T1Diabetes.nih.gov)). Furthermore, a website is maintained by each of the clinical programs participating in TEDDY. These websites promote the TEDDY study locally, make the study more visible in the community, and provide links to the TEDDY Study Group website.
- ▶ TEDDY has organized workshops, in collaboration with NIDDK, JDRF, and NIAID, to solicit broad scientific input. For example, one of the workshops, "Identifying Infectious Causes of Human Disease," helped TEDDY investigators begin their search for potential environmental triggers of diabetes and pre-diabetic autoimmunity. The information provided was valuable for protocol development. Another workshop, "Viral Detection in Type 1 Diabetes," provided a forum for research synergy by bringing together TEDDY researchers and investigators with expertise in proteomics and genomics methodologies, with the aim of promoting identification of viral triggers of type 1 diabetes.

**Recommendation: Develop a Mechanism for Grafting New Technologies as They Become Available**

- ▶ A program and explicit guidelines for ancillary studies have been established to facilitate access to TEDDY materials by researchers who seek to expand and embrace new technologies for inclusion into the TEDDY study group. The NIDDK has developed an initiative to support investigator-initiated ancillary studies to ongoing research efforts, including TEDDY.

**Recommendation: Conduct Hypothesis-Driven Analyses To Help Expedite Translating Laboratory Discoveries into the Clinic**

- ▶ The TEDDY study and its protocol were designed to test scientific hypotheses associated with the initiation and/or promotion of the pathogenic process that results in the development of type 1 diabetes. Specific hypotheses were identified to be confirmed or refuted over the course of the study. The TEDDY study is the clinical, epidemiological study that will provide support for translational science and create new information.

**Recommendation: Maintain Active Oversight by an External Advisory Board To Ensure Resources Are Used Most Effectively and That Study Designs Are Appropriate**

- ▶ The TEDDY study group has an active standing EAB. The EAB meets regularly and is provided updates on all aspects of the study, including progress towards meeting study goals. The EAB is comprised of well respected scientists who contribute their highly relevant individual expertise and collective insights to study planning and evaluation.



**Recommendation:** Bring Investigators from the TEDDY Study and the Trial To Reduce IDDM in the Genetically at Risk (TRIGR) Study Together To Discuss Issues of Coordination and Integration

- ▶ Representatives from both TEDDY and TRIGR participated in a Type 1 Diabetes Consortia Coordination meeting that the NIDDK convened in May 2005. The purpose of the meeting was to identify opportunities to enhance collaboration among all of the research consortia studying type 1 diabetes. Prior to the larger meeting, representatives from consortia studying newborns (TEDDY, TRIGR, and Type 1 Diabetes TrialNet) met to discuss how to obtain the most useful information when looking at these studies as a group. Participants discussed common data variables across the studies and future analytic strategies.

**Ongoing Evaluation**

As noted above, to ensure continued and ongoing evaluation of the study design and the progress of TEDDY, the NIDDK established an EAB composed of scientific experts who are not participating in TEDDY. The EAB meets annually, in person or by conference call, to:

- ▶ Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures; performance of clinical centers, data coordinating center, and core laboratories).
- ▶ Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results.
- ▶ Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

**Coordination with Other Research Efforts**

TEDDY coordinates its efforts with multiple other type 1 diabetes research consortia and networks supported by the *Special Funding Program*, particularly those studying newborns. 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.

Coordinating Research Studies Involving Newborns:

- ▶ TEDDY investigators have met with researchers participating in other type 1 diabetes research studies involving newborns (TRIGR and TrialNet) to discuss opportunities for enhancing coordination and collaboration.
- ▶ TEDDY has shared the following materials with TrialNet investigators who are studying newborns in the Nutritional Intervention to Prevent (NIP) Diabetes Study: genetic-screening procedures, data forms, and parts of the Manual of Operations concerning follow-up of high-risk children.
- ▶ TEDDY and TRIGR share the same Data Coordinating Center. This coordination has resulted in implementation of similar standards in data collection, entry, management of quality control, and analyses for both studies.
- ▶ TEDDY, TrialNet, and TRIGR have coordinated patient recruitment efforts to ensure that they are not adversely competing for patient participants in their studies.
- ▶ TRIGR and TEDDY investigators are considering collaborative efforts on recruitment after TRIGR accrual ends. Both groups are also considering a follow-up intervention protocol.

#### Enhancing Data Comparison Among Studies:

- ▶ TEDDY, T1DGC, TrialNet, and the SEARCH for Diabetes in Youth study are all sharing either the same laboratories or laboratory reagents to analyze genetics data. This coordination will permit comparisons of genetics data across all four studies.
- ▶ TEDDY, T1DGC, and TrialNet share the same North American laboratory for measurement of autoantibodies. This coordination will permit direct comparison of results obtained in each study.
- ▶ TRIGR and TEDDY have implemented similar standards in data collection and entry. This coordination is permitting direct comparison between results obtained in each study relevant to nutrition and to diabetes-associated variants of certain immune system genes (HLA genes).
- ▶ DASP provides tools that TEDDY laboratories use to standardize autoantibody data. Data standardization provides confidence that results are independent of the laboratory performing the measurements.

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

- ▶ TEDDY is repositing biological samples and data into the NIDDK Central Repositories and will make the material available to the broad scientific community. The NIDDK has developed an initiative to support investigator-initiated ancillary studies to ongoing studies, including TEDDY.

#### **TEDDY Administrative History**

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NICHD, NIEHS, CDC, and JDRF
Website	<a href="http://www.teddystudy.org/">www.teddystudy.org/</a>
TEDDY is a consortium of six Clinical Centers and one Data Coordinating Center in the United States, Finland, Sweden, and Germany.	

## Search for Diabetes in Youth (SEARCH)

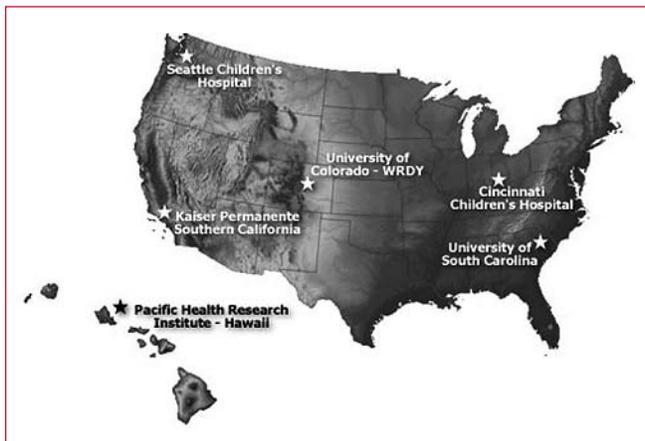
Major impediments to diabetes research and efforts to improve public health include lack of uniform national information on the rates of childhood diabetes, whether these are changing over time, and the clinical course and evolution of different forms of diabetes in children and youth. While substantial increases in the incidence of type 1 diabetes have been reported in Europe, reliable data on changes over time in the U.S., or even how many children in the U.S. have diabetes, were lacking. The SEARCH multicenter epidemiological study is identifying cases of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the U.S. The study aims to identify the number of children and youth under age 20 who have diabetes; learn how type 1 diabetes and type 2 diabetes differ, including how they differ by age and race/ethnicity; learn more about the risk for acute and chronic complications of diabetes in children and youth; investigate the different types of care and medical treatment that these children and youth receive; and learn more about how diabetes affects the daily lives of children and youth in the U.S. Now that the first baseline assessment of diabetes rates in children nationwide has been completed, the study is poised to evaluate trends in diabetes incidence and progression of the disease over time.

### Highlights of Progress

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

- In the year 2001, approximately 3.5 million children less than 20 years of age were under surveillance at the 6 SEARCH centers to estimate how many children/youth had diabetes (prevalent cases).
- Since 2002, approximately 5.5 million children less than 20 years of age (approximately 6 percent of the under 20 years U.S. population) with wide racial/ethnic, socioeconomic, and geographic representation, have been under surveillance at the SEARCH research centers each year to estimate how many children/youth develop diabetes (incidence cases) per year by age, sex, race/ethnicity, and diabetes type.
- Approximately 5,000 children/youth with diabetes, and their families, have participated in SEARCH in-person visits. Nearly 3,000 stored DNA specimens from these participants are being used to extend the genetic component of SEARCH.
- About 8,000 children/youth, and/or their families, have provided basic information on clinical presentation by mailed survey.
- Over 11,200 cases of diabetes in children/youth less than 20 years of age at diagnosis (6,392 prevalent and 4,828 incident) have been identified. Cases identified are highly diverse ethnically (approximately 13 percent Hispanic; 13 percent African American; 3 percent American Indian; 4 percent Asian/Pacific Islander; 68 percent Caucasian). SEARCH provides estimates of 2001 diabetes prevalence (1.8 per 1,000) and based on 2002 and 2003, overall incidence is estimated to be 25.5 per 100,000 per year. Manuscripts reporting final prevalence estimates are in press (*Pediatrics*, 2006), and the initial incidence paper has been submitted.
- Preliminary findings indicate that diabetes incidence varies across U.S. major racial/ethnic groups:
  - ▶ In children less than 10 years of age, the incidence of diabetes is highest in non-Hispanic whites and lowest in American Indians. Children less than 10 years of age who are Hispanic, African American, or Asian/Pacific Islander have diabetes incidence rates that are intermediate between those of non-Hispanic white and American Indian children.

- ▶ In older youth (10-19 years), the incidence of diabetes is higher in African American, Hispanic, and American Indian youth than in non-Hispanic whites. In Asian/Pacific Islanders, the incidence is similar to that of non-Hispanic whites.
  - The SEARCH prevalence data indicate that at least 154,000 children/youth in the U.S. have diabetes. Diabetes prevalence varies across major racial/ethnic groups:
    - ▶ In children less than 10 years of age, non-Hispanic whites are more affected than children of other racial/ethnic groups.
    - ▶ In older youth (10-19 years), the highest burden of diabetes is observed in non-Hispanic whites and African Americans—about 1 in 300 have diabetes. About 1 in 500 Hispanic and American Indian youth and about 1 in 750 Asian and Pacific Islanders have diabetes.
  - Higher Body Mass Index (BMI) was associated with younger age at diagnosis of type 1 diabetes, but only in children with reduced beta cell function. This relationship was independent of the presence of autoantibodies predictive of the disease. These data suggest that, only among individuals with already compromised beta-cell function and/or high rate of beta cell loss, obesity accelerates type 1 diabetes onset.
  - Low birth weight may be a factor in accelerating the onset of type 1 diabetes. These data suggest that the intrauterine environment may be an important determinant of age of onset of type 1 diabetes.
  - SEARCH has shown that nutritional intake in adolescents with diabetes is poor and does not follow current recommendations. Recommendations for total dietary fat intake are met by only 10 percent of youth with diabetes and recommendations for saturated fat intake by only 7 percent.
  - Similarly to the population of youth without diabetes, about 9 percent of adolescents with diabetes have moderate or severely depressed mood. Depressed mood in adolescents with diabetes is associated with poor diabetes control and a higher likelihood of hospitalizations, emergency room visits, and episodes of diabetic ketoacidosis.
  - At onset of diabetes, over half of youth are hospitalized, and one in four suffers from diabetic ketoacidosis at onset.
  - The prevalence of multiple cardiovascular disease (CVD) risk factors is high in children and adolescents with diabetes. CVD risk factors were present in youth with either type 1 or type 2 diabetes, but were more common in adolescents with type 2 diabetes.
  - At similar diabetes duration, youth with type 2 diabetes are more than twice as likely to have microalbuminuria (a sign of deteriorating kidney function) than youth with type 1 diabetes.
  - Fully half of youth with diabetes had HbA1c levels greater than recommended by the ADA.
  - Although more than 95 percent with diabetes had some form of health insurance coverage, minority youth had poorer glycemic control than non-Hispanic white youth.
  - Worse glycemic control is associated with a worse lipid profile, regardless of diabetes type.
  - Type 2 diabetes (versus type 1 diabetes) and longer duration of diabetes, but not HbA1c, are independently associated with measures of increased central and peripheral arterial stiffness, suggesting an increased risk of future cardiovascular morbidity.
-



The map shows the location of the six Search for Diabetes in Youth (SEARCH) clinical centers. (Image courtesy of the SEARCH Study Group.)

### Anticipated Outcomes

Research supported through the SEARCH consortium will enhance understanding of the natural history, complications, and risk factors of diabetes onset in childhood and adolescence. It will also estimate diabetes prevalence and incidence by age, sex, race/ethnicity, and diabetes type, as well as assess the impact of quality of diabetes care in youth on short- and long-term diabetes outcomes, including quality of life. Because the incidence and prevalence of type 1 diabetes in the U.S. have not been precisely known, it has been difficult for researchers to determine with certainty if the number of persons with the disease is increasing or decreasing. Acquiring these data is important in order to ultimately design and implement public health efforts to prevent the disease once prevention strategies are identified. Furthermore, the data that are acquired in the SEARCH study regarding the natural history and risk factors of diabetes can inform the design of new prevention and treatment strategies. Data have already shown that obesity and low birth weight may accelerate onset of type 1 diabetes in some patients (described above). High prevalence of CVD risk factors, including obesity, dyslipidemia,

and hypertension, has been documented in youth with type 1 diabetes, as well as youth with type 2 or hybrid diabetes. The need for identifying effective approaches to improve dietary intake in youth with diabetes has been clearly documented. By building on SEARCH findings, researchers may be able to design interventions that can prevent or delay disease onset in at-risk individuals and, of equal importance, to design interventions to reduce risk for both acute and chronic complications of diabetes.

### External Evaluation by Expert Panel

In addition to ongoing evaluation by an External Scientific Advisory Committee, leading scientific and lay experts were asked to evaluate the progress of SEARCH at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ The strength of the SEARCH study is the collection of careful epidemiological data representative of the U.S. population. The preliminary findings have shown a higher incidence of childhood diabetes than was previously believed; however, it will be easier to assess actual progress once the data are published.
- ▶ Coordinating the genetics of SEARCH with the other genetics consortia supported by the *Special Funds* and linking their repositories would greatly benefit the research community. Samples and data should be available for ancillary studies.
- ▶ SEARCH could be restructured by more clearly developing its secondary aims and by strengthening the management structure through reorganization. Clearer definitions of protocol extensions and establishment of an external advisory board would strengthen the future of the project.

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

### **Recommendations**

SEARCH 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: Coordinate the Genetics of SEARCH with the Other Genetics Consortia Supported by the Special Funding Program and Link Their Repositories/ Databases**

- ▶ There are currently four SEARCH research centers (Cincinnati, Southern California, Seattle, and South Carolina) that are participating as recruitment centers for the T1DGC North American Network. The principal investigator for the T1DGC North American Network provided coordination between TrialNet, SEARCH, and T1DGC through her involvement in all three studies. Procedures across the three studies were standardized to the extent possible. The Colorado site childhood population is participating in TrialNet, among numerous other multicenter, NIH-sponsored research studies.

#### **Recommendation: Make Samples and Data Available to the Scientific Community for Ancillary Studies**

- ▶ SEARCH developed a comprehensive public website with information on samples, data, and resources that are available to the scientific research community ([www.searchfordiabetes.org](http://www.searchfordiabetes.org)). An updated protocol developed in the first few months of the SEARCH renewal (see below) includes specific statements regarding distribution of data.

#### **Recommendation: Create and Clarify Protocol Extensions**

- ▶ In 2005, the SEARCH study was renewed under a competitive Program Announcement. In response to the Program Announcement, SEARCH (Phase 2 [2005-2009]) has revised the study protocol that will be reviewed by

the SEARCH External Advisory Board. The first aim of SEARCH Phase 2 relates to tracking trends in incidence of diabetes; the remaining three aims reflect expansion of work initiated in SEARCH Phase 1 related to evolution of metabolic and clinical characteristics of incident cases, expanded work related to health care utilization and quality of care, and further work toward approaches to public health surveillance of diabetes. As of March 1, 2006, two ancillary studies to SEARCH have been funded by the NIH after competitive peer review, one other ancillary study has been submitted to the NIH, and three ancillary studies have been submitted to professional societies and research foundations.

#### **Recommendation: Establish an External Advisory Board**

- ▶ An EAB has been established for SEARCH Phase 2, and the initial meeting has been scheduled.

#### **Recommendation: Assess the Standard of Care and Access to Treatment Utilizing the Second Phase of SEARCH**

- ▶ One of the main aims of SEARCH Phase 2 is to assess the impact of quality of diabetes care in youth on short- and long-term outcomes, including quality of life, by: completing analytic work initiated in SEARCH Phase 1 and exploring the interrelationships of patient characteristics with important domains of health care outcomes, such as glycemic control, satisfaction with care, receipt of recommended services, complications, and quality of life. A SEARCH paper currently in press evaluates dietary intake of youth age 10 years and older against the ADA's nutrition recommendations for youth with diabetes.

#### **Recommendation: Reconfigure SEARCH To Address the Challenge of Follow-up Rate in Adolescents**

- ▶ A subcommittee of the Protocol Oversight Committee has been formed to regularly review recruitment and retention rates and to develop new approaches to enhance

success in this arena. Site visits are being planned, and targeted discussions of recruitment and retention efforts will be an important component of this effort.

**Recommendation: Include Clinicians Who Understand Complications**

- ▶ An investigator at the SEARCH Ohio site is a well recognized expert in risk factors and primary prevention of cardiovascular diseases in children and youth. An investigator at the Southern California SEARCH site is an ophthalmologist and is now preparing a grant proposal for a SEARCH ancillary study focused on diabetic retinopathy and other microvascular complications of diabetes.

**Recommendation: Obtain Foundation of Epidemiologic Knowledge About the Development of Complications, Particularly Cardiovascular Disease**

- ▶ The 5,000 children and youth who participated in the in-person visits provided information on behavioral and metabolic risk factors for complications; had a special examination to measure body mass index, blood pressure, and waist circumference; gave blood to measure HbA1c and lipids; and provided urine to measure albumin-to-creatinine ratio. Stored blood specimens from 3,004 participants have been used to measure adiponectin, C-reactive protein, lipoprotein (a), apolipoprotein B, and LDL particle size.
- ▶ SEARCH has also conducted a pilot study of sub-clinical cardiovascular diseases using measures of arterial stiffness and brachial distensibility. This pilot study involved 700 SEARCH patients from two sites (Colorado and Ohio). Data are being analyzed, preliminary results were presented at the 2006 ADA annual meeting, and manuscripts are being prepared.

**Ongoing Evaluation**

To ensure continued and ongoing evaluation of the study design and the progress of SEARCH, the CDC and the NIDDK have established an External Scientific Advisory Committee (ESAC). The ESAC is comprised of investigators with scientific expertise relevant to research conducted by SEARCH, but who are not members of the Consortium. The ESAC meets annually to:

- ▶ Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and the performance of research centers, data coordinating center, and central laboratory).
- ▶ Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results.
- ▶ Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

**Coordination with Other Research Efforts**

SEARCH 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.

**Coordinating Patient Recruitment Efforts:**

- ▶ Four SEARCH study sites are participating as recruitment centers for the T1DGC North American Network.
- ▶ The Colorado and South Carolina SEARCH sites are informing participants about TrialNet studies and referring them to the TrialNet coordinator for information on enrollment.

- ▶ Two SEARCH sites (Colorado and California) are assisting with recruitment for TRIGR by providing brochures and other information about TRIGR to potential study participants.

#### Enhancing Data Comparison Among Studies:

- ▶ SEARCH, T1DGC, TrialNet, and TEDDY are all sharing either the same laboratories or laboratory reagents to analyze genetics data. This coordination will permit comparisons of genetics data across all four studies, effectively increasing the power of each individual study in learning which genes play a role in disease onset.

#### Coordinating Research Studies Involving Children:

- ▶ SEARCH, TrialNet, TEDDY, and T1DGC investigators directly collaborate.

#### Facilitating Basic Research Studies:

- ▶ SEARCH investigators receive islets for basic research studies through the Islet Cell Resource Centers (ICRs).

#### **SEARCH Administrative History**

Date Initiative Started	2000
Date <i>Special Program</i> Funding Started	2001
Participating Components	CDC and NIDDK
Website	<a href="http://www.searchfordiabetes.org">www.searchfordiabetes.org</a>

SEARCH consists of a coordinating center, a central laboratory, and six research centers in California, Colorado, Hawaii, Ohio, South Carolina, and Washington state.



## Type 1 Diabetes Mouse Repository (T1DR)

This research resource, located at The Jackson Laboratory in Maine, has been established to collect, preserve, and disseminate approximately 150 mouse strains that are important to research in type 1 diabetes. Mouse models, such as the NOD mouse, are an essential resource for researchers studying the genetic and pathophysiological bases of the disease. It is important that the broad scientific community have ready access to these mouse models to facilitate their research efforts. The repository is enhancing access and ensuring the continued availability of these mouse models to the entire research community.

### Highlights of Progress

The progress that T1DR has made as of March 1, 2006, includes:

- Collected and preserved over 126 mouse models, toward the goal of 150 models.
- Distributed mouse models to over 100 investigators per year in the scientific community.

### Anticipated Outcomes

Animal models of type 1 diabetes can significantly facilitate the translation of laboratory research findings to clinical research. For example, techniques for gene discovery in small model organisms are much more powerful than in humans. Discovery of diabetes-causing genes in animal models will foster research on corresponding genes in human tissue samples and will thus help to uncover the pathways in which the genes function. Furthermore, animal models of the disease are important for testing promising therapeutic agents identified in the laboratory prior to testing in human clinical trials. Therefore, animal models are a crucial resource for translating laboratory results from the bench to the bedside.

### Ongoing Evaluation

Activities and progress of the T1DR are monitored by an EAB comprised of experts in mouse genetics, mouse husbandry, and rodent models of type 1 diabetes. Members of the EAB are not affiliated with the T1DR or with The Jackson Laboratory. The EAB meets annually to:

- ▶ Review status of importation and distribution of stocks, identify and make recommendations for new strains to be solicited, and advise on procedures to advertise repository holdings.

- ▶ Review quality control of genetics data on repository strains, including genome scans, chromosome-of-interest studies, and incidence studies.



Potential new therapies are often tested first in mouse models of a disease. The non-obese diabetic (NOD) mouse is an important research resource for the study of type 1 diabetes and its complications. The Type 1 Diabetes Mouse Resource is collecting, preserving, and disseminating mouse models for use by the scientific community. (Image courtesy of The Jackson Laboratory.)

### Coordination with Other Research Efforts

In coordination with other NIH-sponsored mouse repositories, the T1DR serves as an archive for mouse models generated by all scientists engaged in research relevant to type 1 diabetes. The T1DR also services many basic science consortia engaged in type 1 diabetes research, including the Beta Cell Biology Consortium (BCBC) and the Animal Models of Diabetic Complications Consortium (AMDCC). Mouse models distributed from these NIH-supported repositories support translational research relevant to pancreas development, autoimmunity, and transplantation.

### T1DR Administrative History

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Components	NCRR and NIDDK
Website	<a href="http://www.jax.org/t1dr">www.jax.org/t1dr</a>
T1DR is located at The Jackson Laboratory, Bar Harbor, ME.	

## TYPE 1 AND TYPE 2 DIABETES: COMMON LINKS

Type 1 diabetes is a disease in which the body's immune defense system attacks and destroys the insulin-producing beta cells of the pancreas. It often strikes in infancy, childhood, and young adulthood.

Type 2 diabetes is characterized by the body's resistance to insulin action; is more commonly diagnosed in adulthood; is strongly associated with overweight and obesity; and disproportionately affects minority populations. Although the mechanisms underlying development of the two forms of diabetes differ, type 1 and type 2 diabetes have much in common:

- ▶ They are caused by an interplay of genetic and environmental factors.
- ▶ Impaired function of the insulin-producing beta cells of the pancreas is central to both forms of diabetes.
- ▶ Both involve malfunctions in the body's system for maintaining appropriate blood glucose levels due at least in part to defects in insulin production.
- ▶ They have the same devastating disease complications, such as blindness, kidney failure, nerve damage, lower limb amputations, heart disease, and stroke. The financial burden of treating both forms of diabetes and their complications is tremendous. In 2002, total medical expenditures attributable to diabetes for all Americans were estimated at \$132 billion.<sup>3</sup>
- ▶ The mechanisms of hypoglycemia (dangerous episodes of low blood glucose) are common to both forms of the disease.
- ▶ Both type 1 and type 2 diabetes are being increasingly diagnosed at a younger age, when the disease is more difficult to control. Earlier onset increases diabetes' toll in lost health and productivity.
- ▶ Researchers are increasingly recognizing that patients have "hybrid" forms of diabetes. Careful characterization of patients considered to have type 2 diabetes reveals that a subset also has markers of type 1 diabetes called autoantibodies. Some

patients with type 1 diabetes have "insulin resistance" that was previously considered a hallmark of type 2 diabetes.

These similarities underscore how research progress on one form of the disease can have enormous benefits for people with the other form as well.

The interdependence and synergism of research on type 1 and type 2 diabetes have been clearly demonstrated, and NIH-supported type 1 diabetes research has already contributed greatly to improved management of both forms of the disease. For example, a landmark clinical trial in type 1 diabetes, called the Diabetes Control and Complications Trial (DCCT), proved that intensive glucose control can prevent or delay damage to the small blood vessels in the eyes, kidneys, and nerves (microvascular complications). The findings of this trial paved the way to studies that replicated these impressive results in type 2 diabetes patients. Most recently, the DCCT findings were extended to show that intensive control reduces heart attacks and strokes (macrovascular complications). Because of pioneering research in type 1 diabetes, close control of blood glucose levels is now a keystone to the medical management of both forms of the disease. Moreover, this landmark trial in type 1 diabetes also established the value of hemoglobin A1c (HbA1c) levels—a measurement of blood glucose levels over time—as a measure of disease management and an outcome measure for future clinical trials in both type 1 and type 2 diabetes, dramatically shortening the cost and time required for trials of new therapies and encouraging development of new therapies of diabetes. The use of HbA1c as an outcome measure was the basis for FDA approval of improved forms of injected insulin, inhaled insulin, and several new classes of oral drugs for type 2 diabetes which, used in combination, can delay the need for insulin therapy.

Through support from the *Special Statutory Funding Program for Type 1 Diabetes Research*, the NIH has spearheaded numerous initiatives to increase understanding of type 1 diabetes and its complications. The following examples are highlights of efforts that are advancing both type 1 and type 2 diabetes research.

- ▶ *Beta Cell Biology Consortium*: This Consortium is facilitating interdisciplinary approaches to advance understanding of beta cell development and function. The knowledge gained through these studies is essential for providing clues to increase the beta cell mass in people with type 1 and type 2 diabetes.
- ▶ *Imaging the Beta Cell*: Techniques for imaging the beta cell will be tested in both forms of diabetes and may prove useful for following the disease development and response to therapy for both disorders.
- ▶ *Hypoglycemia Research*: Although intensive insulin therapy is known to reduce the risk of long-term diabetes complications, its use has been limited because of the potential for episodes of hypoglycemia. Researchers are studying how the brain and other critical tissues sense and respond to hypoglycemia, as well as the effects of hypoglycemia on brain function. They are also developing more effective methodologies to prevent hypoglycemia, such as the recently approved continuous glucose monitors, which could help patients achieve close control and reduce episodes of hypoglycemia.
- ▶ *Diabetic Retinopathy Clinical Research Network*: Both forms of diabetes cause damage to the eyes and may lead to blindness. This network is conducting multicenter clinical research studies to test promising therapeutic agents for the treatment of diabetic eye disease. Both type 1 and type 2 diabetes patients are enrolled in the studies.
- ▶ *Genetics of Diabetes Complications*: Several research consortia are studying the underlying genetics of diabetes complications. Increased knowledge about genetics could help researchers predict who will develop complications, as well as inform the development of new targets for prevention and treatment.
- ▶ *Angiogenesis Research*: Angiogenesis is a process in which new blood vessels grow from existing ones. Research has shown that angiogenesis plays a key role in the development of some diabetes complications. Angiogenesis research, which has historically focused on cancer, is now being applied to research on diabetes complications. In turn, new insights could inform the understanding of other diseases in which angiogenesis plays a role.
- ▶ *Animal Models of Diabetic Complications Consortium*: This consortium is developing animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. The animal models developed by this group are also critically important for testing promising therapeutic agents prior to testing in type 1 or type 2 diabetes patients.
- ▶ *Pediatric Endocrinology Training Program*: This program is designed to prepare pediatricians for careers in pediatric endocrinology research related to diabetes. Because type 2 diabetes is now increasingly being observed in children, these specialists could contribute their expertise to children with both forms of the disease.

### What It's Like When Two of Your Children Have Type 1 Diabetes

Aiden Berg was a 14-month-old toddler when he was diagnosed with type 1 diabetes. Two years later his older sister, Heather, was diagnosed with the disease at age 10.

If you ask their parents, Toni and Rob Berg, what is the most difficult thing about raising a family when more than one child has diabetes, without hesitation, the answer comes back: scheduling!

"I think of myself as a pretty organized person," says 38-year-old Toni, who works as an airline customer service agent, "but with this disease, we have to stay on top of things all the time." Even then, things can go wrong.

About a month after Heather was diagnosed, the Bergs inadvertently mixed up Heather's and Aiden's doses of insulin, which resulted in a "mini crisis," says Rob. "Heather's dosage was way too much for Aiden, so we were up the entire night monitoring him. Now we always double check everything," adds the 39-year-old accountant. The Bergs have a third child, Dillon, age 8, who so far does not show any signs of the disease. "We check Dillon's blood sugar at least once a month," says Toni, "and keep our fingers crossed."

#### Understanding the Genetic Link

About 1 out of 5 people with type 1 diabetes has a close family member with the disease. To help scientists better understand the genetics of diabetes, the Bergs are currently taking part in a study called the Type 1 Diabetes Genetics Consortium (T1DGC). This consortium is designed to gather valuable information from 2,800 families like the Bergs, with at least two siblings who have type 1 diabetes. The study, sponsored by the NIDDK and the JDRF, involves researchers from around the world—Europe, North America, Asia-Pacific, and the United Kingdom.



The Berg children.

The T1DGC is different from many other clinical studies in that it does not test a medical intervention, but rather is designed to gather valuable information. Ultimately, information about the genetic basis of the disease may not only help identify new therapies, but also predict which therapy might be best for a particular person. Finding the genes predisposing to type 1 diabetes will also enable those at risk to be identified early so they can benefit from future research. The study is closely aligned with the Type 1 Diabetes TrialNet, which is investigating the development, prevention, and early treatment of type 1 diabetes. Both the T1DGC and TrialNet are supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*.

#### Dealing with the News

Toni and Rob were familiar with diabetes long before Aiden and Heather were diagnosed. Toni's mother died at age 56 from complications of type 2 diabetes, which she developed after having been diagnosed with gestational diabetes during her last pregnancy. Rob's mother also has type 2 diabetes, but she has avoided its complications so far.

According to the Bergs, before Aiden's diagnosis, he was manifesting many of the symptoms of diabetes. "At 12 months he had lost weight and was drinking

## PATIENT PROFILE: BERG FAMILY

lots of water," says Toni. "I said to our family doctor, 'My God, he has diabetes.'" Toni was told that the weight loss was probably because Aiden had started to walk and thus was using more energy. As for drinking lots of liquids, it was summertime and the temperature was very hot. Aiden's symptoms persisted, however, including: lethargy, constant irritability, and extreme thirst. "We were told over and over that children Aiden's age don't get diabetes," say the Bergs. Recent reports from physicians at diabetes centers suggest that type 1 diabetes may be occurring in younger children than was previously recognized. This is a problem, because it is much harder to control the disease in infants and young children who cannot recognize or respond to episodes of dangerously low blood sugar (hypoglycemia).

Finally, Aiden was given a blood test and was diagnosed with type 1 diabetes. By that time, he was so sick he had to be taken immediately to the hospital where he spent 2 days in the intensive care unit. "It just sank in that this was going to be life-long," says Toni. She adds that she was overcome by it all, especially knowing the history of what her mother and others in her family had gone through because of the disease. However, things didn't end there.

Two years later, Aiden's sister, Heather, was diagnosed with the disease. According to the Bergs, Heather's blood sugar was always a bit higher than the levels of the rest of the family. One day, while at a diabetes health exposition in Seattle, where the family resides, Heather used a blood sugar tester and her reading came out well above the healthy range. The vendor for the product told the Bergs to make sure to have Heather's blood sugar checked by a doctor. Toni hesitated. "I was in denial that two of my children could have diabetes," she says. Heather insisted on having the test because she would feel more comfortable knowing one way or the other. Sure enough, Heather's blood sugar number came out high again. "I still didn't want to believe it—until we got the [hemoglobin] A1c test results—which confirmed for me Heather's diagnosis," says Toni.

"I felt overwhelmed," Toni recalls, "but Heather was brave and never shed a tear."

"I can handle it," the precocious Heather told her parents. And handle it, she has.

One year after Heather was diagnosed, she went on an insulin pump. "She wanted to go on the pump the day she was diagnosed, but we decided we should wait a while," says Rob. Heather has taken to the pump well, and it has helped a lot in terms of family scheduling. "Heather is an extremely competent child and pretty much takes care of herself," says Rob.

"It's not as bad as I thought it would be," says Heather, who is now 11. "The shots don't hurt much, and because I'm on the pump, I don't have to have so many pokes. Also, Aiden had diabetes before me, so I kind of knew what to expect." Besides, she adds, "the pump is cool because people think it's a cell phone."

### No Typical Day

The Bergs say that no day is "typical" for their family, but they certainly keep diabetes-related procedures well under control.

Each morning the Bergs check Aiden's and Heather's blood sugar levels and administer insulin according to need. Then, the family goes over what they're going to have for breakfast so they know how many carbohydrates will be taken in; the same for when lunches are made. "There's no such thing as buying lunch at school anymore," says Toni. Most days, the Bergs check in with the school or day-care center to see how the kids are doing. After school, blood sugar levels are checked again, and Aiden and Heather have a snack—either with or without carbohydrates, depending on what their sugar levels turn out to be.

The Bergs also are big on sports. “There is always one sporting event or another that the kids play in,” says Toni. Rob adds that, “We try to keep them active all year round. Whether it’s baseball, swimming, soccer, cheerleading, gymnastics, riding their bikes, or playing in the backyard pool, it makes a big difference in their [blood sugar] numbers.” In the winter months, those numbers are a bit higher because they are not quite as active as in the summer, which, according to Rob, means more of an insulin adjustment.

In the evening, the family has dinner, and blood sugar levels are checked just before bedtime. Depending on how much Aiden’s and Heather’s blood sugars fluctuate on any given day, “either Rob or I will get up in the middle of the night and check them again,” says Toni.

### **Taking Part in Research Studies**

Like many families with a high incidence of diabetes, the Bergs are seeking as much information as possible about the disease. They became involved with the T1DGC study when they stopped by the Benaroya Research Institute’s booth at the Diabetes Expo in Seattle and were asked if they would like to participate in diabetes research. They jumped at the opportunity.

Such studies give hope to families like the Bergs. The T1DGC is expected to provide a better understanding of the

genetics of diabetes, which may suggest valuable new avenues for treating the disease. Furthermore, genetic testing may one day permit very early diagnoses, thereby enabling earlier management of the disease. Early intervention could reduce or delay onset of diabetes complications and prevent some emergency hospital admissions, such as was necessary for Aiden when he was first diagnosed. Indeed, ongoing research studies are using genetic tests to identify some newborns at high risk for developing diabetes. The studies are indicating that, with careful monitoring of such children, it may be possible to dramatically reduce the likelihood of such hospitalizations.

The hope extends beyond early diagnosis. “Knowing the amount of research going on, we’re hopeful that a cure for diabetes will be found by the time our children reach adulthood,” says Toni. “We hope and pray other families will participate in this research. The larger the pool of people they have to study, the more they can learn about combating this disease,” she adds.

More information on participating in the T1DGC and TrialNet can be found at: [www.t1dgc.org](http://www.t1dgc.org) and [www.diabetestrialnet.org](http://www.diabetestrialnet.org)

## THE PANCCHIP: A POWERFUL TOOL FOR DIABETES RESEARCH

Genetics and computer science are the proud parents of the burgeoning new field of bioinformatics—the application of information technology and computational methods to manage a deluge of biological data. Although, as a discipline, bioinformatics may be in its infancy, it has already hit its growth spurt by propelling the development of novel tools for studying the genomes of entire organisms (genomics) and the protein expression from entire cells and tissues (proteomics). The *Special Funding Program* has fostered bioinformatics research in its quest to comprehend and cure type 1 diabetes. The Endocrine Pancreas Consortium—an early *Special Funding Program* project initially funded in 1999—developed tools to more fully characterize the genes involved in the hormone-secreting function of the pancreas.

A complementary project, the Beta Cell Biology Consortium (BCBC), which subsumed the Endocrine Pancreas Consortium in 2002, has a mission to facilitate interdisciplinary approaches that will advance understanding of the development and function of the pancreatic islet. These research teams and their collaborators have developed a microarray specifically tailored to the endocrine pancreas—the “PancChip”—that can be used to study gene expression in this tissue and may provide insights into diabetes. The story behind the creation of the PancChip illustrates how targeted research funding—like that provided by the *Special Funding Program*—can catalyze the adaptation of cutting-edge technology into valuable tools targeted toward diabetes.

### What Is a Microarray?

With only a few exceptions, every cell of the body contains a full set of chromosomes and identical genes. Only a fraction of these genes is turned on in any given cell at any given time, however, and it is the subset that is “expressed” that confers unique properties to

each cell type. “Gene expression” is the term used to describe the multi-step process whereby information contained within the DNA is first transcribed into an intermediary molecule, messenger RNA (mRNA), and subsequently translated into the proteins that carry out important cellular tasks. Scientists study the kinds and amounts of mRNA in a cell to learn which genes are expressed—and how that expression might change—under certain conditions or at certain times. Gene expression is a highly complex and tightly regulated process that allows a cell to respond dynamically both to environmental stimuli and to its own changing needs. Importantly, gene expression is not just a simple “on/off” switch, but may also be thought of as a “volume control,” increasing or decreasing levels of expression as necessary.

A microarray is a tool for analyzing gene expression that consists of a small membrane or glass slide containing small samples of many genes. A microarray works by exploiting the ability of a given mRNA molecule to bind specifically to the DNA template from which it was transcribed. By using an array containing many DNA samples, scientists can determine—in a single experiment—the expression levels of hundreds or thousands of genes within a cell by measuring the amount of genetic material bound to each site on the array. With the aid of a computer, the amount of labeled genetic material bound to the spots on the microarray is precisely measured, generating a profile of gene expression in the cell. Microarrays are therefore useful when one wants to survey a large number of genes quickly or when the sample to be studied is small. Microarrays may be used to assay gene expression within a single tissue or cell type as a function of some treatment or developmental change, to compare gene expression in two different cell types or tissue samples, or to monitor changes in gene expression that coincide with the onset of disease.



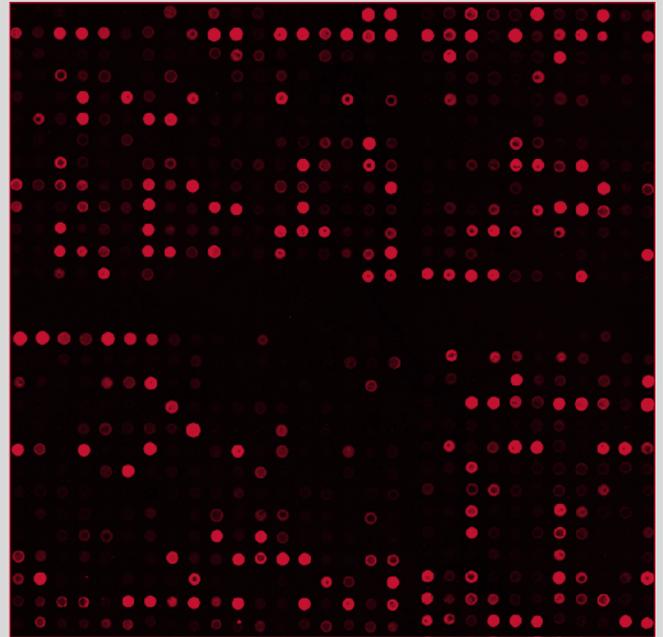
Over the past decade, microarrays have greatly facilitated large-scale analysis of gene expression in a wide range of tissues. Although commercially available arrays have not been specifically geared to represent the cells and organs known to be affected by diabetes, they have nevertheless been used in studies of both type 1 and type 2 diabetes. Perhaps not surprisingly, given their relative lack of specificity, many of these studies have shown few differences in gene expression in the disease state. It was this relative dearth of genomics tools geared specifically to diabetes that spurred the NIH to act to develop a more powerful tool to advance the science of diabetes genomics.

### **Building the PancChip**

Before the PancChip could be created, it was first necessary to generate a pancreas-specific “library” of genes expressed in this tissue. How does one go about defining which genes are specifically expressed in a particular tissue?

To do this, researchers used a combination of gene expression analysis and database mining. Using a variety of pancreatic tissues, including whole pancreas from adult and fetal mice, mouse insulinoma cells (a tumor of pancreatic islet cells), and human islets, the researchers identified genes that were highly expressed in these cells. Second, they identified additional genes by examining previously prepared libraries generated from human islets and human or mouse whole pancreas. The scientists in the Consortium used this information to assemble the first version of the PancChip, a microarray that contained 3,400 genes. Of these, 3,139 represented genes whose expression is enriched in the pancreas, 231 represented genes expressed in cell signaling pathways important in diabetes, and 30 represented so-called “housekeeping” genes that are responsible for general cellular function and metabolism. Of the pancreas-specific genes, 2,369 had been previously identified while 310 represented novel, theretofore undescribed genes.

In a report published in the July 2002 issue of the journal *Diabetes*, the researchers describe the generation of the



An image of a PancChip. (Image courtesy of Dr. Klaus Kaestner.)

PancChip and its use in the characterization of changes in gene expression patterns in the mouse pancreas from mid-embryonic development through adulthood. They reported that the profile of gene expression in the pancreas—as measured using the PancChip—changed markedly from the embryonic stage through adulthood, with proteins involved in binding DNA and RNA highly expressed during embryonic development and enzymes highly expressed in adulthood. The ability to generate a profile of gene expression in this tissue at various time points during development demonstrates the value and utility of the PancChip as a research tool.

### **Growing Family of PancChips**

The efforts of the Consortium to identify and characterize the genes expressed in the pancreas have allowed these researchers to identify over 160,000 individual sequence fragments. Analysis of these sequence fragments has identified close to 14,000 unique human gene sequences and over 9,400 mouse gene sequences. Furthermore, the researchers have identified roughly 4,300 sequences in both human and mouse tissue that have never been previously

described. These discoveries have allowed the members of the Consortium to expand and improve the PancChip. The current mouse PancChip (Version 6) contains over 13,000 unique elements that can be used to measure gene expression levels in a single assay. In 2004, the Consortium offered investigators the first version of a Human PancChip with over 12,000 genetic elements from the pancreas.

Of the vast amounts of genetic material in the body, only 1.5 percent of the DNA codes for proteins. Some of the non-protein-coding DNA helps to regulate whether or not a particular gene is expressed, and to what extent. New bioinformatics technologies allow researchers to probe beyond the coding DNA into the regulatory DNA, once thought of as “junk DNA.” In 2005, the Consortium produced two new microarrays of non-coding DNA, called promoter chips, that allow researchers to screen over 35,000 regulatory regions on the mouse DNA.

The promoter chips employ a new technology called the ChIP-on-Chip assay, so named because it combines DNA microarray chips with DNA/protein binding experiments called chromatin immunoprecipitation (ChIP). Every cell type has a unique set of proteins, called transcription factors, that bind to specific regulatory regions of the non-coding DNA, thereby controlling the pattern of gene expression. Researchers can use transcription factors from pancreatic islets as fishing bait to isolate the regulatory regions of DNA that are important in these cells. By matching this isolated DNA to the DNA embedded on the promoter chips, researchers can quickly identify the specific DNA hot spots that give beta cells their unique properties. As of April 2006, the Consortium had distributed over 400 of these promoter chips to labs all over the world.

## Future of Diabetes Bioinformatics Research

The generation and availability of the PancChip represent a major success of an initiative funded through the *Special Funding Program for Type 1 Diabetes Research*. The BCBC prints PancChip microarrays for all its members and distributes them at low cost to researchers around the globe. Data, protocols, resources, a searchable database, scientific highlights, and references are easily accessed on their website ([www.betacell.org](http://www.betacell.org)). The availability of these tools will be of great assistance as other researchers pursue new avenues of investigation. Areas in which the PancChips may provide important insights include:

- ▶ *Islet cell transplants:* Does increased (or decreased) expression of a particular gene or set of genes correlate with success of the transplant? If so, is it possible to manipulate gene expression in the islets prior to transplant in order to improve outcomes?
- ▶ *Stem cell therapy:* What genes give islet or pancreatic cells their unique nature? Is it possible to influence the differentiation of stem cells so that they can be efficiently coaxed into islets?
- ▶ *Profiles of gene expression:* Using the PancChip, it may be possible to generate “snapshots” of gene expression within the pancreas under various physiologic conditions. How might gene expression differ in people predisposed to developing diabetes? How does it change early in disease progression? Is it possible to influence pancreas gene expression—either through drugs or gene therapy—and alter the course of disease development?
- ▶ *Target discovery:* More comprehensive knowledge of gene expression patterns in the pancreas may identify novel genes important in normal function of the organ. What new targets for therapy might there be? Such research could increase treatment options for people with diabetes and those at risk.

- ▶ *Beyond diabetes:* The PancChip provides an important resource for other diseases of the pancreas. Researchers studying pancreatic cancer are using this tool to explore patterns of gene expression in pancreatic tumors. Thus, the benefits of the *Special Funding Program* extend beyond diabetes and may help to characterize pancreatic cancers and identify new targets for their therapy.

Overall, it is anticipated that a more complete understanding of the mechanisms involved in the development of the endocrine pancreas may allow researchers to better coax human stem cells into pancreatic endocrine cells for treatment of type 1 diabetes. Insights from these efforts may also provide new approaches to improve insulin secretion in people with type 2 diabetes.

## 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).

### Genetic Causes

Create Resources for the Study of Type 1 Diabetes Genetics:

- ▶ Complete the T1DGC—an unlimited source of DNA for type 1 diabetes gene discovery from informative families representing various ethnic groups.
- ▶ Establish a resource of biological materials that will facilitate research on the genetic basis of type 1 diabetes in those who develop the disease later in life.

Identify Human Genes Causing Type 1 Diabetes:

- ▶ Identify the mechanisms by which the genes within the human MHC contribute to the major genetic susceptibility in type 1 diabetes, and estimate the influence of HLA on other genes with respect to type 1 diabetes risk.
- ▶ Identify and elucidate the mechanism of non-MHC type 1 diabetes susceptibility loci, and develop, test, and validate appropriate statistical methods for characterizing genome-wide gene-gene interactions.
- ▶ Utilize newly developed genomic resources to facilitate testing and cataloging of genomic architecture (SNPs and haplotype blocks) to discover all genes and gene variants affecting susceptibility to type 1 diabetes through a genome-wide association study.
- ▶ Test in prospective clinical studies which genetic factors affect the development of islet autoimmunity, progression to type 1 diabetes, or both.

Use Knowledge About the Genetic Underpinnings of Type 1 Diabetes To Prevent and Treat the Disease:

- ▶ Integrate knowledge of genetic susceptibility into risk assessment targeted at prevention and treatment of type 1 diabetes.

- ▶ Develop scientifically based methods of communicating risk information.
- ▶ Use genetic information to guide the selection of immunomodulatory treatment in new onset patients and islet transplant recipients.

### Environmental Causes

Monitor Rates of Type 1 Diabetes:

- ▶ Monitor the incidence of type 1 diabetes in a representative sample of the U.S. population, as well as in informative populations around the world, to further define the course, and possibly the causes, of the recent rise in type 1 diabetes.

Assess Environmental Causes of Type 1 Diabetes:

- ▶ Complete enrollment into the TEDDY study, and begin well powered and nested case-control studies of children enrolled in TEDDY who have developed persistent autoantibodies to GAD65, IA-2, or insulin, in order to systematically evaluate candidate environmental causes of islet autoimmunity.
- ▶ Define the effects of intrauterine environmental exposures (e.g., nutrition, stress, infections) on islet development and islet (beta cell) gene expression and function.
- ▶ Identify molecular genetic mechanisms by which specific environmental agents may trigger islet autoimmunity and promote progression to type 1 diabetes *in utero*, in early postnatal life, and later in development.
- ▶ Explore the possible role of emerging infectious agents, orphan viruses, and intestinal bacteria in the etiology of type 1 diabetes.

- ▶ Translate novel findings about reduced herd immunity through specific vaccination in the general population and relate this to a possible decrease in herd immunity to common viruses such as human enteroviruses.
- ▶ Explore candidate environmental agents (e.g., food elements, toxins, stress, infectious agents) as triggers for islet autoimmunity and type 1 diabetes in animal models of type 1 diabetes.
- ▶ Establish a resource of biological materials that will facilitate research on the environmental basis of type 1 diabetes in the older population.

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# **GOAL II**

**PREVENT OR REVERSE  
TYPE 1 DIABETES**

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**The *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of large-scale collaborative research groups and clinical trials networks that seek to identify and test novel type 1 diabetes prevention and reversal strategies.**

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The *Special Statutory Funding Program for Type 1 Diabetes Research* has sparked a major expansion of research efforts aimed at preventing or reversing type 1 diabetes. Type 1 diabetes is an “autoimmune” disease that results when the body’s own immune system launches a misguided attack on the insulin-producing beta cells in the pancreas. Harmful immune system cells, including some T cells, are normally eliminated during their maturation. However, in susceptible individuals, these disease-causing T cells initiate an inflammatory process in the pancreas that eventually leads to the destruction of beta cells. The other arm of the immune system—the B cells—produces antibodies that also recognize beta cell proteins. These “autoantibodies” are well-established markers that predict a person’s risk of developing type 1 diabetes. Tests of these antibodies together with tests for genes affecting type 1 diabetes risk in the siblings or offspring of type 1 diabetes patients can predict with great reliability whether the unaffected relatives will develop the disease. This predictive tool, coupled with other new technologies, has given researchers the remarkable ability to design and conduct primary prevention clinical trials.

Attempts to turn advances in understanding the autoimmune basis for type 1 diabetes into a cure have been made for nearly three decades. Importantly, more progress has been achieved in the last 5 years than in the previous 25 years combined, due largely to support by the *Special Funding Program*. Until greater knowledge of genetic and environmental causes of type 1 diabetes is achieved, strategies to prevent or reverse the disease are currently focused on intervening in the immune system’s misguided assault. These strategies must be two-pronged: they must squelch autoimmunity in those who are at risk for or already have the disease, while maintaining or restoring the patient’s own insulin producing capacity. (Goal III addresses another approach for reversing the disease by transplanting insulin-producing cells obtained from donor pancreatic tissue or regeneration of beta cells.)

The immune system provides critical protection against infection, so it is vital that any treatment that modifies its activities is as selective as possible in damping down autoimmunity, while leaving the protective aspects of the immune defense system intact. This delicate balancing act will be achieved by leveraging knowledge about the immune system in general, combined with insights into disease causation, to the development of new treatments.

The *Special Funding Program* supports research consortia and clinical trials networks that promote: collaboration between basic and clinical investigators; delivery of therapeutic agents from the bench to the bedside; improved measurements of disease markers to facilitate the conduct of clinical trials; identification of novel therapeutic strategies; and testing of promising therapeutic agents in people. Notably, the *Special Funding Program* has enabled the creation of a pipeline of therapeutic agents for testing in clinical trials and has also created the infrastructure to test them. As new knowledge is gained about the underpinnings of disease development (e.g., immune system function, beta cell biology, genetic and environmental causes), more strategies for disease prevention and reversal will be identified, which will feed into this critically important pipeline made possible by the *Special Funds*.

## 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 prevent and reverse type 1 diabetes 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.

### **Identification of Insulin as a Possible Disease-**

**Initiating Autoantigen in Type 1 Diabetes:** For years, researchers have struggled to determine which beta cell proteins are key targets of autoimmune attack. Findings in a mouse model of type 1 diabetes, supported by the Autoimmune Disease Prevention Centers, as well as research in humans, now support the notion that the insulin molecule itself is an important, potentially disease-initiating autoantigen. Additionally, other studies have recently identified antigenic targets of the cellular immune response in non-obese diabetic (NOD) mice (islet specific glucose-6-phosphatase catalytic subunit related protein and dystrophin myotonia kinase). There is also continuing interest in the potential role that proteins of neuroendocrine origin may play in the disease in both human type 1 diabetes, as well as in animal models. To a large extent, many of these recent discoveries regarding autoantigen identification were dependent on the development of improved tools for characterizing the immune response associated with beta cell destruction, as well as on access to human tissues made available for research purposes.

### **Development of Outcome Measures for Clinical**

**Trials:** In addition to immune markers, a variety of metabolic markers and their associated tests have also proven valuable to studies of human type 1 diabetes. Long-term studies of type 1 diabetes patients have shown that preservation of the ability to make even small amounts of insulin is strongly

associated with improved control of blood glucose, less hypoglycemia, and reduced risk of eye, kidney, and other diabetes complications. Endogenous insulin production can be determined in patients requiring insulin treatment by measuring C-peptide, a byproduct of insulin production which is co-secreted from the beta cell with insulin. Particularly notable are the recent improvements in the ability of researchers to determine the metabolic activity of individuals with or at-risk for type 1 diabetes. These improvements (e.g., standardization of the C-peptide assay, information on how best to stimulate and characterize residual insulin production in type 1 diabetes patients on insulin therapy) were made possible by the *Special Funding Program*. The FDA is considering use of these measures, which would make clinical trials shorter and less expensive, as a basis for approval of new therapies.

### **Completion of the Diabetes Prevention Trial Type-1 (DPT-1) Oral Insulin Arm in Type 1 Diabetes TrialNet:**

The DPT-1 studied whether injected or oral insulin administration could prevent or delay type 1 diabetes in persons at high- or moderate-risk for the disease. While the DPT-1 did not find an overall protective effect of injected or oral insulin, a subset of trial participants who had higher levels of insulin autoantibodies seemed to benefit from oral insulin treatment, though this result was not definitive. TrialNet is planning a trial to confirm the suggested benefit of oral insulin therapy in people with elevated insulin autoantibodies.



**Tolerance and Regulation of the Immune System:**

Recent studies of animal models have provided insights into type 1 diabetes, such as ascertaining the molecular and cellular defects that underlie the failure to maintain tolerance to beta cells; and identifying immune system cells that are key to regulating tolerance in type 1 diabetes. It is important to note that currently, many of these disease aspects can only be addressed through studies of animal models due to issues of both practicality and technical ability—providing but one of many examples of the importance of animals to type 1 diabetes research. Progress toward understanding tolerance and regulation of the immune response in human type 1 diabetes has also occurred, implicating defects in many cell types as potentially causative in autoimmune disorders such as type 1 diabetes. Similarly, several genes have been identified that contribute to susceptibility to autoimmune disorders because of their ability to modify immune reactivity.

**Advances in Preventing or Reversing Type 1 Diabetes:**

Recent years have seen much excitement about possible treatment strategies stemming from proof-of-principle

experiments in animal models. These include, but are not limited to: anti-CD3, which depletes and/or modifies the function of T cells; CTLA4-Ig, which antagonizes immune activation, e.g., “costimulatory blockade;” and anti-thymocyte globulin, which also depletes T cells. In addition, research on immunosuppression associated with islet transplantation efforts, as described in Goal III, also contributes to the identification of agents that could be used to control autoimmunity in the setting of disease prevention or reversal. Those agents that demonstrate adequate safety profiles have and will continue to move forward in human type 1 diabetes clinical trials, through such programs as Type 1 Diabetes TrialNet or the Immune Tolerance Network. Anti-CD3 is one example of an agent that has seen experimental translation from animal models to investigations in humans. Two research trials of anti-CD3 reported the ability of this agent to preserve metabolic function when administered to people with recent onset type 1 diabetes. With time, it is hoped that this or other agents will become proven components of a cure for type 1 diabetes by promoting disease reversal.

## EVALUATION OF MAJOR RESEARCH CONSORTIA, NETWORKS, AND RESOURCES RELATED TO PREVENTING AND REVERSING TYPE 1 DIABETES

**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.

### Type 1 Diabetes TrialNet (TrialNet)

TrialNet is an international network of investigators, clinical centers, and core support facilities that recruits patients and conducts research to advance knowledge about type 1 diabetes and to test strategies for its prevention and early treatment. TrialNet supports the development and implementation of clinical trials of agents aimed at preventing the disease in at-risk patients and slowing the progression of type 1 diabetes in new onset patients. The network's "Natural History Study" will enhance understanding of how the disease develops in individuals at risk and will thus help in the formulation of future trials. Biological samples collected from study volunteers are being stored at the NIDDK Central Repository, and these valuable resources will be made available to the broader scientific community for further research on type 1 diabetes.

#### Highlights of Progress

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

- *Completed the Diabetes Prevention Trial Type-1 (DPT-1) clinical trial of insulin for the prevention of type 1 diabetes in individuals at moderate and high risk for disease development:* The trial showed that oral or injected insulin administration did not delay or prevent the disease in relatives of type 1 diabetes patients. However, in a subset of the moderate risk patients studied (those with high titers of insulin-reactive autoantibodies), protection may have been observed. Because this result was not definitive, TrialNet is developing an additional study to further evaluate the role of oral insulin in delaying or preventing type 1 diabetes in this subset (scheduled for launch in late 2006).
- *Launched the Natural History Study:* This trial was begun to identify risk factors for type 1 diabetes and document disease characteristics and progression. The Natural History Study will also identify and maintain a pool of individuals who would be candidates for participation in clinical trials. The first phase of the Natural History Study involves identification of those at risk by using a blood test for the presence of diabetes-related autoantibodies to screen close relatives of people with the disease. Thus far, over 13,100 individuals have been screened. Of these, over 300 were found to have positive autoantibodies (indicating increased type 1 diabetes risk) and are undergoing evaluation at regular intervals to monitor for signs of progression to type 1 diabetes. The study expects to increase to a rate of screening of about 20,000 individuals per year. Participants will be offered enrollment in diabetes prevention and early intervention studies as they become available.
- *Launched the Mycophenolate Mofetil-Daclizumab (MMF/DZB) Clinical Trial:* This trial will test whether two immunosuppressive agents, MMF and DZB, will stop the ongoing destruction of any beta cells that are still functioning in new onset type 1 diabetes patients, and if the combination of the two drugs is superior to MMF alone in this regard. Type 1 diabetes results from progressive autoimmune destruction of beta cells. Preservation of remaining beta cells at disease onset is clinically important, because the ability to secrete even small amounts of insulin can make the disease easier to

control and help minimize complications associated with years of inadequate glycemic control. To date, about half of the required participants have been enrolled.

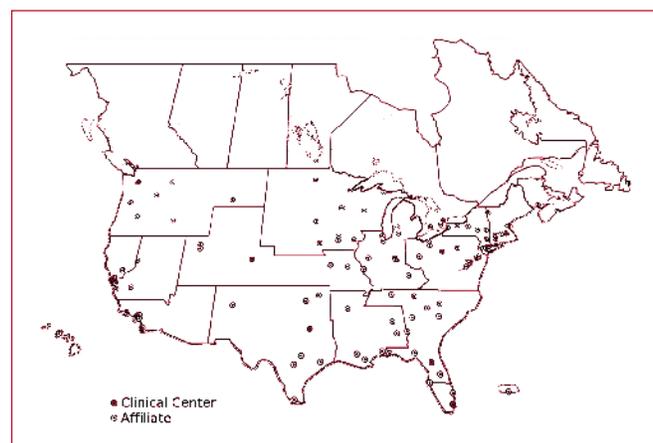
- *Completed recruitment for a clinical study to compare reliability of two tests for beta cell function—the Mixed Meal Tolerance Test (MMTT) and intravenous Glucagon Stimulation Test (GST):* The study has met its recruitment target; 138 patients completed the study. Residual beta cell function (insulin secretion) in patients with type 1 diabetes is known to result in improved glycemic control, reduced hypoglycemia, and reduced risk for complications. This beta cell function is currently best measured by determining levels of C-peptide. C-peptide is useful as an outcome measure in clinical trials: for example, those testing agents to preserve beta cell function in new onset diabetes. There are different ways to stimulate insulin production and, concomitantly, C-peptide production, but it has not been clear which of these conditions is optimal for enabling C-peptide measurement. The MMTT/GST clinical trial compared the reliability and burden on patients of two test conditions for stimulating insulin/C-peptide: one, MMTT, is a liquid meal; the other, GST, is an injection of the hormone glucagon. Results of this study, soon to be reported, will inform the design of future type 1 diabetes clinical trials to prevent or reverse type 1 diabetes in which C-peptide must be measured to determine if the intervention is successful.
- *Launched the T cell Validation Study:* The purpose of this study is to learn which T cell assays are most reliable and reproducible in identifying differences between people with and without type 1 diabetes. This study will facilitate further research toward understanding how type 1 diabetes occurs. Thus far, about half of the required participants have been enrolled toward a goal of 60-100 (30 with diabetes, 30-100 controls).
- *Designed a study to test the effects of the agent “rituximab” (anti-CD20) on progression of type 1 diabetes in new onset patients for launch later in 2006:* This study addresses the role of B cells in the autoimmune destruction of beta cells. In type 1 diabetes, B cells produce antibodies directed against components of the beta cell. Although B cells and autoantibodies do not directly attack insulin-producing cells, it is thought that they may exacerbate such an attack by certain T cells. Rituximab is approved by the FDA for use in other autoimmune diseases. This study will investigate the therapeutic potential of rituximab in type 1 diabetes by investigating whether it can help lower the number of immune B cells in newly diagnosed type 1 diabetes patients and thereby prevent destruction of insulin-producing beta cells that remain at diagnosis.
- *Designed a pilot study to test the role of omega-3-fatty acids in preventing type 1 diabetes:* The Nutritional Intervention to Prevent (NIP) Diabetes Study, for launch later in 2006, is based on observations from epidemiologic studies that children who have received more omega-3 fatty acid (such as from fish)—either in the womb or during the first year of life—have a lower risk of developing type 1 diabetes. This pilot feasibility study will enroll either infants or pregnant women and will randomly assign them to one of two groups: (1) daily omega-3 fatty acid supplements; or (2) placebo (no supplements). During the course of the study, the participants will undergo assessments for immunological markers of type 1 diabetes. Upon fulfillment of the study’s objectives, researchers plan to launch a full-scale trial to test if omega-3 fatty acid supplementation can prevent type 1 diabetes.
- *Designing a study to further evaluate the role of oral insulin in delaying or preventing type 1 diabetes in a subset of the population studied in DPT-1:* See first bullet; expected launch in late 2006. Extensive standardization of antibody measurement is under way to optimize the conduct of this study.

- **Designing Anti-CD3-Exenatide Clinical Trial:** The immunomodulatory agent anti-CD3 has been shown to slow the loss of metabolic function in newly diagnosed type 1 diabetes patients. However, this effect wanes over time. This trial will test whether anti-CD3, combined with exenatide, a newly approved drug for type 2 diabetes that increases insulin production and shows the added benefit of preserving or increasing beta cell mass in animal models, will slow or stop the ongoing destruction of residual beta cells in new onset type 1 diabetes patients. Recruitment will begin in late 2006. This combination is also being considered for a prevention study in relatives of type 1 diabetes patients who are at high risk for developing the disease.

### Anticipated Outcomes

TrialNet is an international clinical research network focused on individuals at risk for or newly diagnosed with type 1 diabetes. Its efforts span the time period from birth in those at high genetic risk to the development of signs of increased risk (for example, autoantibodies), when prevention strategies are particularly urgent, and on through the time soon after diagnosis, when residual beta cell function may afford a unique opportunity for interventions to mitigate disease severity. TrialNet will test the ability of agents to slow or prevent type 1 diabetes, sparing those at risk from developing this devastating disease. TrialNet is also studying agents that can modulate the immune system of recently-diagnosed patients so as to preserve remaining beta cell function and thus make it easier for them to control glucose levels and reduce their burden of complications. In addition to the conduct of clinical trials, the network's extensive recruitment of individuals at risk or with new onset disease is facilitating research into disease progression. Other clinical studies conducted by TrialNet will improve the methodologies used in future type 1 diabetes clinical trials, for example, to assay T cells involved in autoimmune attacks and to stimulate C-peptide production as a measure of residual beta cell function. The infrastructure of TrialNet is also used to enhance other efforts supported by the *Special Funding Program*, such as aiding the Type 1 Diabetes Genetics Consortium with identification of families with two siblings affected with type 1 diabetes and collection of samples for genetic studies from these families.

There is a rigorous process for consideration of studies proposed for conduct through this coordinated clinical research infrastructure, which involves review by experts in diabetes and immunology. As new therapeutic agents are identified through additional studies supported by the *Special Funding Program*, TrialNet's standing infrastructure will be indispensable for the testing of these promising agents in patients. Furthermore, the knowledge gained from TrialNet's Natural History Study will help to spur the design of new prevention and treatment approaches. TrialNet's current position of strength is the result of years of effort in outreach to the diabetes care and research communities, intensive training in



Type 1 Diabetes TrialNet is a network of 18 Clinical Centers working in cooperation with affiliated sites throughout the United States, Canada, Finland, United Kingdom, Italy, Germany, Australia, and New Zealand. This map shows the broad distribution of TrialNet sites throughout the U.S. and Canada. (Image courtesy of Type 1 Diabetes TrialNet.)

research procedures, including sample collection and storage for mechanistic assays (in collaboration with the Immune Tolerance Network), and the establishment of close collaborative ties among clinical diabetes and immunology researchers. TrialNet investigators also take proactive roles in critically reviewing, identifying, and prioritizing promising candidates for trials, considering both clinical feasibility and scientific merit.

### **External Evaluation by Expert Panel**

To supplement evaluation and guidance by TrialNet's Data Safety and Monitoring Board, leading scientific and lay experts were asked to evaluate the progress of TrialNet at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ The concept of a standing infrastructure to test promising therapeutic agents to prevent or slow the onset of type 1 diabetes is of critical importance.
- ▶ TrialNet's completion of the DPT-1 was a significant achievement.
- ▶ It is important to conduct studies that will add scientific knowledge to the field of type 1 diabetes research, even if results are negative.
- ▶ The panel discussed several factors that have limited the rapidity with which TrialNet implements new protocols, including: (1) expansion from the U.S. to international sites; (2) effects of decentralized leadership on management complexity; (3) revised screening procedures; (4) large number of required patients; and (5) current limited availability of therapeutic agents to test.
- ▶ Panel members commended TrialNet for critically analyzing protocols before they are approved and implemented; it is not appropriate to test proposed agents solely because the TrialNet infrastructure exists.

- ▶ Caution in selecting proposed agents for testing should be balanced with the importance of promoting the testing of agents that potentially may be a "breakthrough" in the prevention or treatment of type 1 diabetes.

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

TrialNet 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 the Number of Protocols**

- ▶ TrialNet currently has one completed protocol, three active protocols, and four more scheduled for launch later in 2006. Two additional studies are nearing launch with the Immune Tolerance Network (ITN) as the lead, but with full partnership and recruitment participation from TrialNet. These studies will bring TrialNet near its goal of providing a therapeutic opportunity for nearly every category of diabetes risk.

#### **Recommendation: Identify Highly Innovative Projects**

- ▶ TrialNet has implemented a new process for strategizing and prioritizing the best ideas for implementation. The "Strategies and Prioritization" Committee has been established, which includes top scientists in the diabetes field both within and outside of TrialNet. This Committee considers the universe of ideas, whether formally submitted to TrialNet or gleaned from the field.

**Recommendation: Decrease Time Required for Protocol Implementation**

- ▶ TrialNet has restructured and streamlined the protocol review and implementation process. A subgroup of representatives from the Executive Committee, including the TrialNet Chairman's office, the coordinating center, and the NIDDK, met numerous times to evaluate the procedural roadblocks and to develop a better process. The new process has shortened the review of proposals considerably, as subcommittees now review proposals based on scientific merit, clinical feasibility, ethics, strategy, and prioritization.

**Recommendation: Create a More Rigorous Mechanism To Critically Assess the Scientific Rationale for and Aid in Prioritization Among Agents Proposed for Study**

- ▶ TrialNet has established a rigorous Scientific Review Committee, including members outside of TrialNet. This Committee also considers strategies to improve the innovation and impact of the proposals.

**Recommendation: Institute an Advisory Group Consisting of External Scientists with Expertise in Both Basic and Clinical Research**

- ▶ TrialNet is establishing an External Advisory Committee (EAC) as recommended, which will meet in 2006. In addition, the NIDDK has undertaken to critically review the operations of TrialNet, starting with a review of the Data Coordinating Center on March 2-3, 2006, by a panel of experts in the operation of multicenter clinical trials. The recommendations of this panel regarding the TrialNet Data Coordinating Center will be shared with the EAC. The NIDDK has also appointed a panel of advisors to review TrialNet's procedures and policies for the implementation of mechanistic studies and mechanistic sample collection and distribution. This panel is scheduled to

meet in April 2006, and its recommendations will also be shared with the EAC.

**Recommendation: Enhance Collaborations Between TrialNet and the Immune Tolerance Network (ITN)**

- ▶ TrialNet is committed to working together with ITN at every level. Leadership from both networks have had numerous meetings to discuss joint recruiting, comparable reimbursement of recruiting and clinical costs, prioritization of studies, and sharing data and mechanistic assay policies and procedures. ITN and TrialNet will directly partner on two studies in which ITN takes the lead role. In addition, ITN and TrialNet will work together to implement immunophenotyping using common reagents and a core facility, and for consistency of quality control and data analysis (see section on "Actions Taken in Response to Expert Panel Recommendations" under the ITN later in this chapter for additional examples of collaboration).

**Ongoing Evaluation**

Ensuring continued and ongoing evaluation of TrialNet's study design and progress are a Data and Safety Monitoring Board (DSMB), Steering Committee, and other TrialNet committees, as well as external scientific experts. TrialNet protocol (study) proposals are evaluated by the TrialNet Steering Committee, and relevant protocols are also evaluated by the ITN Steering Committee. The DSMB reviews all TrialNet protocols and informed consent materials and must approve them before implementation. Multiple subcommittees within TrialNet have also been established to address relevant issues. To critically assess the scientific rationale and aid in prioritization among agents proposed for study, TrialNet has established a rigorous Scientific Review Committee, including members external to the TrialNet network. This Committee also considered strategies to improve the innovation and

impact of the proposals. TrialNet is also establishing an External Advisory Committee that will have its first meeting later in 2006, following earlier external advisory committee assessments of specific components of TrialNet, such as the function of the Data Coordinating Center.

### **Coordination with Other Research Efforts**

TrialNet 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.

#### Coordinating Patient Recruitment Efforts:

- ▶ TrialNet and the ITN jointly introduced and advertised the TrialNet Natural History Study and the ITN Insulin Vaccine Study.
- ▶ The SEARCH for Diabetes in Youth study is helping TrialNet recruit eligible participants.
- ▶ All 14 North American TrialNet centers are participating as recruitment centers for the Type 1 Diabetes Genetics Consortium (T1DGC) North American Network.
- ▶ T1DGC assisted TrialNet in establishing international recruitment sites.
- ▶ TrialNet, The Environmental Determinants of Diabetes in the Young (TEDDY), and the Trial To Reduce IDDM in the Genetically At-Risk (TRIGR) have coordinated recruitment efforts to ensure that they are not adversely competing for patient participants in their studies.

#### Enhancing Data Comparison Among Studies:

- ▶ TrialNet, TEDDY, and T1DGC share the same North American laboratory for measurement of autoantibodies. This coordination will permit direct comparison between

results obtained in each study.

- ▶ TrialNet uses laboratories certified through the HbA1c standardization program.
- ▶ The C-peptide Standardization Program included two laboratories from TrialNet in an international comparison effort, the results of which illustrated the need to identify and minimize the major sources of variation in C-peptide measurements in multicenter, multi-laboratory clinical studies.
- ▶ The Diabetes Autoantibody Standardization Program (DASP) provides tools that TrialNet laboratories use to standardize autoantibody data.
- ▶ T1DGC, TrialNet, SEARCH, and TEDDY are all sharing either the same laboratories or laboratory reagents to analyze genetics data. This coordination will permit comparisons of genetics data across all four studies, effectively increasing the power of each in learning which genes play a role in disease onset.

#### Sharing of Other Resources and Information:

- ▶ TrialNet uses services of the ITN, such as biological sample preparation and processing and certification of laboratory coordinators, for the MMF/DZB clinical trial, the anti-CD20 clinical trial, the T Cell Validation Study, and the Natural History Study. These ITN services will be used for most TrialNet protocols currently in development.
- ▶ Protocols potentially of interest to ITN and TrialNet are considered by both consortia to assess the possibility for joint sponsorship.
- ▶ TrialNet and ITN use a common DSMB.

#### Coordinating Research Studies Involving Newborns:

- ▶ TrialNet investigators meet with investigators participating in other type 1 diabetes research studies involving newborns (TEDDY and TRIGR) to discuss opportunities for enhancing coordination and collaboration.

- ▶ TEDDY has shared the following materials with TrialNet investigators who are studying newborns in the NIP Diabetes Study: genetics-screening procedures, data forms, and parts of the Manual of Operation concerning follow-up of high-risk children. Through concerted action to define exclusive study geographic areas, investigators in the two studies have also avoided direct competition for eligible study participants.

**TrialNet Administrative History**

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Components	NIDDK, NIAID, NICHD, NCRR, JDRF, ADA
Website	<a href="http://www.diabetestrialnet.org">www.diabetestrialnet.org</a>
TrialNet consists of 18 centers in North America, Europe, Australia, and New Zealand working in cooperation with 66 additional patient recruitment sites.	



## Immune Tolerance Network (ITN)

The ITN is an international consortium of over 70 scientists and physicians dedicated to evaluating therapies to reduce autoimmunity and other adverse immune responses by inducing, maintaining, and monitoring “tolerance” in humans for islet, kidney, and liver transplantation; autoimmune diseases; and allergy and asthma. The goal of immune tolerance research is to identify strategies to reprogram the immune system in a highly specific way to prevent or inhibit disease-causing or aberrant immune responses. Such damaging autoimmune processes include those that destroy insulin-producing beta cells in type 1 diabetes, or the immune response that destroys transplanted islets. It is important, however, that these strategies not dampen the body’s normal disease-fighting immune mechanisms. Investigators within and outside of the ITN are invited to submit clinical trial proposals for review. The ITN then assists investigators with study development, monitoring, and analysis; access to cutting-edge technologies; and a wide range of other expert scientific and technical support. Clinical trials are augmented by mechanistic studies designed to uncover basic biological features of clinical tolerance which will, in turn, help guide the design of future clinical trials.

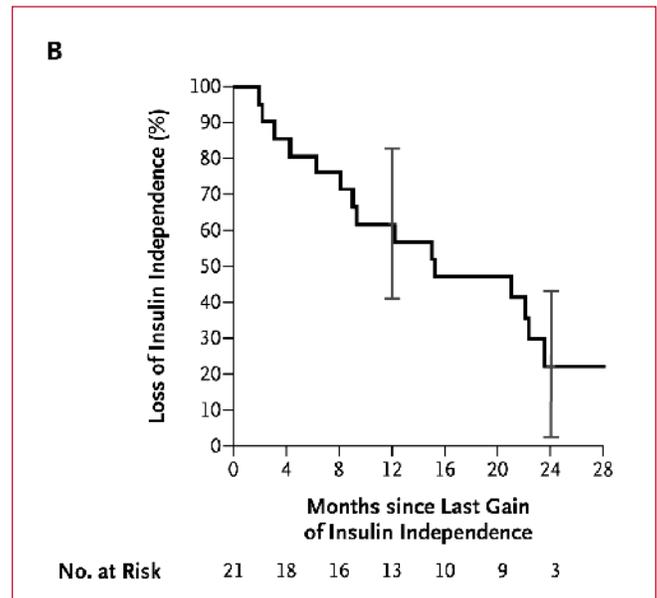
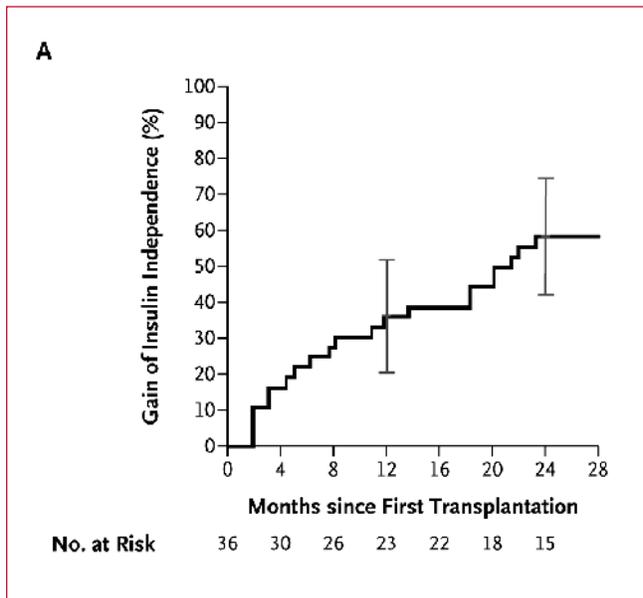
### Highlights of Progress

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

- *Conducted first multicenter trial of islet cell transplantation:* Nine sites in North America and Europe have successfully replicated the “Edmonton protocol” for islet transplantation in the ITN’s multicenter study from 2001-2006. Islet transplantation is still an experimental treatment for type 1 diabetes. (For extensive information on islet transplantation, see Goal III.) The Edmonton protocol was a revolutionary new procedure developed in Canada that greatly improved the outcomes for islet transplantation. As of 1 year post final transplant, 16 of the 36 (44 percent) enrolled participants in the ITN trial have achieved insulin independence with good glycemic control; 5 of 36 patients achieved insulin independence with a single donor islet infusion. Twenty-four of 36 patients remain C-peptide positive (a measure reflecting beta cell function) but continue to require small doses of insulin. 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 confirm and 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. This effort has also established a network of qualified investigators and centers for future islet transplantation studies and will serve as a baseline for future tolerance studies.
- *Determined that autoantibody titers may predict islet transplant success:* Among the aberrant immune processes that occur in type 1 diabetes is the production of “autoantibodies” that recognize beta cell components. Autoantibody levels were measured pre-transplant in patients enrolled in the ITN multicenter study of the Edmonton Protocol. Investigators found that pre-transplantation levels of autoantibodies to two beta cell proteins correlate indirectly with long-term graft survival and insulin-free status following the transplant. If confirmed, this result may lead to the development of biomarkers of graft survival. It also underscores the need to abrogate both the immune system’s reaction to transplanted donor cells and the ongoing autoimmune response.
- *Supported research on a potential therapeutic agent for new onset type 1 diabetes, called the “hOKT3gamma1(Ala-Ala) monoclonal antibody,” or “anti-CD3” monoclonal antibody:* Residual beta cell function in type 1 diabetes patients is

associated with improved glycemic control and reduced hypoglycemia and risk for complications. Thus, it would be greatly beneficial to be able to blunt autoimmunity before all beta cells are destroyed. The anti-CD3 monoclonal antibody being studied is a genetically-engineered antibody that recognizes T cells, a type of immune cell involved in the autoimmune attack. Results from an ITN pilot study confirmed previous work showing that a single course of treatment with the anti-CD3 monoclonal antibody reduced insulin requirements for glycemic control during 18 months of follow up. In addition, this treatment attenuated the decline in patients' endogenous insulin production (as assessed by C-peptide levels in response to the MMTT). The ITN has also launched a larger, open-label, phase II study. As of February 2006, the study had recruited 7 of a planned 81 patients to investigate whether a second course of this anti-CD3 monoclonal antibody administered 1 year after the first treatment, with standard diabetes management, is able to have prolonged or improved effects in people with recently diagnosed type 1 diabetes compared to standard diabetes management alone.

- *Demonstrated that a combination of assays detects type 1 diabetes with high sensitivity and specificity:* ITN investigators showed that no single assay (such as an autoantibody test or any of several other types of assays) distinguishes normal individuals from those with type 1 diabetes. However, the combination of an autoantibody test and two types of assays for T cells identified a high proportion of patients with type 1 diabetes with no false positives. Additional patients are being recruited for this study for further optimization of these techniques. With refinements, assays such as these will play an important role in large-scale screening efforts to identify individuals at risk for development of type 1 diabetes, but who lack first-degree relatives with this disease.
- *Began a study to determine the safety of a potential diabetes antigen-specific immunotherapy, incorporating the insulin B chain, in patients with new onset type 1 diabetes:* Insulin is one of several beta cell proteins recognized by the immune system in type 1 diabetes. It has been hypothesized that treatment with insulin may arrest or slow ongoing autoimmunity in type 1 diabetes so as to preserve beta cell function. ITN-supported scientists have completed enrollment of 12 participants in a study, with follow-up through March 2007. This double-blinded, phase I/II pilot study was designed to examine the safety of a potential insulin B-chain peptide. The study was unblinded in December 2005 to evaluate the interim data in consideration of conducting a larger phase II study in the near future. To date, three participants have completed follow-up on the study. Results of the unblinded data are being reviewed by both the ITN and TrialNet.
- *Plan to launch trial testing thymoglobulin therapy in newly diagnosed type 1 diabetes patients:* Researchers plan to conduct an early phase II study of the safety and efficacy of treating new onset type 1 diabetes patients with an antibody to T cells (thymoglobulin) to determine if it can induce tolerance and thereby preserve beta cell function in these patients. The FDA placed this protocol on clinical hold in November 2005, pending modifications to the study design. The study team will revise the protocol, respond to the FDA's letter, and launch the trial for enrollment in Summer 2006.



The Immune Tolerance Network (ITN) conducted the first multicenter clinical study of islet transplantation using the Edmonton protocol. Panel A shows the interval between the first islet transplant and insulin independence (attained in 21 of 36 patients), and Panel B shows the subsequent loss of insulin independence among 16 of these 21 patients during the next 28 months. However, despite the loss of insulin independence, all patients with an islet transplant who continued immunosuppressive therapy maintained some insulin production. The partially functioning islet transplants protected patients from hypoglycemia. (Images courtesy of Dr. A.M. James Shapiro and reprinted from Shapiro, A.M. et al. *N Eng J Med.* 355: 1318-1330, 2006. Copyright © 2006 Massachusetts Medical Society. All rights reserved.)

### Anticipated Outcomes

The efforts of the ITN are strengthening knowledge of the autoimmune response in type 1 diabetes, testing strategies for blocking destruction of patients' beta cells, and investigating approaches to improve success of transplantation of donor islets. ITN research on assays of the immune system to detect those at risk may help in mitigating the severity of disease onset. Once beta cell-preserving therapies are further developed and tested, improved identification of those at risk will permit more patients to begin early therapy. Research on tolerance-inducing agents brings hope of arresting the autoimmune destruction of beta cells; preservation of some insulin producing function would facilitate glucose control with less risk of hypoglycemia. For those who may undergo islet transplantation, modulation of the immune system is necessary, not only to block the diabetes-specific autoimmune

reactions that destroy beta cells, but also to prevent the general immune rejection that can occur with any transplanted tissue. When cells or organs are transplanted from a donor into a patient, the patient's immune system appropriately sees these as foreign (unless the donor is an identical twin). Consequently, immunosuppressive drugs are necessary to prevent transplant rejection. As another potential treatment strategy, scientists are exploring whether beta cells can be coaxed to regenerate to sufficient levels to restore greater insulin production. Such a treatment would also require blocking of the autoimmune response. However, long-term immunosuppression may carry increased risk of infections and certain types of cancer. Furthermore, many drugs that are effective in suppressing the immune system are actually harmful to beta cells. The ITN's research may lead to more specific drugs that blunt unwanted immune responses without impairing essential immune

functions or damaging beta cells. Thus, these efforts hold promise for improving the lives of patients with type 1 diabetes and for those at risk.

### External Evaluation by Expert Panel

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

- ▶ The goal of creating immune tolerance is critical to combating type 1 diabetes. Significant accomplishments and progress have been made.
- ▶ The ITN conducts studies that have the potential for long-term benefit to type 1 diabetes patients.
- ▶ Major strengths include the ITN's productive interactions with the transplant community and the emphasis on investigator-initiated studies.

### Actions Taken in Response to Expert Panel

#### Recommendations

The ITN 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: Enhance Collaborations with TrialNet

- ▶ The ITN collaborates with TrialNet on the development and implementation of protocols in type 1 diabetes where both parties agree it is beneficial. The studies in which TrialNet and the ITN collaborate include: (1) Natural History Study; (2) MMF/DZB; (3) T Cell Validation Study; and (4) the Effects of Rituximab on the Progression of Type 1 Diabetes in New Onset Patients.
- ▶ The ITN supplies collection kits and training to laboratories for isolating peripheral blood mononuclear cells (PBMCs).
- ▶ The ITN provides RNA isolation on batched specimens.

- ▶ The ITN coordinates the transfer of frozen PBMCs, RNA, and plasma specimens to the NIDDK Repository from laboratories for studies, as applicable.
- ▶ The ITN coordinates the collection of blood and the transfer of samples from the clinical sites to the Flow Core Laboratory for analysis.
- ▶ Research staff from the ITN and TrialNet collaborate on joint studies, communicating daily and convening for 1 hour weekly to discuss critical site/study/technical issues. They also use this time to update each other regarding each Center's status in ongoing studies.
- ▶ The ITN and the TrialNet Coordinating Center participate in monthly meetings, which key study members attend to discuss the status of and any pending problems or issues with ongoing studies.

#### Recommendation: Share Resources with Researchers in Other Consortia

- ▶ The ITN's comprehensive website has publicly available information, such as protocols and descriptions of ongoing studies ([www.immunetolerance.org](http://www.immunetolerance.org)).

### Ongoing Evaluation

Several mechanisms exist to ensure continued and ongoing evaluation of the study design and the progress of the ITN. The ITN Scientific Review Committee is the major decision-making body that evaluates proposals for clinical and mechanistic studies. Recommendations are subject to final approval by the Network Executive Committee. Studies selected for implementation are developed by the Principal Investigator in collaboration with the ITN Clinical Trials Group, the Tolerance Assay Group, and industry partners. During protocol development and implementation, the NIAID provides regulatory, medical affairs, and project management support. Additionally, several external organizations, under contract with the NIAID, provide clinical monitoring, data management, and drug distribution services.

### Coordination with Other Research Efforts

The ITN 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.

#### Coordinating Patient Recruitment Efforts:

- ▶ The ITN and TrialNet jointly introduced and advertised the ITN Insulin Study and the TrialNet Natural History Study.

#### Collaborating To Enhance Islet Transplantation Efforts:

- ▶ Islet Cell Resource Centers (ICRs) isolate and supply human islets for multicentered clinical study sites using the Edmonton Protocol.
- ▶ The Collaborative Islet Transplant Registry (CITR) archives trial results.
- ▶ The Clinical Islet Transplantation Consortium (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 CIT, the ITN, and the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPC-SG) are interested in using similar reagents for islet transplantation or as immune modulators for the treatment of type 1 diabetes.
- ▶ The NHPCSG and ITN share information about scientific priorities and interests for research planning.
- ▶ 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.

#### Sharing of Other Resources and Information:

- ▶ TrialNet uses services of the ITN, such as biological sample preparation and processing and certification of laboratory coordinators, for the MMF/DZB clinical trial and the Natural History Study. These ITN services will be used for most TrialNet protocols currently in development.
- ▶ Protocols potentially of interest to ITN and TrialNet are considered by both consortia with the consideration of joint sponsorship.
- ▶ TrialNet and the ITN use a common DSMB (more information on TrialNet and ITN collaboration can be found in the section titled: “Actions Taken in Response to Expert Panel Recommendations”).
- ▶ ITN-supported investigators have used the Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program for provision and pre-clinical testing of novel reagents.
- ▶ TRIGR and the ITN are coordinating their efforts in the area of T cell assays.
- ▶ ITN researchers receive islets for basic research studies through the ICRs.

#### ITN Administrative History

Date Initiative Started	1999
Date <i>Special Program</i> Funding Started	2001
Participating Components	NIAID, NIDDK, JDRF
Website	<a href="http://www.immunetolerance.org">www.immunetolerance.org</a>

The ITN consists of over 70 world leaders in the clinical and basic science of immune tolerance from academic research institutions around the world.

## Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers)

The Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers) engages in scientific discovery to advance knowledge toward the prevention and regulation of autoimmune diseases such as type 1 diabetes. The Prevention Centers aim to create improved models of disease pathogenesis and therapy to better understand immune mechanisms. These models will provide opportunities for prevention strategies and be used as validation platforms with which to test new tools applicable to human studies. They will also encourage core expertise and collaborative projects designed for rapid translation from animal to human studies—emphasizing the development of surrogate markers for disease progression and/or regulation, which could be used in the context of clinical trials. This research will help uncover new approaches for halting the development of autoimmune diseases prior to clinical onset by mechanisms other than global immunosuppression.

### Highlights of Progress

The progress that the Prevention Centers have made as of March 1, 2006, includes the following advances. Researchers are building understanding of the cells, molecules, and pathways involved in the autoimmune destruction of beta cells and are revealing opportunities for the design of new therapeutic approaches.

- Identified insulin as a primary target for the autoimmune response in the NOD mouse model of diabetes: Mice have two insulin genes, and generation of a NOD mouse lacking the insulin 1 gene revealed that it is required for development of insulinitis and diabetes. Subsequent experiments showed that diabetes did not develop in NOD mice engineered to produce a slightly altered insulin molecule not recognized by the mouse's immune system. This research suggests that autoimmune reaction against insulin may be a critical initiator of the pathway toward beta cell destruction.
- Developed biological tools to identify certain types of T cells that can attack beta cells based on recognition of the beta cell protein GAD65: These tools are "MHC class II tetramers," which are constructed to contain a segment of the GAD65 protein. Researchers can use these tools to retrieve, quantify, and characterize GAD65-reactive T cells from patients and individuals at-risk for the disease. Such T cells are a potential marker of early disease, and this research will increase understanding about the destructive autoimmune response that underlies type 1 diabetes.
- Characterized functional properties of cells called "CD4+CD25+ regulatory T cells," which can help protect against autoimmune disease by suppressing the activities of the autoimmune-reactive T cells, as well as functional defects in this T cell subset in humans with autoimmune disease.
- Initiated the "NOD Roadmap" project to build understanding of type 1 diabetes through intensified research on the NOD mouse model of the disease: This research will involve creating a comprehensive description of genes that are turned on, proteins that are made, and functioning of the immune system in the NOD mouse during development of insulinitis (a condition preceding type 1 diabetes) and diabetes.
- Developed tools for using proteomics technology (which enables analysis of large numbers of proteins) to facilitate detection of autoantibodies and other markers of autoimmune disease.
- Determined mechanisms by which blockade of a particular molecular interaction between immune cells can prevent or modulate the course of diabetes and other autoimmune diseases: In these studies, scientists administered to mice an agent that blocked the interaction between two important molecules. One molecule, called CD154, exists on the surface of many T cells, and another molecule, called CD40, is present on other types of immune cells. One of their findings

was that blocking the CD154-CD40 interaction resulted in induction of a novel type of cell that is able to prevent the onset of type 1 diabetes in mice.

- Funded 48 pilot projects, including investigations to test hypotheses about the biology of type 1 diabetes, and projects to develop reagents and resources for further research.

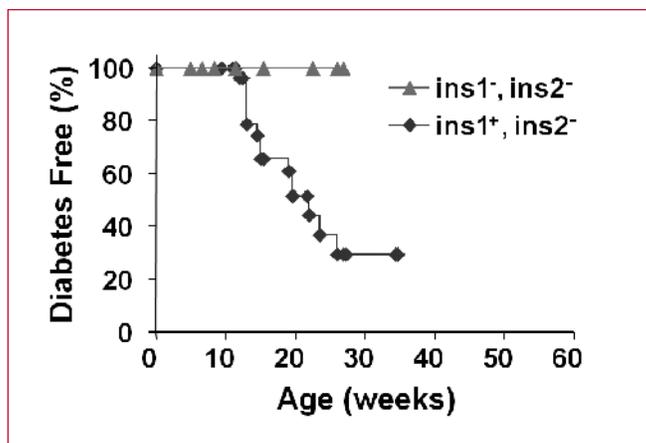
### Anticipated Outcomes

The Prevention Centers support a multidisciplinary collaborative network of investigators focused on understanding the immune mechanisms that underlie autoimmunity and autoimmune diseases, approaches to modulation of the immune system, and the application of this knowledge toward the prevention of these chronic, debilitating diseases. The immune system is enormously complex, with the capacity to attack an extraordinary number of different types of substances. As the immune system targets and fights numerous types of infectious agents, it also produces cells and antibodies that recognize parts of the body, or “self.” Normally, the immune system employs mechanisms, not yet completely understood, for eliminating self-reactive components; this process is referred to as “tolerance.” In type 1 diabetes, however, the immune system goes awry and attacks insulin-producing beta cells. Any medical intervention to prevent type 1 diabetes should ideally be as selective as possible to squelch autoimmunity without impairing the immune system’s capacity for fighting infection. An example of one area of the Prevention Centers’ research is thus to identify and characterize cells of the immune system, such as certain types of T cells that attack and destroy the body’s beta cells. Another research area is to define the beta cell-derived molecules that are targeted for autoimmune attack. The Prevention Centers are also investigating how other aspects of the immune system, or experimental manipulations that alter the immune system, may confer protection against autoimmunity. Results of this research will open avenues for the design and testing of new therapeutic strategies for modulating the immune system to prevent autoimmune destruc-

tion and for developing markers for disease progression or regulation.

### External Evaluation by Expert Panel

To supplement evaluation and guidance received from external advisors who attended the Prevention Centers’ 2005 all-investigator meeting, leading scientific and lay experts were asked to evaluate the progress of the Prevention Centers at an *ad hoc* planning and evaluation meeting convened by the NIH



Insulin is a key autoantigen in the development of type 1 diabetes: Mice have two insulin genes—insulin 1 (ins1) and insulin 2 (ins2). To address the role of insulin in type 1 diabetes development, researchers in the Cooperative Study Group for Autoimmune Disease Prevention genetically engineered mice to make a special insulin molecule that lowered glucose but was not recognized by the immune system, while at the same time, “knocking out” one or both of the mice’s own insulin genes. Mice that lacked both of their insulin genes did not develop diabetes (▲). In contrast, most of the mice that expressed ins1 developed diabetes (◆). These data suggest that insulin may be the critical initiator of the autoimmune destruction of insulin-producing pancreatic beta cells that leads to type 1 diabetes. (Figure courtesy of Dr. George Eisenbarth and adapted by permission from Macmillan Publishers Ltd: Nature. 435: 220-223, 2005.)

in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ This research effort is important to pursue because understanding autoimmunity in general is a cornerstone of type 1 diabetes research.
- ▶ Research supported through this Group is carried out through two major arms: (1) the five members; and (2) pilot and feasibility projects.
- ▶ This research Group has made progress toward all of its major goals.
- ▶ An interesting project is the “NOD Roadmap,” which aims to study the life history of the NOD mouse (a model for type 1 diabetes) from 1-20 weeks of age. The Group has made progress in this research endeavor.
- ▶ Expansion of regulatory T cells is a promising area for future investigation.
- ▶ Future research opportunities include: (1) increasing synergy by tackling large scientific projects; and (2) identifying ways to translate research studies from mice to humans.
- ▶ The panel stressed that the existence of a Cooperative Study Group is crucial to advancing the autoimmunity research field. Increased interaction among individual researchers in this Group would help to achieve synergistic scientific progress “over and above” what could be supported through regular investigator-initiated research projects.
- ▶ The panel endorsed the Group’s pilot and feasibility award mechanism as a venue to attract new research talent. Awards are made to participants within and outside the Group. The NIH and the Group should identify ways to advertise the pilot and feasibility program widely and make it available to the broader research community. For example, the Group could develop a website, and funding opportunities could be announced on relevant NIH websites.

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

The Prevention Centers 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: Promote Research in the Expansion of Regulatory T Cells**

- ▶ Four new pilot projects on the expansion and function of regulatory T cells were initiated since January 2005. Three focus directly on the generation of regulatory T cells; one of these and the fourth project also include deeper mechanistic studies of regulatory T cell function.

### **Recommendation: Increase Sharing of Data and Information Between Prevention Centers**

- ▶ The generation of complex amounts of data from the NOD Roadmap project emphasized to the individual Prevention Center investigators the importance of establishing data-sharing mechanisms. It has been agreed that these data will be initially hosted by the Barbara Davis Center website and mirrored at other locations. Further sharing of data and information will be facilitated by implementation of a dedicated Prevention Centers website in the next grant year (see below).

### **Recommendations: Increase the Synergy of the Prevention Centers by Tackling Large Scientific Projects and Increase Interaction Among Individual Researchers in the Group**

- ▶ In recognition of the need to increase synergy within the limitations of a budget that would allow only a few projects the size of the NOD Roadmap, the Prevention Centers have recently focused on projects that will promote synergy through use of common research platforms and datasets. Examples include:



- A pilot project on generation of genetically-engineered mouse models, in which retroviral vectors are used to drive the expression of autoreactive T cell receptors. This experimental system could promote synergy among the Prevention Centers. Identical retroviral constructs can be used in different experimental settings, thereby permitting useful comparison and verification of results, and facilitating group planning and future directions.
- A project focused on identification of mechanisms of heritable immune trait variations by combining the HapMap with high-throughput cellular and immunologic phenotyping of Human Genome Diversity Cell Line Panel (HGDP). This project will begin to bridge—in an unbiased way—the gap between genetic susceptibility to autoimmune disease, as defined by gene association and family studies, and the biochemical mechanisms of susceptibility or resistance to disease. The tools developed in this project will provide a common technological platform and phenotype dataset that will not only promote synergy among the Prevention Centers investigators, but should also be of great use to other investigators.

**Recommendation: Identify Ways To Translate Research Studies from Mice to Humans**

- ▶ Although the overall mission of the Prevention Centers focused on pre-clinical studies, often using small animal models, the Centers are sensitive and responsive to the need for both human and animal studies, and for translation from animal to human studies (and vice versa). Thus, while only 3 of the 11 main projects originally funded to establish the Centers were focused on human studies, 20 of the 48 pilot projects funded to date (42 percent) are primarily or completely focused on human studies, reflecting the Centers’ emphasis on using discretionary funds to bridge gaps between animal and human studies.

Primary examples include:

- A project that aims to recapitulate the development of diabetogenic autoreactivity in a mouse model;
- A project that is adapting a genetic library to probe functions of human T regulatory cells;
- Ongoing discussions within the Group of ways to pursue a project similar to the NOD Roadmap project in humans (this project is not yet funded).

**Recommendation: Identify Ways To Widely Advertise the Pilot and Feasibility Program To Make It Available to the Broader Research Community (Develop a Website)**

- ▶ A website will be implemented after the award of the new Prevention Centers grants, currently scheduled for July 2006. This website will integrate all Prevention Centers activities, including availability of the pilot and feasibility program and sharing of data among the Centers and with the immunology community.

**Ongoing Evaluation**

Continued and ongoing evaluation of the study design and the progress of the Prevention Centers are ensured through Steering Committee meetings, annual all-investigator meetings, and external input. The Prevention Centers Steering Committee meets to discuss ongoing pilot projects and new pilot proposals as well as the overall progress of the group. External reviewers attended the 2005 all-investigator meeting to provide feedback on the accomplishments and direction of the program.

**Prevention Centers Administrative History**

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Components	NIAID, NICHD, NIDDK, ORWH, JDRF
This Consortium consists of five centers in the United States.	

## **Standardization Programs: Diabetes Autoantibody Standardization Program (DASP); C-peptide Standardization; and Improving the Clinical Measurement of Hemoglobin A1c (HbA1c)**

The purpose of these programs is to develop and implement standardization programs designed to improve the measurement of: (1) aberrant molecules called “autoantibodies,” which are predictive of type 1 diabetes; (2) C-peptide as an indicator of insulin production; and (3) hemoglobin A1c (HbA1c) as an indicator of glycemic control. Such improvements and standardization will greatly advance both research and patient care.

### **DASP**

DASP seeks to improve the measurement of autoantibodies in blood that are predictive of type 1 diabetes, and to decrease laboratory-to-laboratory variation. Autoantibody production reflects abnormal and destructive immune system functioning. A normal immune system is designed to fight infections; one part of this complex process is the production of antibodies that target infectious agents. The immune system of a person who has—or is developing—type 1 diabetes, however, also makes “autoantibodies” that recognize insulin and other beta cell-derived molecules. Autoantibodies are currently the best predictors of the onset of type 1 diabetes before the appearance of clinical symptoms. In combination with genetic screening, autoantibody tests are used to identify individuals at elevated risk of developing type 1 diabetes and to characterize autoimmunity. DASP sets of serum samples are used as standards to evaluate the performance of diabetes laboratories throughout the world and serve as reference materials for developing new methods and technologies. DASP also provides training and information to guide other laboratories in improving their performance.

### **C-peptide Standardization Program**

This program aims to establish reliability in measurements of C-peptide, which is a byproduct of insulin production by beta cells and thus useful as a marker of beta cell function. In clinical trials of agents designed to prevent the disease in at-risk persons, or to preserve beta cell function in individuals with new onset type 1 diabetes, C-peptide will be used as an outcome measure that indicates insulin production. Residual beta cell function is associated with better glycemic control, lower risk of hypoglycemia (discussed in Goal IV), and lower risk of long-term diabetic complications.

### **National Glycohemoglobin Standardization Program (NGSP; HbA1c Standardization Program)**

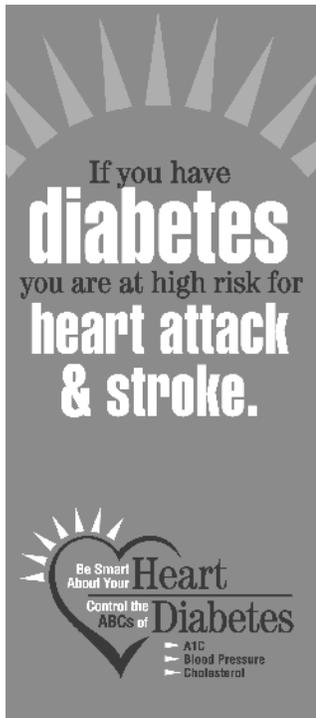
The purpose of the NGSP is to achieve standardization and reliability in measures of HbA1c, a component of blood that is a good surrogate measure of long-term blood glucose control and, as such, reflects risk of diabetic complications. The correlation between HbA1c levels and risk for complications was demonstrated in the Diabetes Control and Complications Trial (DCCT), as well as another trial, the United Kingdom Prospective Diabetes Study. Through efforts to improve HbA1c testing so that clinical laboratory results can be related directly to the results of the DCCT, this program will enable healthcare providers and patients to accurately and meaningfully assess glycemic control and risks for complications. The standardization of HbA1c measures is essential to public health efforts, such as those of the National Diabetes Education Program (NDEP), to improve diabetes control nationwide so that the public can reap the benefits of clinical trials proving that complications can be delayed or prevented. This effort also allows researchers to better evaluate a patient’s risk for complications and fosters comparison of results across

multiple studies worldwide. The NGSP consists of a Steering Committee and a Laboratory Network. The NGSP network interacts with manufacturers and laboratories to assist with calibration and to certify methods as traceable to the DCCT. The NGSP also works with the College of American Pathologists to assign HbA1c values to proficiency testing specimens for better evaluation of HbA1c results in clinical laboratories.

### Highlights of Progress

The progress that the Standardization Programs have made as of March 1, 2006, includes:

- DASP conducted and presented workshop evaluations of key international diabetes laboratories in 2000, 2002, 2003, and 2005.
- DASP validated improvement of two different technologies for measuring autoantibodies.
- DASP documented improvement in performance of the insulin autoantibody assay for laboratories with consistent participation in the DASP Training Program.
- DASP created laboratory reference materials (blood samples) from type 1 diabetes patients and healthy people that are available to ensure assay quality and to support further technology development.
- The C-peptide program evaluated the stability of C-peptide and effects of common interferences. The program also coordinated an international laboratory comparison of C-peptide measurement. The results of the first inter-laboratory comparison trial are being prepared for publication. This research is crucial for optimizing measurement techniques and standardizing results.
- The CDC HbA1c laboratory and the NGSP have participated in efforts of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) to develop a “higher level” reference method for measuring HbA1c. This reference method was approved by the IFCC and is now the basis for uniform standardization of HbA1c assays worldwide. The IFCC Working Group also developed a mathematical equation to facilitate comparison among results obtained by this IFCC reference method and the NGSP, as well as with methods in Sweden and Japan.
- For HbA1c measurements, between 1996 and 2006, there was an increase in the number of methods and laboratories certified by the NGSP as traceable to the DCCT. Methods and laboratories are certified each year. In 2005, the NGSP certified 63 HbA1c diagnostic methods and 41 laboratories. Nearly all laboratories worldwide are using methods that are traceable to and certified by the NGSP.
- Proficiency testing data also showed a decrease in the variability of HbA1c measurements among laboratories.



Standardization of the HbA1c test supported the development of a national education campaign based on “knowing your HbA1c number.” Most people with diabetes are encouraged to keep their HbA1c level below 7 percent to prevent or delay the development of diabetes complications, including heart attack and stroke. The campaign is sponsored by the National Diabetes Education Program, which is a partnership of the NIDDK and CDC ([www.ndep.nih.gov](http://www.ndep.nih.gov)).

### Anticipated Outcomes

The autoantibody, C-peptide, and HbA1c standardization programs are extensive efforts to improve laboratory measures of critical markers for type 1 diabetes risk and disease progression. Such improvements are important to the success of multicenter clinical trials as different participating laboratories must be able to obtain measurements that are comparable and can be meaningfully analyzed together. Research progress will also be enhanced when the results of different trials are based on standardized measures to facilitate comparison. Patients and their healthcare practitioners will be better able to ascertain what a given blood test means in terms of health risks and treatment plans when test results are sufficiently reliable for comparison with relevant research studies. As a result of research toward standardizing autoantibody testing and identifying new biomarkers for predictive assays, those at risk for type 1 diabetes may be diagnosed earlier, permitting earlier

intervention to diminish disease severity. Improved measurement techniques for C-peptide will impact research on agents that can preserve beta cell function, particularly in those with new onset diabetes. Improvements in HbA1c testing will facilitate implementation of a national and global strategy to reduce the complications associated with diabetes through proper blood glucose control. The standardization programs will thus have wide-reaching implications for researchers, clinicians, and patients.

### External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance received from participants at workshops and meetings of the Immunology of Diabetes Society (IDS) and others with relevant expertise, leading scientific and lay experts were asked to evaluate the progress of the Standardization Programs at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ These programs are key for advancing research on predicting susceptibility to type 1 diabetes and preventing the disease. For example, autoantibodies are used to predict if a person may develop type 1 diabetes, and C-peptide measurements are used to determine if strategies to prevent or reverse the disease are successful.
- ▶ The programs have had many accomplishments, have been managed well, and can be considered a “success story.”
- ▶ An important component of the programs is the training that is provided to other laboratories and researchers.
- ▶ These studies would not be successfully funded through an NIH R01 grant mechanism, so these programs are an appropriate mechanism for conducting this type of research.
- ▶ This investment of type 1 diabetes *Special Funds* could have a large payoff in terms of the importance of these assays to future clinical research efforts.

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

The Standardization Programs 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: Pursue Research To Identify New Surrogate Markers That Can Predict Disease Onset or Monitor Disease Progression**

- ▶ In addition to providing samples for research for several individual groups, a collaboration with the NIDDK-funded Proteomics Consortium was established. Studies are under way using DASP samples to evaluate the potential for proteomics to improve the sensitivity and specificity of the prediction and diagnosis of type 1 diabetes.
- ▶ A new request for applications was issued entitled, “Biomarkers of Autoimmunity of Type 1 Diabetes” for first funding in FY 2006. This initiative will fund grants focused on biomarker identification/validation in humans.

### **Recommendation: Bolster the Research Efforts on C-Peptide Measurement and Standardization**

- ▶ The C-peptide standardization program completed an initial stability study and laboratory comparison study in 2005. In early 2006, another laboratory comparison study was initiated to evaluate improvement in C-peptide results since the initial comparison.

### **Recommendation: Encourage International Research Laboratory Participation in Standardization Programs**

- ▶ Participation in DASP is encouraged by the efforts of the IDS and by publication manuscript reviewers. DASP data play a key role in harmonizing the autoantibody assays in type 1 diabetes consortia. Forty-seven key diabetes laboratories in 18 countries participated in DASP 2005.

- ▶ Over 70 percent of all laboratories certified by the NGSP are outside the U.S. The NGSP certified laboratories are located in the U.S., Europe, Asia, South America, and Australia. Laboratories in the U.S., Europe, and Asia are currently participating in C-peptide comparison studies.

## **Ongoing Evaluation**

Continued and ongoing evaluation of the research and progress of the Standardization Programs is carried out as described below.

*DASP:* DASP efforts are managed by the IDS Autoantibody Standardization Committee and the CDC collaborator. The activities and progress are reviewed by IDS participants at the workshop presentations at the IDS meetings, and additional input is periodically sought from the IDS president and other prominent scientists in the field.

*C-peptide:* The C-peptide standardization program has project oversight from the CDC. In addition, a C-peptide Standardization Advisory Committee makes recommendations for research studies and assists in evaluation of results.

*HbA1c:* The effort to improve and standardize the measurement of HbA1c is divided between the CDC and the NGSP (with CDC support) at the University of Missouri. The CDC and the NGSP Laboratory also participate as members in the International Federation of Clinical Chemistry Reference Laboratory Network for HbA1c Measurement.

## **Coordination with Other Research Efforts**

The Standardization Programs 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 collaborative efforts, please see Appendix 2.

#### Enhancing Quality and Standardization of Laboratory Measures in Multicenter Clinical Trials:

- ▶ DASP interacts with the TEDDY, T1DGC, and TrialNet autoantibody labs, by providing laboratory materials and proficiency testing to facilitate their autoantibody measurements.
- ▶ The C-peptide program included two laboratories from TrialNet in an international comparison effort, the results of which illustrated the need to identify and minimize the major sources of variation in C-peptide measurements in multicenter, multi-laboratory clinical studies.
- ▶ TrialNet, EDIC, and other clinical studies supported by the *Special Funding Program* use laboratories certified through the NGSP.

#### Improving and Developing Technology:

- ▶ Because of limitations associated with autoantibody testing, DASP is working with NIDDK-supported investigators studying proteomics and type 1 diabetes, and collaborating with the Pacific Northwest National Laboratory, to find new biomarkers to improve diagnosis of and prediction of risk for this disease. This collaborative project will use blood samples collected by DASP from newly diagnosed type 1 diabetes patients and healthy people. The samples will be analyzed with proteomic and metabolomic technologies: that is, large-scale profiling and characterization of the component proteins and small molecules, respectively. Differences identified between samples from patients and healthy individuals can be further investigated for potential predictive or diagnostic value.

#### Standardization Programs Administrative History

##### DASP

Date Initiative Started	1998
Date <i>Special Program</i> Funding Started	1998
Participating Components	CDC, NIDDK, Immunology of Diabetes Society
Website	<a href="http://www.idsoc.org/committees/antibody/dasphome.html">www.idsoc.org/committees/antibody/dasphome.html</a>

##### C-peptide

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2003
Participating Components	CDC, NIDDK, C-peptide Standardization Advisory Committee, and University of Missouri

##### NGSP (HbA1c)

Date Initiative Started	1996
Date <i>Special Program</i> Funding Started	1998
Participating Components	CDC, NIDDK, NGSP
Website	<a href="http://www.ngsp.org">www.ngsp.org</a>

The HbA1c program is carried out at the CDC-supported National Glycohemoglobin Standardization Program (NGSP), as well as the National Diabetes Laboratory at CDC, both members of the International Federation of Clinical Chemistry (IFCC) Reference Laboratory Network for HbA1c; the NIDDK also funds this effort.

## **Trial To Reduce IDDM in the Genetically at-Risk (TRIGR)**

TRIGR is an international clinical trial to determine, for infants at risk for type 1 diabetes, whether weaning to extensively-hydrolyzed formula, as compared to standard cow's milk formula, will reduce the risk of developing diabetes-predictive autoantibodies and, ultimately, type 1 diabetes. Environmental factors, such as exposure during infancy to foreign proteins from food, may interfere with normal immune system development in genetically-susceptible individuals, and formula is usually the first foreign food given to infants as they are weaned from human breast milk. Standard cow's milk formula contains proteins that are intact and thus capable of inciting the immune system. Hydrolyzing proteins breaks them into very small pieces, which are much less likely to elicit an immune response, and prior research has suggested that weaning to hydrolyzed (versus intact-protein) formula may reduce risk of type 1 diabetes. The first phases of TRIGR are extensive, multi-national efforts to identify several thousand infants at risk for type 1 diabetes by recruiting pregnant women who have the disease, or an affected family member, and subsequent screening of the infants for diabetes-associated variants of certain immune system genes (HLA genes). As part of the study, exclusive breastfeeding will be encouraged, but once this is no longer possible, babies will enter the intervention portion of the study by being randomly assigned to receive either standard or extensively-hydrolyzed formula (up to age 8 months). Follow-up monitoring will assess autoantibody development and diabetes incidence up to age 10 years.

### **Highlights of Progress**

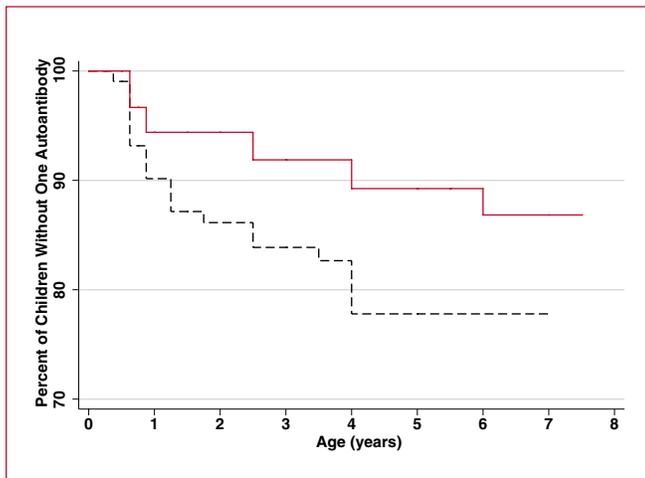
The progress that TRIGR has made as of March 1, 2006, includes:

- Recruited over 4,740 pregnant women toward the goal of 4,936.
- Screened over 4,220 infants for diabetes-related HLA genotype.
- Entered 1,770 eligible infants into the intervention portion of the study (began receiving hydrolyzed or intact-protein formulas).
- Collected over 70,280 blood samples for antibody analyses.
- Met all study milestones in terms of recruitment and protocol compliance with forms, tests, and visits.
- Successfully applied for continuation of the study in competitive NIH peer review.

### **Anticipated Outcomes**

TRIGR is a large-scale, well-coordinated clinical trial to test the effect of a dietary intervention during infancy on the development of type 1 diabetes in genetically-susceptible individuals. If the results of this trial show that weaning to hydrolyzed infant formula, as compared to standard formula, reduces incidence of type 1 diabetes, then it will have validated a practical way to alter the course of autoimmunity development and reduce type 1 diabetes incidence in young children. TRIGR builds on prior research in animals and on a pilot study in humans that investigated the association of different

infant formulas with autoantibody appearance. It has been hypothesized that diabetes-related autoimmunity may be triggered when the immature gut of an at-risk infant encounters foreign dietary proteins. The use of extensively-hydrolyzed formula during weaning would delay the introduction of more complex, intact foreign proteins. Thus, TRIGR may also shed further light on the role of the gut and its immune system in the development of type 1 diabetes. Additionally, upon completion of recruitment, TRIGR will have the largest international experience in the identification, recruitment,



Results of a pilot study preceding the ongoing Trial to Reduce IDDM in the Genetically At Risk (TRIGR), which randomized newborns receiving formula to either an intervention formula (hydrolyzed proteins; solid red line) or standard cow's milk formula (dashed line). Follow-up analysis showed that 22 percent of children who received the standard formula developed at least one autoantibody predictive of type 1 diabetes, while only 13 percent of children who received the intervention formula developed at least one autoantibody. This finding in the small pilot study is now being tested in the full-scale TRIGR study, which is currently under way. (Figure courtesy of Dr. Hans Åkerblom and adapted with kind permission of Springer Science and Business Media from Åkerblom, HK et al. *Diabetologia*. 48: 829-837, 2005.)

and follow-up of newborn infants at risk. The blood specimen and information repository may permit potential contribution to other research on environmental determinants of diabetes, such as the TEDDY study (see Goal I). The potential for a dietary modification in infancy to reduce type 1 diabetes (along with biological data on the very large number of genetically susceptible infants being recruited for study) makes the TRIGR study enormously beneficial to families at risk.

### External Evaluation by Expert Panel

To supplement ongoing evaluation and guidance from an External Data Safety Monitoring Board/Advisory Panel focused on TRIGR, leading scientific and lay experts were asked to evaluate the progress of TRIGR 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 study has made excellent progress.
- ▶ If the results of the trial are affirmative and show a decrease in autoantibodies in children first exposed to an extensively-hydrolyzed formula, then the study has the potential for making a positive impact on patient care.
- ▶ The natural history aspect of the study could provide insights into disease pathogenesis, particularly if it is integrated with the TEDDY study.
- ▶ A major strength of this study is that the participant retention rate is extremely high.

### Actions Taken in Response to Expert Panel Recommendations

TRIGR 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 Collaboration, Integration, and Coordination with the TEDDY Consortium

- ▶ Representatives from both TRIGR and TEDDY participated in a type 1 diabetes consortia coordination meeting that the NIDDK convened in May 2005. The purpose of the meeting was to identify opportunities to enhance collaboration among all of the research consortia studying type 1 diabetes. Prior to the larger meeting, representatives from consortia studying newborns (TEDDY, TRIGR, and Type 1 Diabetes TrialNet) met to discuss how to obtain the most useful information when looking at these studies as a group. Common data variables across the studies and future analytic strategies were discussed.
- ▶ TRIGR and TEDDY study investigators have met to consider using the TRIGR network to enhance accrual to TEDDY for first-degree relatives when TRIGR accrual ends.



- ▶ TRIGR and TEDDY laboratory investigators are participating together in harmonization efforts to bring uniform standards to autoantibody assays.

**Recommendation:** Combine Data from TEDDY and TRIGR To Foster the Future Conduct of Analyses

- ▶ TRIGR and TEDDY have implemented similar standards in data collection and entry, thus permitting direct comparison between results obtained in each study relevant to nutrition and to diabetes-associated variants of certain immune system genes (HLA genes).

**Recommendation:** Create Mechanisms To Make Results of the TRIGR Studies Generalizable to the U.S.

- ▶ TRIGR recruits from both the U.S. population as well as sites worldwide. Eligibility criteria are based upon HLA risk levels, thus the results of the study would be generally applicable to anyone in the U.S. population who has a risk-conferring HLA genotype. In addition, U.S. sites contribute the majority of minorities to the study from which study results can be assessed for these special populations. Also, U.S. infant feeding practices are readily identifiable and can serve as a basis for considering the generalizability of study results specifically to the U.S.

**Ongoing Evaluation**

To ensure continued and ongoing evaluation of the study design and the progress of TRIGR, the NICHD has established an External Data Safety Monitoring Board/Advisory Panel for this trial. Additional critical entities include the trial's International Coordinating Center, which integrates operations for all regions of the TRIGR Study Group, maintains and validates documents related to the operations of TRIGR, and is in charge of developing study forms and the Manual of Operations. A Data Management Unit is responsible for data management systems; monitoring the study for protocol

compliance, adverse events, and other issues; and data analysis and reporting. There are also a number of working committees focused on such topics as nutritional intervention, ancillary studies, and internal safety monitoring, among others.

**Coordination with Other Research Efforts**

TRIGR 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.

Coordinating Research Studies Involving Newborns:

- ▶ TRIGR investigators have met with investigators participating in other type 1 diabetes research studies involving newborns (TEDDY and TrialNet) to discuss opportunities for enhancing coordination and collaboration.
- ▶ TEDDY and TRIGR share the same Data Coordinating Center. This coordination has resulted in implementation of similar standards in data collection, entry, management of quality control, and analyses for both studies.
- ▶ TRIGR and TEDDY investigators are considering collaborative efforts on recruitment after TRIGR accrual ends. Both groups are also considering a follow-up intervention protocol.

Coordinating Patient Recruitment Efforts:

- ▶ Two SEARCH sites are assisting with TRIGR recruitment by providing brochures and other information about TRIGR.
- ▶ TRIGR, TrialNet, and TEDDY have coordinated recruitment efforts to ensure that they are not adversely competing for patient participants in their studies.

Enhancing Data Comparison Among Studies:

- ▶ As described previously, TRIGR and TEDDY have implemented similar standards in data collection and entry.
- ▶ TRIGR and the ITN are coordinating their efforts in the area of T cell assays.

**TRIGR Administrative History**

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Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Date TRIGR Successful Recompensation	2006
Participating Components	NICHHD, the Canadian Institutes of Health Research, the European Foundation for the Study of Diabetes, the European Union, JDRF, the Netherlands Diabetes Foundation, and industry
Website	<a href="http://www.trigr.org">www.trigr.org</a>

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TRIGR is taking place at 77 sites in 15 countries including the United States, several European countries, Canada, and Australia.

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## 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 preventing or reversing type 1 diabetes responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- ▶ "The grant has had a huge impact on my career. Being my first extramural grant award, it enabled me to establish my laboratory and publish my first several papers, which became the basis of a successful R01 application. I also recently received tenure and promotion at my institution."
- ▶ "Support from this *Program* allowed me to develop an interest in diabetes and gain new expertise in autoimmunity. As a result, type 1 diabetes is presently the major focus of my research. Most importantly, this high-risk application allowed me to make a career shift from performing basic science to bench to bedside research."
- ▶ "Support by this *Program* has given me the opportunity to enter into and focus my research career on a new research problem, type 1 diabetes. It afforded me the opportunity to assemble a critical mass of investigators that work in a variety of disciplines, but often studying similar signaling mechanisms.... Support of these types of collaborations will significantly accelerate our understanding of the causes of type 1 diabetes, and will expedite the development of successful therapeutic treatments aimed at diabetes, as well as other diseases."
- ▶ "Type 1 diabetes has been a leading model in the field of complex disease genetics and this has occurred, in large part, due to the availability of this funding source."
- ▶ "This funding source was of critical value to the ongoing and future research in my laboratory. All ongoing research, and all grant applications currently pending, stem from projects that arose from this grant."
- ▶ "The grant enabled me to establish an innovative research program and international reputation in type 1 diabetes and organ-specific T cell tolerance research. From that base, I have continued to expand my research team in diabetes, recruiting several Ph.D. students, postdoctoral fellows, and a Senior Lecturer to the team to initiate both deeper analyses of NOD diabetes susceptibility and genome-wide strategies for discovering diabetes-suppressing genes and mechanisms."

## IMMUNE TOLERANCE

The key to a healthy immune system is its remarkable ability to distinguish between the body's own cells—referred to as “self”—and foreign cells—“nonself.” The body's immune defenses normally coexist peacefully with cells that carry distinctive “self” marker molecules. But when immune defenders encounter cells or organisms carrying markers that say “nonself,” they quickly launch an attack. The tendency of the cells of the immune system to ignore the body's own tissues is known as “immune tolerance.”

Tolerance occurs through at least two processes. During their development, cells of the immune system are educated by the body to recognize foreign molecules while at the same time they are taught to ignore, or tolerate, normal cells and self molecules. This process, known as central tolerance, occurs during the development of disease-fighting immune cells.

However, maturing immune cells do not encounter every molecule in the body during their development, so they must also learn to ignore mature cells and tissues. In *peripheral tolerance*, circulating immune cells that happen to recognize a self molecule are unable to respond because some of the chemical signals required to activate the immune cell are absent. This requirement for more than one signal, therefore, keeps potentially harmful immune cells switched off.

Maintaining tolerance is important because it prevents the immune system from attacking its fellow cells. It is the safeguard that invariably fails in type 1 diabetes and other autoimmune diseases. The ability to induce, maintain, and monitor immune tolerance would be an important step forward in the treatment of type 1 diabetes. If initiated early, it could prevent destruction of insulin-producing beta cells. Inducing and maintaining immune tolerance in patients with advanced type 1 diabetes with transplanted islets would obviate the need for lifelong drug regimens to prevent rejection of the transplant and their attendant risks.

*This sidebar was adapted from “Understanding the Immune System,” published by the NIAID and available at: [www.niaid.nih.gov/publications/immune/the\\_immune\\_system.pdf](http://www.niaid.nih.gov/publications/immune/the_immune_system.pdf)*

### A Personal Interest in Curing Type 1 Diabetes

At age 49, Kevan Herold, MD, is highly accomplished. He is Professor of Immunobiology and Medicine at Yale University in New Haven, CT; an endocrinologist and groundbreaking medical researcher; a husband; a father to three daughters; and an avid tennis player.

He also has type 1 diabetes.

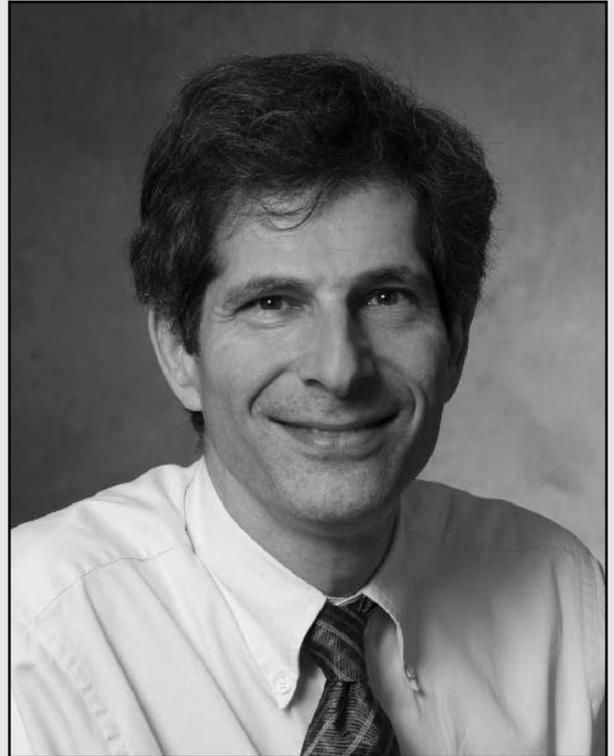
"I was 17 years old and in the first month of my freshman year at Penn State when I started experiencing classic symptoms of type 1 diabetes, including loss of weight, fatigue, and the need to urinate and drink a great deal of water," says Dr. Herold. He was diagnosed with the disease shortly thereafter.

Although his first medical interest, even before entering college, was cardiology, it's not surprising that today Dr. Herold is one of the nation's leaders in type 1 diabetes clinical research. His important work is supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*, the NIDDK, the NIAID, the JDRF, and others.

"Living with diabetes is a great motivator for me to help find a cure for this disease," he says. Like his research, Dr. Herold's message to others with the disease is practical and important: "Avoid diabetes-related health complications by controlling blood sugar levels now, because clearly good, new treatments and technologies for those of us with diabetes are coming."

### A Focus on Diabetes

Type 1 diabetes is an autoimmune disease that results when the body's immune system turns on itself and destroys the pancreatic cells that produce insulin. People with type 1 diabetes typically require insulin injections three to four times a day to stay alive. Many type 1



Dr. Kevan Herold

diabetes patients grapple with the long-term complications of diabetes, including blindness, kidney failure, and heart disease.

Fortunately for Dr. Herold, after living with diabetes for more than 30 years, he has experienced no disease-related complications. But even for a doctor with diabetes, living with this disease has not been easy. "In 1974, when I was diagnosed, we had no idea what blood sugar control was like or all about; we could only measure sugar in the urine," says Dr. Herold. Since then, he adds, there has been enormous growth in the understanding and technology related to this disease.

"Our understanding and treatment of diabetes now is nothing like it was even 10 years ago," says Dr. Herold. "With new developments in cellular and immune therapies, I am sure this pace will continue. The recent developments suggest that even the most fundamental

approaches to treatment will change over the next several years and that the primary problem of beta cell deficiency will be solved.” To that end, Dr. Herold’s research, which includes both immune and cellular therapy, attacks type 1 diabetes on several fronts.

### **Manipulating the Immune System**

Dr. Herold and other immunologists in two NIDDK-, NIAID- and *Special Program*-supported networks, TrialNet and the ITN, have been searching for ways to control autoimmunity to reverse autoimmune diseases such as type 1 diabetes. However, current therapies, including immunosuppression, could compromise the immune system’s ability to fight disease. The challenge is to find a way to manipulate the immune system to specifically target the disease-causing immune cells (T cells).

Dr. Herold and his colleagues have made significant progress toward the goal of reversing recently diagnosed type 1 diabetes with a promising new therapy that can effectively alter the clinical course of the disease. The drug, an anti-CD3 antibody developed by Dr. Jeffrey Bluestone, binds to the T cell receptor. In a groundbreaking NIDDK- and NIAID-supported clinical trial, Dr. Herold and colleagues treated patients with anti-CD3 for 2 weeks shortly after their diagnosis. The drug helped patients by reducing the decline in their ability to produce insulin for at least 2 years after diagnosis compared to a placebo treatment. These impressive results were confirmed in a second industry-supported clinical trial. “The new antibodies alter the signal that otherwise causes T cells to attack insulin-secreting cells,” explains Dr. Herold. He is now expanding these studies to find out what treatment regimens are the most effective at stopping the disease and how long the treatment can last before it requires a booster.

### **Beta Cell Regeneration**

Dr. Herold is also searching for ways to naturally replenish beta cells through regeneration. In a *Special Program*-supported initiative on “Innovative Partnerships in

Type 1 Diabetes Research” (see Goal VI), Dr. Herold has collaborated with Dr. Virginia Papaioannou at Columbia University, to develop new approaches to stimulate beta cell regeneration in the setting of immune tolerance. These studies have involved strategies to stimulate the growth of the stem cells that develop into mature beta cells. In studies also supported by this *Special Program* initiative, preclinical studies pairing anti-CD3 therapy with the drug exenatide has led to a new clinical study that is planned to be conducted by TrialNet.

### **Disease Prevention**

A successful prevention strategy needs to be both long-lasting and specific to the disease. Anti-CD3 provides systemic modulation of the entire immune system but may only confer temporary protection and may lead to side effects. Conversely, another strategy is to induce disease-specific tolerance by using molecules that cause the disease (antigens) to stimulate the expansion of beneficial immune system cells. However, type 1 diabetes antigens have not been clearly identified, and such targeted interventions have thus far only been successful in the prediabetic phase, thus limiting their therapeutic potential. Dr. Herold’s team has worked with Dr. Matthias von Herrath, at LaJolla Institute of Allergy and Immunology, to develop an exciting new strategy that combines these two therapies and has exhibited long-lasting success in reversing type 1 diabetes in two different animal models.

### **Improving the Health of Type 1 Diabetes Patients**

“I’ve always liked science and research, and I’m always looking for ways to apply science to treating patients,” says Dr. Herold. “In my mind, all of these research efforts are related.”

As someone who lives with type 1 diabetes every day, Dr. Herold says that he can easily recognize and relate to what his patients are going through, right down to the daily details of what they need to carry with them in case their blood sugar levels should suddenly drop, often referred to

as hypoglycemic episodes. These episodes can be life-threatening. Despite checking his own blood sugar on average seven to eight times a day, Dr. Herold, too, experiences hypoglycemic episodes from time to time and personally looks forward to the development of new therapies that

will prevent them. Thus, in addition to all the people with type 1 diabetes that Dr. Herold has focused on helping all these many years, he too may end up reaping the benefits of his own research.

### Mother and Daughter Living with Type 1 Diabetes

Katie Clark spent weeks denying her 5-year-old daughter's symptoms of type 1 diabetes. Up to that point, Katie thought that the fact that everyone wanted to touch Ellie's beautiful curly blond hair would be her daughter's burden to bear. She was wrong.

When sugar was found in Ellie's urine on what was supposed to be her first day at a new preschool, Katie learned that Ellie had type 1 diabetes. Katie was devastated. She spent her 30th birthday at the hospital and was deeply depressed for most of the next 2 weeks. She was also very angry. "Anger isn't the most common emotion at the beginning," Katie observes. "However, we're not new to the disease. I've had type 1 diabetes for 28 years."

At the time this profile was written, 10 months after being diagnosed, Ellie had already suffered many unwanted side effects from disease treatment. She had calluses on her fingers. Her bottom had scar tissue from her insulin pump sites. She had undergone 1,494 finger pricks and 98 pump site changes. Ellie's insulin pump site must be changed every 3 days. Ellie will ask, out of the blue, "Is it day three?" Katie laments, "I cannot tell you how heartbreaking it is for me to see my daughter worrying about an impending pump site change. There is relief on her face on those days when we can say, 'No honey, not today.' The devastation in her eyes is almost more than I can stand when we have to say, 'Yes, today is day three, sweetheart.'" Katie is concerned that "Ellie is spending her time worrying about diabetes when she should be playing with her baby dolls and learning to read."

One of the greatest difficulties Katie finds in dealing with Ellie's disease is knowing firsthand the challenges that Ellie will face as she grows up. Katie knows just how type 1 diabetes will affect every detail of Ellie's life. Katie



Ellie and Katie Clark

states, "There is no escape...there are no vacations from type 1 diabetes." Ellie will have to endure constant finger sticks and worry about when her next meal will be. Like Katie, Ellie is at risk of developing devastating disease complications, such as blindness, kidney disease, and heart disease, which could ultimately reduce her life span by approximately 15 years. Katie recalls, "I can very vividly remember reading a magazine article about the complications of diabetes when I was 8 years old. I was horrified. I can see Ellie will be going through these same thoughts and dealing with these same issues, and it's horrible. This is not the life I dreamt of for my precious daughter."

Other less common but very memorable events will leave their imprint as well, as they have during some of the happiest moments of Katie's life. Recalling the insulin reaction she had on her wedding day, Katie laments, "My newly styled hair got messed up, and orange juice I needed to take immediately to adjust my blood sugar level was spilled on my veil." For each of her pregnancies, Katie saw her high-risk pregnancy obstetrician once a week, and in the months leading up to the births, she saw her doctors twice a week. While in labor, Katie was forced to check her blood sugar every hour. After the births, the nurses whisked the babies away to check their blood sugar levels, because newborns of mothers with diabetes often have low blood sugar. The



nurses had to put a tube down their throats to pump sugar into their stomachs to normalize their blood sugar levels.

Ellie's diabetes hits Katie and her husband particularly hard when they're tucking Ellie into bed at night. That's when she asks questions such as; "Mommy, why do some people get diabetes and some people don't?" Or she says, "Daddy, I don't want diabetes anymore." Katie and her husband face a new challenge now that Ellie has begun school. "We have to teach Ellie's teachers how to take care of her," Katie observes.

The Clarks dream of giving Ellie back the life she was living before her diagnosis and having a future brighter than one clouded by diabetes. "I'd give everything I have—even my own life—for Ellie not to have to endure another day of this dreadful disease," Katie stresses. "We must do everything we can to find a cure. Our sweet little girl with the curls deserves it."

## Hope Through Research

In type 1 diabetes, a genetic predisposition for the disease is believed to be triggered by environmental factors. Researchers have already identified genetic regions that play a key role in disease development. However, there are other important genes that have not yet been identified, and it is still unclear how gene-environment interactions may promote the disease. Therefore, the *Special Statutory Funding Program for Type 1 Diabetes Research* is supporting multifaceted research efforts to uncover important genes and environmental factors that promote the onset of, or confer resistance to, type 1 diabetes. For example, the T1DGC is a monumental effort to analyze the genetic makeup of families in which two or more siblings have type 1 diabetes to determine which genes confer disease susceptibility. Because not just a single gene "causes" type 1 diabetes, this

type of large-scale effort is crucial to understanding the complex genetic underpinnings of the disease. Another example is a multicenter, multinational, NIH-funded epidemiological study called TEDDY. In this study, researchers are following newborns who are known to be genetically at risk for developing type 1 diabetes until they are 15 years old, to see who develops the disease. Researchers will use the population to pinpoint the environmental factors that either triggered the disease or provided protection from it. An NIDDK website describes opportunities for patients and family members to enroll in these and other type 1 diabetes clinical research studies ([www.T1Diabetes.nih.gov/patient](http://www.T1Diabetes.nih.gov/patient)).

How will new knowledge about genes and environmental triggers help people with type 1 diabetes, like Katie and Ellie Clark? The potential for this research to positively affect the lives of people with type 1 diabetes is far-reaching. Genetic and environmental factors identified through these research efforts could be used as targets for researchers to develop novel disease prevention strategies. If a certain virus were found to contribute to disease onset, researchers could pursue the development of a vaccine against the virus. In addition, knowledge about which genes are passed down from one generation to the next will allow researchers to more easily identify who is at high risk for developing the disease and therefore intervene earlier in the disease process, before the destruction of insulin-producing beta cells even starts. Preventing disease onset means that children like Ellie would never have to endure the thousands of finger sticks or pump changes/insulin injections that are now part of their everyday lives. Disease prevention also prevents the development of life-threatening complications. Therefore, pursuing research on the genetic underpinnings and environmental triggers of type 1 diabetes has great potential for allowing children, like Ellie, to live the life that their parents dreamt for them.

## 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).

### Risk Assessment

Identify and Optimize the Detection of Immunologic, Genetic, and Metabolic Markers of Type 1 Diabetes:

- ▶ Achieve accurate identification of those at risk in the general population by improved measurement of autoantibodies and other autoimmune markers.
- ▶ Achieve accurate type 1 diabetes risk assessments by exploiting additional genetic markers.
- ▶ Achieve accurate type 1 diabetes risk assessment using metabolic parameters.

### Immunopathogenesis

Understand the Interplay Between Early Environmental Encounters and the Immunoregulatory Defects That Results in Beta Cell Destruction in Human Type 1 Diabetes:

- ▶ Improve understanding of the interplay between the environment and the immune system, which leads to the autoimmune destruction of beta cells in humans.
- ▶ Create a database of the genes expressed in the pancreas at sequential stages of type 1 diabetes development, as well as accessible tissues involved in the (auto)immune response.

Advance Basic Understanding of Facets of the Human Immune Response (e.g., Regulatory T Cells, Innate Immunity) That Have Recently Been Appreciated as Key Mediators of Beta Cell Destruction:

- ▶ Improve the understanding of the generation and function of regulatory T cells in type 1 diabetes.
- ▶ Develop better assays to measure the autoimmune response and to serve as biomarkers of response to therapy.

- ▶ Detect and measure the autoimmune response, as well as the mass and function of beta cells, at the level of the pancreatic islet.

### Clinical Trials

Identify an Intervention Capable of Long-term Reversal of Recent Onset Type 1 Diabetes Without Concomitant Short- or Long-term Adverse Effects:

- ▶ Standardize trial design and outcome measures.
- ▶ Determine whether combination therapies offer improvements in terms of efficacy over monotherapies directed solely at the immune system.
- ▶ Identify novel therapeutic agents.
- ▶ Assess the safety of all immunomodulating or immunosuppressive therapies tested in type 1 diabetes.
- ▶ Enhance animal models for the study of relevant immune mechanisms and potential interventions.

Develop a Safe and Universal Means for the Primary Prevention of Type 1 Diabetes:

- ▶ Further investigate the potential utility of autoantigens as “vaccines” for prevention of anti-beta cell autoimmunity.
- ▶ Determine the importance of exposure to cow’s milk protein in the development of islet autoimmunity and type 1 diabetes via TRIGR.
- ▶ Begin the design and implementation of clinical trials aimed at reducing the impact of environmental factors that trigger islet autoimmunity and type 1 diabetes *in utero*, during early postnatal life, and later in development.

# **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.

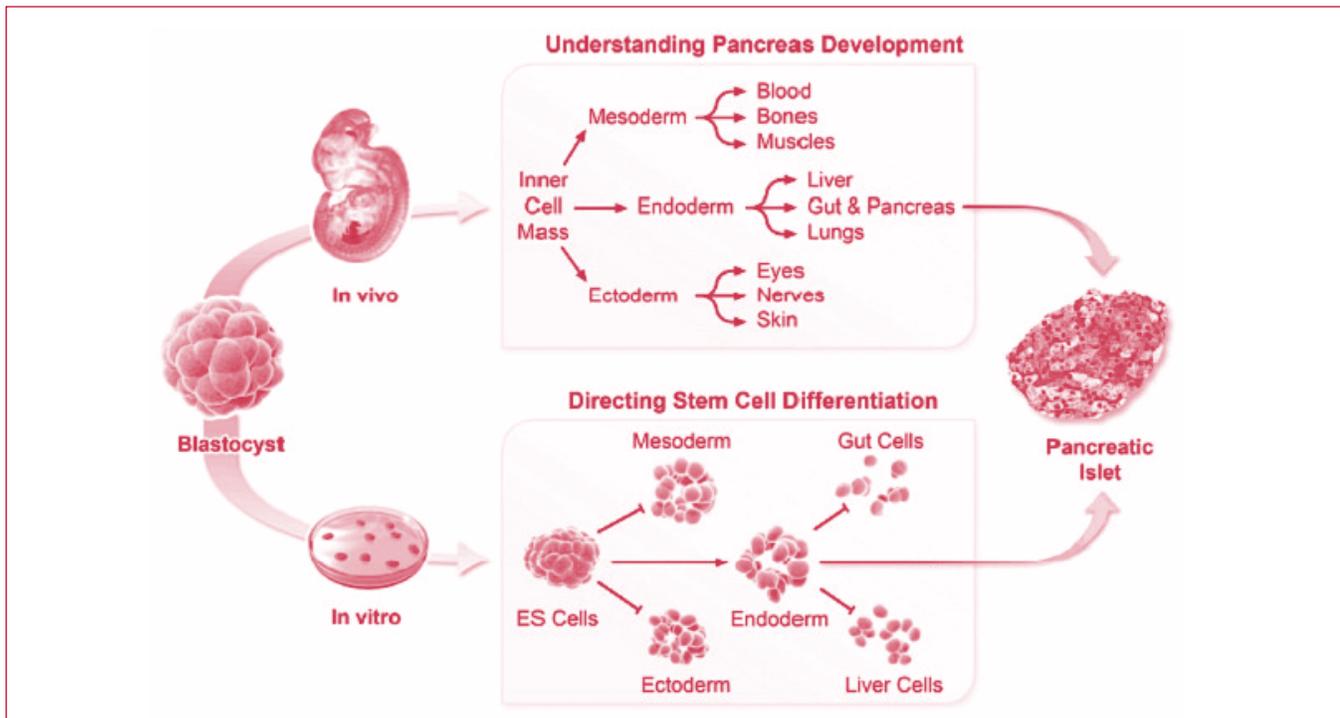
#### Highlights of Progress

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)**

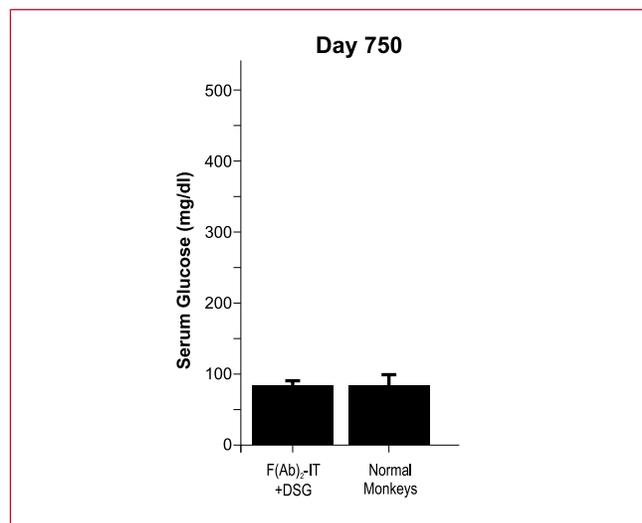
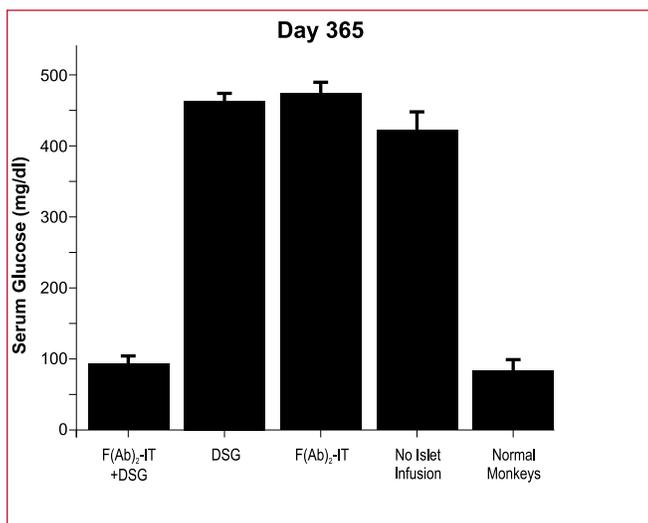
The NHPCSG is a multi-institution Consortium collaboratively evaluating the safety and efficacy of novel therapies to induce tolerance in non-human primate (NHP) models of islet, kidney, heart, and lung transplantation. The program also supports research into the underlying molecular mechanisms of immune 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



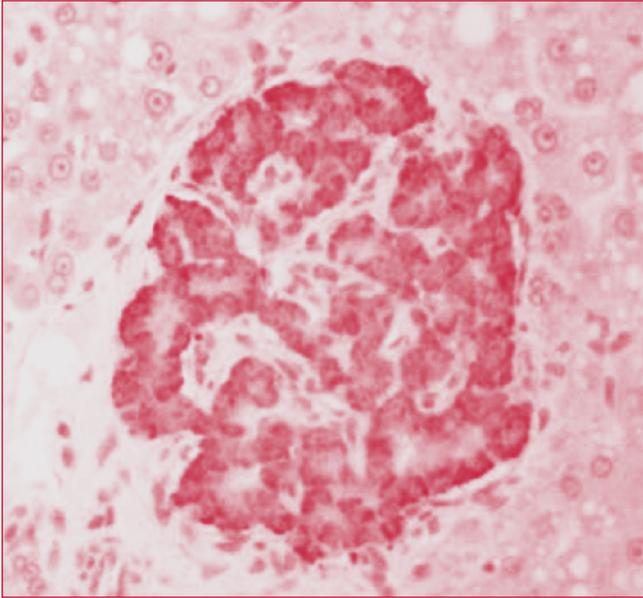


Image of porcine (pig) islets stained red for insulin in the liver of a non-human primate recipient on day 187 after transplantation while receiving maintenance immunosuppression. The research conducted by the Immunobiology of Xenotransplantation Consortium includes investigations of porcine islets as 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

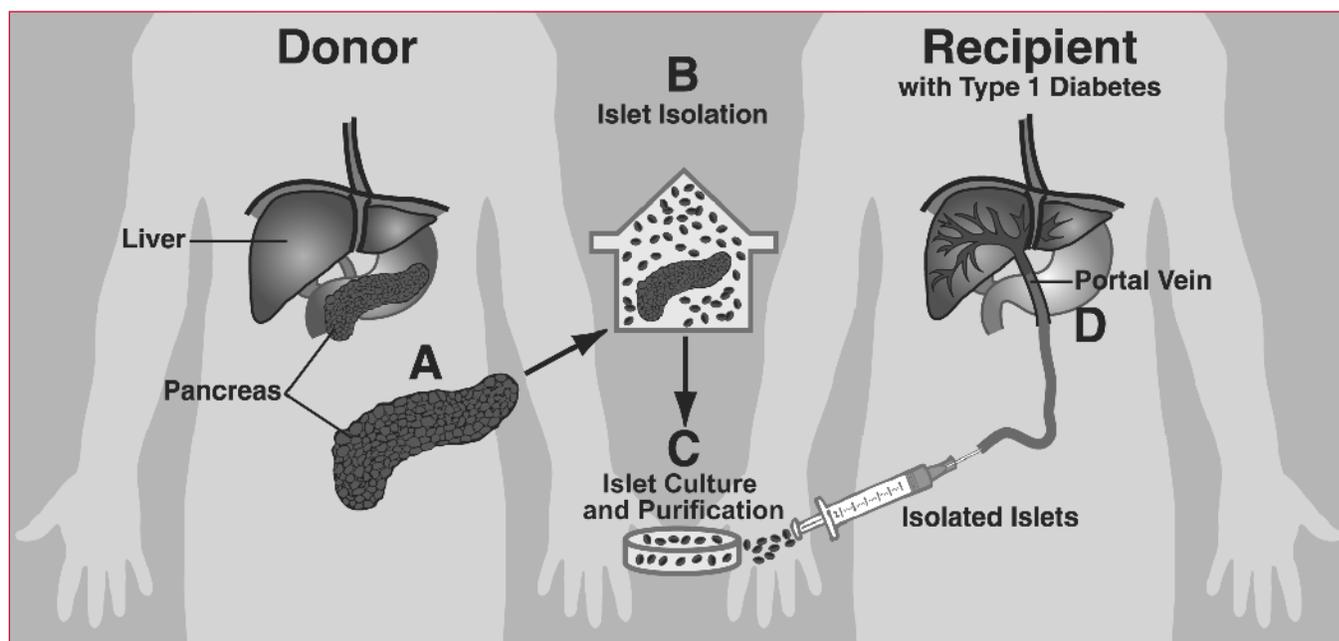
- ▶ The ongoing clinical trials are accompanied by a comprehensive program of mechanistic studies that address the physiology, immunology, and psychological effects of islet transplantation.

### 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)

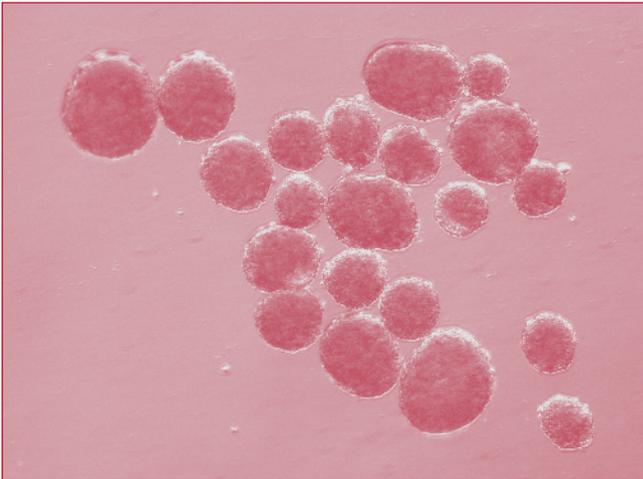
The ICRs represent some of the most critically important resources needed to establish the efficacy and safety of islet transplantation as a treatment for type 1 diabetes. Their mission has three components: (1) to purify clinical-grade pancreatic islets from whole pancreata and distribute them for clinical 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.

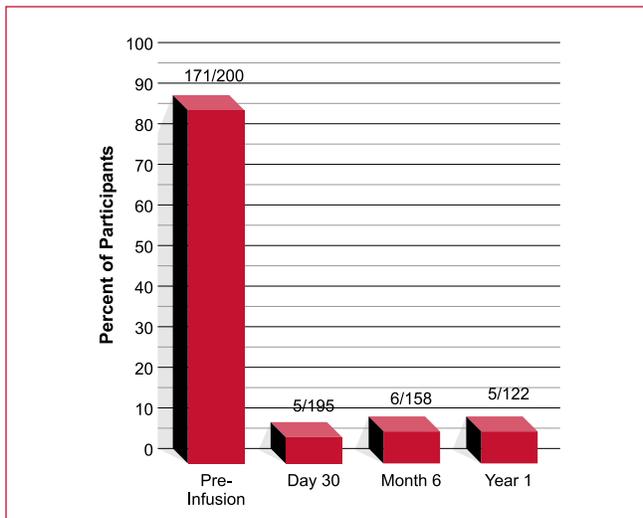
### **Anticipated Outcomes**

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.



# **GOAL IV**

**PREVENT OR REDUCE  
HYPOGLYCEMIA IN  
TYPE 1 DIABETES**

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**Hypoglycemia is the major obstacle to achieving the tight glucose control that has been proven to reduce the deadly complications of type 1 diabetes. To overcome this obstacle, the *Special Statutory Funding Program for Type 1 Diabetes Research* has supported multifaceted efforts ranging from fundamental research to understand how the body recognizes and defends against hypoglycemia and how diabetes impairs this defense, to applied research in partnership with industry to develop technology for continuous glucose monitoring and automated insulin delivery, and has established a clinical network to test the latest technology that can stabilize glucose levels and prevent or reduce hypoglycemia in children with diabetes.**

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Research supported by the *Special Funding Program* has concentrated on helping patients manage their blood glucose levels while also avoiding the terrifying acute dangers of abnormally low blood glucose (hypoglycemia). Excessive treatment with insulin relative to food intake and physical activity can cause blood glucose levels to fall dangerously below a minimal threshold required to fuel the body's activities, particularly brain function. The immediate effects of hypoglycemia can be severe, including changes in cardiovascular and central nervous system function, cognitive impairment, increased risk for unintentional injury, coma, and death. Thus, the potential for hypoglycemic episodes has limited the use of intensive insulin therapy protocols that are known to reduce the risk of long-term diabetic complications, such as eye, heart, and kidney disease. Even with newer forms of insulin that provide more control, hypoglycemia remains an extremely serious, life-threatening concern.

Normally, a drop in blood glucose triggers the body's warning system to release stress hormones, including adrenaline, and to stimulate a part of the nervous system that raises glucose and results in symptoms such as shaking and sweating. However, in diabetic individuals who experience repeated episodes of hypoglycemia, these counter-regulatory mechanisms are impaired so the typical signs and symptoms disappear. These affected individuals do not recognize, and therefore cannot correct for, the low blood glucose—a syndrome known as hypoglycemia unawareness. A vicious cycle is initiated as each hypoglycemic event makes it more likely these compensatory signals will fail in the future, leading to another unrecognized hypoglycemic event. Patients, especially children, are particularly vulnerable to hypoglycemia unawareness while they are asleep. Therefore "nocturnal hypoglycemia" is a primary concern and the source of many anxious nights for parents of type 1 diabetes patients who stay awake to check on the well-being of their children throughout each night. To better understand the causes of hypoglycemia, the *Special Funds* have supported multiple initiatives that explore the integration of glucose sensing information in the body or that measure or image changes in brain function. By discovering the mechanisms involved in the body's reaction to hypoglycemia, scientists may be able to develop therapies that break the vicious cycle of recurrent hypoglycemia.

The widespread introduction and use of reliable, accurate, and relatively "user-friendly" glucose self-monitoring devices and portable insulin pumps have transformed the management of type 1 diabetes in the past two decades. The future holds enormous promise following the recent introduction of continuous glucose monitors—a major advance representing the culmination of years of NIH and *Special Funding* research and industry partnerships. The *Special Funds* also support a clinical trial network for reducing hypoglycemia in children. This network tests the effectiveness of these new technologies and employs the new technologies to learn about how daily activities such as sleeping and exercise affect blood glucose. The network is providing information to help bring to fruition a "closed-loop" insulin delivery system or artificial pancreas that may be on the near horizon to relieve patients from frequent painful finger sticks and injections, and the ubiquitous fear of hypoglycemia. Successful islet transplantation has also reduced the incidence of hypoglycemic episodes significantly, and the progress toward making that therapy a reality for more patients was discussed in the previous chapter.

## 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 prevent or reduce hypoglycemia in type 1 diabetes 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.

**Approval of New Glucose Monitoring Technologies:** In April 2006, the FDA approved a continuous glucose monitoring device paired with an insulin pump for use in patients over age 18. Additional continuous glucose monitors developed by other manufacturers with NIH support are either under FDA review or have recently been approved. Instead of frequent, painful finger sticks, sensors inserted under the skin constantly take glucose measurements, whether the patient is awake or asleep, and trigger an alarm if levels become too high or too low. NIH support contributed to the development of each of these devices. This major technological advance represents the culmination of years of effort by HHS and the *Special Funding Program* in bringing together and funding collaborations of clinicians, engineers, and basic biologists from industry and academia to develop both the technology underlying the glucose sensors and the algorithms used to assist insulin delivery decisions. The new continuous glucose monitoring devices are a major milestone in the future development of an artificial pancreas. They have the potential to dramatically improve patients' ability to control glucose levels—key for preventing complications. They can also improve quality of life by reducing the need for frequent monitoring and alleviating the fears that patients and their parents have of nocturnal hypoglycemia.

**Practical Steps To Avoid Nocturnal Hypoglycemia:** Despite the many long-term complications of diabetes, many children with diabetes and their parents express the greatest fear of nighttime hypoglycemia (please see patient profiles in this chapter) or “dead-in-bed” syndrome. This phenomenon of low blood glucose during sleep despite having normal levels before bed prompts many parents to wake up in the middle of

the night to check their child's glucose level. Recent data using continuous glucose monitoring have shown that low glucose levels are even more common than previously thought, but low levels sometimes go back up before the morning blood glucose check. The Direct Research in Children Network (DirecNet) Consortium has examined factors that contribute to nocturnal hypoglycemia in children. Using the new continuous glucose sensors, investigators found that exercising in the late afternoon caused a delayed nighttime drop in glucose levels and nearly tripled adolescents' risk for nocturnal hypoglycemia relative to exercise-free days. Exercise is important for these children, particularly in keeping blood glucose from rising too high, but these findings point to the importance of adjusting patients' diabetes regimen on active days. This work yields the practical suggestion of increased bedtime snacks on days when children with diabetes are particularly physically active even if the bedtime glucose measurement is not low.

**Counteracting Hypoglycemia:** The pancreatic islets are comprised of several cell types. The counterpart to the insulin-producing beta cell is the glucagon-producing alpha cell. Just as insulin injections control high blood sugar, glucagon injections can be used in an emergency to raise glucose levels that fall dangerously low after insulin therapy. These dangerous episodes of hypoglycemia reflect the failure of the body to trigger normal warning systems (like adrenaline and glucagon) that wake the patient and increase blood sugar in response to hypoglycemia. Glucagon is the major counter-regulatory hormone that causes blood glucose to be released by the liver to raise the blood sugar. Researchers have long recognized that patients with type 1 diabetes do not secrete

glucagon in response to hypoglycemia, despite their ability to secrete glucagon under other circumstances. New findings suggest that a decrease in intra-islet insulin is necessary for glucagon secretion, explaining why the protective glucagon response is impaired in type 1 diabetes.

**Protecting the Brain from Hypoglycemia:** Therapies designed to protect the brain from injury due to hypoglycemia require a basic understanding of brain fuel usage and its adaptation to recurrent episodes of hypoglycemia. Recent progress has revealed how glucose and other fuels are transported into the brain despite a blood-brain barrier that blocks most molecules from entry. Surprisingly, new measurements show that glucose levels bathing the brain are only 25 percent of those in blood, which indicates that the glucose supply is very tenuous, particularly during hypoglycemia. Recent studies in rodents suggest that glucose transport into the brain may be increased by prior exposure to hypoglycemia and that brain glycogen (“starch”) may also serve as a short-term fuel reserve to partially protect the brain from injury. Studies in patients suggest that hypoglycemia may induce the brain to more efficiently use other (non-glucose) fuels to meet its energy needs. Ironically, while these adaptive mechanisms do partially protect the brain from being damaged by impending hypoglycemia, they attenuate the ability of the individual to actually recognize and respond to hypoglycemia quickly (i.e., before dangerously low glucose levels impair brain function). This work explains how responses to hypoglycemia, which are beneficial in the short term and acutely protect the brain from damage, set the stage for a vicious cycle in which the brain becomes progressively less able to recognize and initiate action to halt future occurrences of hypoglycemia.

**Mapping Metabolic Sensing:** Maintenance of normal glucose balance (homeostasis) not only depends on the pancreas to release hormones in response to glucose levels, but also requires the communication of signals from all over

the body with the brain, as well as within the brain itself. The *Special Funding Program* has propelled significant advances that revealed where and how the brain measures the body’s metabolic status. To measure glucose levels in the blood, cells with specialized molecular sensors—some of which are similar to those used by the pancreas—line vessels that lead to the liver and brain, as well as the gastrointestinal tract. These peripheral sensors are linked to groups of specialized glucose sensing nerve cells (neurons), which are localized within a distributed, interconnected network within the brain, including the hypothalamus, forebrain, and hindbrain. Functional brain imaging and electrophysiology techniques have allowed neurobiologists to map the activity of these brain regions. To help the brain integrate different signals, some of these same brain neurons also respond to a variety of metabolic substrates (e.g., lactate, ketone bodies, fatty acids) and hormones (e.g., insulin, leptin, corticotropin releasing hormone), which are involved in the control of metabolism in the body. Identifying molecules and pathways for metabolic sensing may lead to targeted drug development to reduce hypoglycemia.

**Brain Function Not Permanently Damaged by Hypoglycemia:** The landmark Diabetes Control and Complications Trial (DCCT) found that tight control—while reducing complications—increased the risk of severe hypoglycemia three-fold. There was fear that in addition to its dangerous short-term effects—confusion, irrational behavior, convulsions, and unconsciousness—hypoglycemia might also lead to a long-term loss of cognitive ability. Twelve years after the conclusion of the DCCT, researchers report results of a study in which patients were evaluated using the same neuropsychological tests administered during the DCCT trial. The tests analyzed problem solving, learning, immediate memory, delayed recall, spatial information, attention, psychomotor efficiency, and motor speed. The tests revealed no link between multiple severe hypoglycemic reactions and impaired cognitive function in people with type 1 diabetes in the study. The lead

investigator concluded that while acute episodes of hypoglycemia can impair thinking and can even be life-threatening, patients with type 1 diabetes do not have to worry that such episodes will damage their mental abilities and impair their long-term abilities to perceive, reason, and remember. With

the help of the *Special Funds*, DCCT patients continue to be followed more than 20 years after the study was launched and to provide valuable insights about diabetes and its treatment.

# EVALUATION OF THE MAJOR RESEARCH TRIAL NETWORK TESTING TECHNOLOGY TO PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

**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.

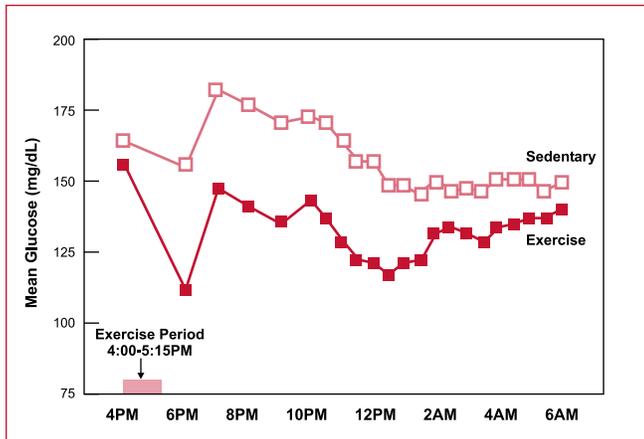
## Diabetes Research in Children Network (DirecNet)

DirecNet is a multicenter clinical research network investigating the use of technology advances in the management of type 1 diabetes in children and adolescents. DirecNet is also developing a better understanding of hypoglycemia, the dangerous drops in blood sugar that can lead to seizures, loss of consciousness and, in extreme cases, coma or death. Specific goals for DirecNet have been to: (1) assess the accuracy, efficacy, and effectiveness of devices that continuously monitor blood glucose levels in children with type 1 diabetes, the population of patients at highest risk for consequences of hypoglycemia; (2) determine the optimal utilization of continuous glucose monitors in the management of diabetes in children; (3) determine the extent to which exercise contributes to the risk of hypoglycemia; (4) assess the impact of continuous glucose monitoring on quality of life for the child and family; (5) develop tools to incorporate continuous glucose monitors into diabetes self-management; (6) evaluate and develop distinct, age-appropriate treatment approaches to type 1 diabetes in children; (7) characterize the daily blood sugar profile of nondiabetic children with continuous monitoring; and (8) develop statistical methods for the analysis of continuous glucose monitoring data.

### Highlights of Progress

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

- Successful completion of six protocols on children with or without type 1 diabetes, with one more in progress, and one pending initiation.
- Demonstrated that counter-regulatory hormone responses to spontaneous nocturnal hypoglycemia are blunted throughout the nighttime period with or without antecedent exercise.
- Showed that the risk of hypoglycemia can be markedly reduced in insulin pump-treated patients by suspending the basal insulin infusion during exercise.
- Demonstrated that continuous glucose monitoring is a better method compared with 8-point glucose profiles as an outcome measure to assess glucose variability in diabetes clinical trials.
- Developed and tested new treatment satisfaction and adherence measures for use in clinical trials of continuous monitoring systems.
- Developed standard algorithms for patients and clinicians to use to adjust basal and bolus insulin doses based on continuous glucose monitoring data.
- Determined sensor accuracy, sensitivity, and specificity of first generation continuous glucose monitors in detecting hypoglycemia.



Effects of exercise on nighttime hypoglycemia: Data from the Diabetes Research in Children Network (DirecNet) show children's mean blood glucose levels on sedentary days (open squares) and exercise days (solid squares). Blood glucose levels are similar in the two groups up to the point of exercise (4:00 p.m.), but the children who exercised had lower glucose levels during the evening and overnight period, and hypoglycemia developed more often on the exercise days than on the sedentary days. This study suggests that food intake and insulin administration need to be adjusted on the evenings of days on which children are active, to help avoid overnight hypoglycemia. (Reprinted from *J Pediatr* (147) Tsalikian E, Mauras N, Beck RW, Tamborlane WV, Janz KF, Chase HP, Wysocki T, Weinzier SA, Buckingham BA, Kollman C, Xing D, Ruedy KJ; Diabetes Research in Children Network (DirecNet) Study Group. *Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus: 528-534, 2005, with permission from Elsevier.*)

### Anticipated Outcomes

In the absence of a functioning pancreas, diabetes patients are unable to respond to changes in blood sugar levels with insulin release. Over the past 80 years, improvements in technology have allowed patients to measure glucose levels and calculate the amount and variant of insulin to inject. These technological advances have saved many lives, but are far from perfect. The static measurement of glucose levels does not account for changes in diet or activity; there is a lag time between injecting insulin and its effect on the body; and too much injected insulin can lead to dangerous hypoglycemic episodes. The fear and danger of hypoglycemic episodes impede patients from achieving optimal control of blood sugar levels despite definitive evidence from the Diabetes Control and Complications Trial and the Epidemiology of Diabetes

Interventions and Complications Trial that rigorous control can prevent diabetes complications. To address these issues, DirecNet has been testing the next generation of technologies: sensors that continuously monitor glucose levels and sound an alarm if levels cross certain thresholds; measurements that are sensitive to the rate of glucose change, not just the absolute amount of glucose; and insulin pumps that control insulin delivery under the skin. The ultimate goal of the network is to “close the loop” between automatic glucose level measurements and appropriate insulin delivery responses. The ideal artificial pancreas would relieve the patient of the burden of constantly testing and adjusting glucose levels. The role of DirecNet is to determine if the new technologies are safe and effective, particularly for use in children.

DirecNet is a prime example of the interface between industry, academia, health care, and government-sponsored research. DirecNet has carried out independent and scientifically rigorous studies to determine the true benefit of new monitoring technologies. Without the commitment of DirecNet to perform these studies, it could be many years before the manufacturers of these devices would be willing to conduct studies in the pediatric population. The DirecNet group is well positioned to assess new devices for their accuracy, as well as their clinical usefulness in the home environment.

### External Evaluation by Expert Panel

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

- ▶ DirecNet is an independent and scientifically rigorous program that has published and recruited well.
- ▶ An important undertaking of the network was to define a child's normal glucose profile.
- ▶ DirecNet could benefit from the participation of external scientists with expertise in hypoglycemia.

- ▶ Currently, islet transplantation studies are appropriately limited to adults. However, as the field of cell-based therapies progresses, the goal is to apply these therapies to children. When safer and more effective cell-based therapies are developed, DirecNet investigators could be crucial in designing a clinical trial to compare the efficacy of different cell-based therapies. Therefore, the panel stressed that having this network infrastructure in place could be valuable for future projects.

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

#### **Recommendations**

DirecNet 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: Make Plans for Future Directions if the Pilot Studies Do Not Yield Promising Results (Such as the Therasense Navigator)**

- ▶ Recent DirecNet pilot studies with the Navigator monitoring system have yielded extremely promising results, and project directors expect that the Medtronic Guardian RT and other second and third generation sensors will also offer new research opportunities. The next phase of this research network will begin with the recompetition of the current network. It is expected that the new cooperative research network will evaluate a wide range of factors and mechanisms contributing to hypoglycemia and will set up clinical trials to test novel therapies and prevention strategies designed to focus on hypoglycemia prevention in type 1 diabetes. To further assist in this effort, the NINDS will be participating with the NICHD and the NIDDK in this next phase of the network, as neuroscience and neuroimaging measures will be added to the studies of hypoglycemia.

#### **Recommendation: Broaden the Scope of DirecNet**

- ▶ The recently-completed exercise studies and planned hormonal counter-regulation studies reflect the broader scope of DirecNet's highly productive research activities. Furthermore, in 2007, DirecNet will be renewed by soliciting competitive proposals, in response to a Request for Applications (RFA) that will significantly broaden the scope of research.

#### **Recommendation: Study the Barrier of Linking Glucose Monitoring with Insulin Delivery ("Closing the Loop")**

- ▶ The next step toward the development of a closed-loop system will be to develop the communication between the continuous glucose monitoring technology and the subcutaneous infusion pump, a device that can function like an artificial pancreas. DirecNet has demonstrated an improvement in continuous glucose monitoring technology in the past 4 years, especially at low glucose levels. As these systems become available, DirecNet will be well positioned to test their efficacy in children, adolescents, and young adults with type 1 diabetes.

#### **Recommendation: Test DirecNet Technologies in Adults with Type 1 Diabetes**

- ▶ The next phase of DirecNet, starting in FY 2007, will include such studies in adults.

#### **Recommendation: Encourage Participation of External Scientists with Hypoglycemia Expertise**

- ▶ The 2007 research solicitation will add an advisory group of outside experts. The NIH has already convened a panel of scientists with hypoglycemia expertise to obtain input on the 2007 research solicitation.



**Recommendation:** Organize a Workshop To Obtain Input on Future Directions of DirecNet from Experts in Hypoglycemia, Pediatric Diabetes, and FDA Regulations

- ▶ A workshop is planned in the next fiscal year (Summer 2007) to determine future directions of the Network.

**Recommendation:** Create a Network of Investigators To Aid in Design of Clinical Trials To Compare the Efficacy of Cell-Based Therapies

- ▶ The 2007 research solicitation encourages such therapies to be tested in clinical trials. Studies of cell-based therapies will therefore be a priority in the discussions of future clinical trials.

**Ongoing Evaluation**

The DirecNet Data and Safety Monitoring Board (DSMB) is an independent group of experts who meet every 2 months to review clinical research protocols in the Network and to advise the DirecNet Steering Committee (SC). The primary responsibilities of the DSMB are to: (1) periodically review

and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy; and (2) make recommendations to the DirecNet Steering Committee concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data, as well as relevant background knowledge about the disease, technology, or patient population under study. Meetings involve DSMB members as well as DirecNet investigators, coordinating center staff, and NIH representatives. The advisory role of the DSMB will be replaced by a separate Protocol Review Committee in the next funding period.

**DirecNet Administrative History**

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Components	NICHD, NIDDK
Website	<a href="http://public.direc.net">http://public.direc.net</a>

DirecNet consists of a Coordinating Center, five pediatric diabetes centers, and a central laboratory.

## EVALUATION OF INVESTIGATOR-INITIATED RESEARCH

**I**n addition to the clinical trial network 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 hypoglycemia responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- ▶ "Since the completion of this project, I have been recruited to head a major biomedical imaging initiative (>\$40 million effort) focusing on metabolic and functional imaging. In this context, I am committed to pursue this line of research and strongly motivated to expand into other challenges in type 1 diabetes research, such as imaging beta cell mass."
- ▶ "We have made the development of this sensing motif the highest priority of our laboratory. Our work in this area won the American Association of Clinical Chemistry Zigi Zering Award."
- ▶ "I am a tenured professor in a university department of bioengineering and this award had little direct effect on my career. Nevertheless, I could not have done the research without the award. The award was instrumental in recruitment of an MD-PhD student who has been involved in the work and intends to further some of the outcomes in his research and patient-care career."
- ▶ "Possession of this grant was essential in my promotion to Associate Professor. Results of this grant have spurred continued research in type 1 diabetes, and were the basis of two grant submissions currently under review. Contacts with diabetes researchers resulted in my participation in an NIH study section."
- ▶ "This long-term (5 year) R01 has helped significantly to provide stable funding for my lab, and has significantly increased my interest in the field of diabetes and hypoglycemia. This grant has considerably altered my career funding from more basic mechanisms of neuronal functioning to clinically relevant topics."
- ▶ "This grant has been very influential in my academic career. It has enabled me to recruit personnel, to develop my research basis, and to remain in the field of type 1 diabetes research. It was also the first major step I made in becoming an established investigator in this field. Without this grant I would probably have returned to clinical medicine."

## DEVELOPING BETTER WAYS TO TREAT DIABETES: A CLOSED LOOP ARTIFICIAL PANCREAS

An artificial pancreas based on mechanical devices requires, at a minimum, three basic components: a continuous blood glucose sensor, an insulin delivery system, and a way to link the two in a loop. Such a system would automatically turn the measurement of blood glucose levels into a practical, precise, and “real-time” insulin-dosing system for patients. Technology that can replace intermittent finger sticks with continuous, accurate measures of blood glucose levels is a key element. Whereas conventional methods of testing glucose levels provide only snapshots in time, a continuous glucose monitoring device, by contrast, can reveal the dynamic changes in blood glucose levels that are the bane of close control and, in turn, can enable responsive insulin delivery in a way that mimics the exquisitely timed responsiveness of a normally functioning pancreas.

The NIH has accelerated the pace of research on glucose sensing technologies through research solicitations and investigator-initiated projects. Over the last decade, these efforts have led investigators in academia and industry to explore a variety of approaches to continuous glucose monitoring, including devices to measure glucose in body fluid extracted from skin, in eye fluid using a contact lens as a sensor, noninvasively with optical sensing of glucose in the blood, and with minimally invasive sensors inserted into the skin. Researchers have also been exploring the benefits and drawbacks of sensors designed for external use versus more permanent, fully implantable devices. Studies have also focused on validating and optimizing the different technologies. These multifaceted approaches have borne fruit. New continuous glucose monitoring devices from three companies (Medtronic, Inc., DexCom, and Abbott Laboratories) have recently been approved or are currently under review by the FDA. These devices represent a significant improvement over the first devices approved by the FDA in 1999. NIH support was instrumental in technology development for all of them. The devices employ a similar basic approach in their technologies: a slender sensor that can detect the biochemical reaction of glucose with an enzyme (glucose oxidase) present on the sensor tip. Inserted

under the skin, these minimally-invasive sensors take glucose measurements every few minutes, whether the patient is awake or asleep, and trigger an alarm if levels become too high or too low. Importantly, both current glucose readings and glucose “trends” indicate whether blood glucose levels are increasing or decreasing—and how quickly—and are reported in “real time” to patients. This information permits patients to take immediate action to avoid low and high blood sugar episodes. Finger sticks are not entirely eliminated because they are needed for calibrating the devices and for directly measuring blood glucose levels before adjusting an insulin dose. However, the burden of care can be significantly reduced and further improvements in these devices can be expected with additional research and development.

One of the FDA-approved devices (Medtronic, Inc.) has been “paired” with an insulin pump through a wireless transmitter so that information about current and past glucose readings is displayed on the pump, making it easier for the patient to adjust the insulin dose. This pairing does not constitute an artificial pancreas. However, it does represent the first step in joining glucose monitoring and insulin delivery systems using the most advanced current technology. To help “close the loop,” the NIH is supporting research on the algorithms that will be needed to enable “proactive” insulin dosing by the insulin delivery device based upon current glucose monitor data, insulin usage data, and patient trend data.

Although the new continuous glucose monitors are not fully integrated into an artificial pancreas, they represent an important opportunity, for now, to help patients better manage their disease and reap the proven benefits of achieving close glucose control. Continuous glucose monitors may be especially helpful to patients to prevent “excursions” into high and low glucose levels on a daily basis, which may go undetected in long-term assessments of glucose control, but which researchers now believe may silently contribute to long-term health complications.

Already, patients using the new devices have been shown to reduce time spent in excessively high and low ranges of blood glucose. However, the wealth of data these devices offer means that patients will need to be well trained in order to achieve their optimal benefits and to avoid over-aggressive management.

New insights about the use of continuous glucose monitoring technologies have been gained from the Diabetes Research in Children Network (DirecNet), which is investigat-

ing the use of technological advances in the management of type 1 diabetes in children and adolescents. It seeks to determine if the new technologies are safe and effective, particularly for use in children. Thus far, the Network has carried out several independent and scientifically rigorous studies to determine the true benefit of new continuous glucose monitoring technologies, including their accuracy and efficacy. Without the commitment of DirecNet to perform these studies, it could be many years before studies would be conducted in the pediatric population.

### Using Advanced Technology To Help Control Glucose Levels

It's the middle of the night, and the Burkhalter family of Jacksonville, Florida, is sleeping more soundly and peacefully than they have in a long time because of a newly-developed technology called a continuous glucose monitoring system, or CGMS. This promising device is being tested by their 14-year-old daughter, Casey, as part of a research network, called the Diabetes Research in Children Network (DirecNet), sponsored by the NICHD, NIDDK, and the *Special Funding Program*.

Casey has type 1 diabetes. The device she is testing monitors her blood glucose levels almost constantly throughout the day. It's when Casey is asleep at night, however, that the CGMS is a lifesaver for her and her family. Should Casey's glucose levels become too high or too low, the CGMS sets off an alarm that alerts her parents to take action. If her glucose level is too low, the Burkhalters give Casey orange juice to raise her blood glucose levels; if it's too high, they administer insulin through Casey's insulin pump.

Caring for children with diabetes requires great diligence, and CGMS technology has the potential to ease some of that burden. "Prior to Casey using the CGMS," says Casey's mother, Leslie Burkhalter, "my husband and I would wake up every 2 hours to prick Casey's finger and check her glucose levels." Their nightly vigil was part of an all-out effort to keep their daughter's blood glucose levels as close to the normal range as possible to prevent diabetes-related seizures and other complications.

NIDDK-supported research—including the landmark Diabetes Control and Complications Trial (DCCT) and a follow-up study, the Epidemiology of Diabetes Interventions and Complications Study (EDIC)—demonstrated that intensive blood glucose control offers remarkable long-term benefits when it comes to preventing or delaying the damage diabetes can have on a patient's eyes, kidneys, and nerves,



Casey and Leslie Burkhalter

as well as the harm the disease can inflict on large blood vessels that can lead to heart attacks and strokes.

Most people with diabetes report checking their glucose levels every couple of hours, at best. The CGMS device Casey is testing is designed to provide, among other valuable information, glucose readings every minute—without a finger prick. The hope is that this technology will enable people of all ages with diabetes to better gain control over their blood glucose levels and reduce their risk of diabetes complications.

"I want to tell the world about this device," says Mrs. Burkhalter, who works in sales and is also actively involved in the Juvenile Diabetes Research Foundation (JDRF).

### About the Continuous Glucose Monitoring System

In 2006, new continuous glucose monitoring devices were approved for use in adults. In 2007, a device was approved for use in children. However, Casey wears her monitor because of her participation in the DirecNet study, which is investigating the potential use of CGMS technology and its impact on the management of type 1 diabetes in children. She received her CGMS when she enrolled in the study in December 2005.

Casey's CGMS comes with a 5-day sensor, a transmitter, and a wireless receiver with a built-in glucose monitoring system. The tiny glucose sensor is placed just under the skin of Casey's abdomen. This procedure is similar to inserting the catheter of an insulin pump, is quick, and usually is not very painful. Tape is used to hold it in place. When used during the day, the wireless receiver allows Casey to attach the monitor to a belt or the waistline of her pants. When she goes to bed, she leaves it on her night table. The system automatically records an average glucose value every minute for up to 5 days, at which time the sensor needs to be replaced and repositioned on Casey's abdomen.

Casey's CGMS, when connected to a computer, also provides charts and graphs that indicate trends in her glucose levels over time and how often her glucose levels may be out of range. Although Casey's blood glucose control was excellent when she entered the trial, while wearing the CGMS she was able to further improve her blood glucose control without causing hypoglycemia. The family had great comfort knowing Casey's blood glucose level all the time and in real time.

"This technology is unbelievably helpful in controlling glucose levels. It's a huge step toward an artificial pancreas," says Mrs. Burkhalter. She is referring to the day when glucose monitoring and insulin delivery technologies merge, allowing insulin pumps to not only recommend proper insulin dosages, but automatically deliver them as well.

### **The Burkhalters' Vigil Before the CGMS**

Casey was diagnosed with diabetes at about age 10 and a half. Her 18-year-old brother, Tyler, was diagnosed with the disease in November 1999. "Both came as a surprise," says Mrs. Burkhalter. "There is no other history of diabetes in our family."

Night after night of awaking every 2 hours to check Casey's levels was taking its toll on the family. "It created a lot of wear and tear on my husband and me," says

Mrs. Burkhalter. "Lack of sleep was making us both irritable and cranky. However, we didn't want Casey to go into a diabetic seizure in her sleep, and fortunately, she never has."

The CGMS has provided the Burkhalters with more than just a good night's sleep. It has provided their daughter with a new attitude toward managing her diabetes.

Casey, whom her mother describes as outgoing and determined, is also an athlete who plays basketball, rides horses, and is a member of a crew team—all rigorous physical activities that can make controlling glucose levels even more difficult than normal.

"I hate having my fingers pricked (to check glucose levels), and the calluses they make aren't very attractive," says Casey. "With the CGMS, I only need to prick my finger, on average, once instead of 7 to 12 times a day." Casey adds that her CGMS is easy to wear "because it's not technically connected to me." At night, she keeps the transmitter on her nightstand. Should its alarm beep, "my parents don't even need to wake me."

As helpful as it may be, the technology is not perfect. There can be as much as a 10-minute delay between sensing and reading out glucose levels, and every 5 days, when the sensor needs replacing, it takes 10 hours to recalibrate, both of which timeframes users would like to see shortened, says Mrs. Burkhalter. Making the device smaller would also make it more convenient, she adds.

### **Participating in DirecNet**

The Burkhalters learned about the DirecNet CGMS study when, in the fall of 2005, Mrs. Burkhalter read an article in *Countdown*, a publication of the JDRF, entitled, "Artificial Pancreas: How Close Are We to Closing the Loop?" It piqued her interest, and shortly thereafter she spoke with Casey's endocrinologist, Dr. Nelly Mauras at the Nemours Children's Clinic, one of the five participating centers, who recruited Casey into the study and started the ball rolling. Casey was

one of the first 30 children in the U.S. to participate in this DirecNet study. Today there are about 100. "One reason Casey is a good candidate for the study is that she recognizes when her blood glucose level is low during the day but, unlike Tyler, not at night," says Mrs. Burkhalter.

The Burkhalters have been extremely pleased with their participation in the DirecNet study. "We believe in the potential of this technology and very much appreciate how those running the study have provided information to us, as well as taken information from us," says Mrs. Burkhalter. "We've recommended the study to many of our friends, and several of their children are now participants." Tyler, the Burkhalter's son, is not a

study participant. "He's averse to wearing anything, including an insulin pump, and unlike Casey, he doesn't seem to mind the finger pricks as much. But he's beginning to change his mind [about using a CGMS]," says Mrs. Burkhalter.

Five clinical centers presently participate in DirecNet: Yale University, The Barbara Davis Diabetes Center (Denver), Nemours Children's Clinic-Jacksonville, University of Iowa, and Stanford University. For more information on participating in DirecNet, please visit: <http://public.direc.net/>

### What It Is Like To Care for a Young Child with Type 1 Diabetes

The day after two-and-a-half-year-old Hannah Beauregard was diagnosed with type 1 diabetes, her parents, Doug and Mary, were being trained at their local hospital by a team of medical personnel on how to measure Hannah's blood sugar level. Blood sugar is measured in milligrams per deciliter of blood. Although people with diabetes have higher than normal blood sugar levels, they can also occasionally experience dangerous episodes of seriously low blood sugar. "At one point," Doug recalls, "I told the medical team that I must be doing something wrong because the monitor read 20 (milligrams per deciliter)." The proper target range for Hannah, if she hasn't eaten recently, is substantially higher. Before he knew what was happening, attending residents whisked Hannah from his arms and out of her hospital bed into what Doug can only describe as a "little emergency-type" room. "They shut the door and would not allow me in," he vividly recalls.

What Doug didn't know at the time was that Hannah was being administered a medication that acts like "instant sugar." Because Hannah's blood sugar levels had dropped precipitously, this treatment was necessary to prevent her little body from going into a coma. What Doug did quickly realize was that having a child with diabetes was going to alter life for the Beauregard family dramatically.

#### **"You Are Not Alone"**

Doug Beauregard is a third grade teacher and longtime soccer coach. His wife, Mary, is a registered nurse. Given their professions, one would think that they should know a thing or two about children and medical care—and they do—a great deal. But having a young child with type 1 diabetes is often as difficult for them as it is for anyone else. "You are not alone," Doug wrote recently in an e-mail to another parent seeking advice on how to



Hannah Beauregard

deal with a toddler with type 1 diabetes who was refusing to eat after taking her insulin. "We're facing the same problem with Hannah."

People with type 1 diabetes must carefully monitor their blood sugar levels throughout the day to determine when they need to eat, and administer insulin, either through injections or an insulin pump, to help their bodies use the sugar from carbohydrates in food. Both steps are also necessary to help keep blood sugar levels within a healthy target range. A constant challenge faced by people with type 1 diabetes is matching food intake, physical activity, and insulin doses in order to maintain healthy blood sugar levels. For example, although too little insulin leads to high blood sugar (hyperglycemia), administering too much insulin for the body's needs at a given time can cause blood sugar levels to fall too low (hypoglycemia). Dramatic rises and drops in blood sugar levels can have immediate and life-threatening consequences, and need to be avoided. Moreover, research has shown that carefully controlling blood sugar levels over the long term is crucial to help prevent serious complications of diabetes, such as diabetic eye, kidney, and nerve disease, and cardiovascular disease.



## Controlling Sugar Levels Is a Constant Chess Match

Carefully controlling blood sugar levels, especially in a young child with type 1 diabetes, is no easy task. Just ask the Beauguards.

According to Doug, since November 14, 2002, the day Hannah was diagnosed with type 1 diabetes, he and Mary have had few uninterrupted nights of sleep. “If Hannah snores, whimpers, cries, moves, or whatever, we wake up,” he says. “We can tell by the way she is sleeping if her blood sugar is low or high. If I think it is low, I will check her. If not, I try to comfort her.”

Since Hannah was diagnosed, the Beauguards have been relatively successful at developing systems for keeping Hannah’s blood sugar levels within a normal range, especially at night when levels tend to drop, a phenomenon called nocturnal hypoglycemia.

To compensate for sugar level drops over the night, Hannah’s parents try to put her to bed with a high enough blood sugar level so that she will wake up in the normal range. At least that’s the goal, but it’s a lot easier said than done. “It’s a constant chess match,” says Doug. “Her body makes a move; we make a counter move.”

For example, physical activities tend to decrease blood sugar levels. Hannah’s activities, like playing soccer, end at about 7:00 p.m. To bring her sugar level up before she goes to bed, which is around 9:30 p.m., the Beauguards usually give Hannah a snack—a fruit snack, sometimes followed by a protein-rich food.

“There are many nights, however, when Hannah will wake up, get out of bed, and tell us she’s hungry,” says Mary. “I’ll check her levels and find that she’s in a low but not dangerous range. I’ll give her something to bring her level up a bit so she can safely get through the night. It’s as if her body is talking to her and telling her what she needs.”

But there are no hard and fast rules to this chess game. Hannah can go to bed with an acceptable blood sugar level on one night and wake up with a higher sugar level, but on another night, she might wake up with very low blood sugar, even if she started at the same point.

Then there are the real “Sugar Monster” nights when, according to Doug, there are no obvious reasons why Hannah’s blood sugar will surge. Last spring, for example, Hannah lay in her bed crying uncontrollably, with a very high blood sugar level. Doug gave her extra insulin to bring her level down, and 15 minutes later she stopped crying, was peaceful and sound asleep. “But we worried about her all night and wondered what her numbers would be like in the morning,” says Doug. In addition, the Beauguards run the battle of having to prick Hannah’s little fingers yet again to test her sugar levels—fingers that have already been pricked thousands of times. “It’s a question of whether we have faith in what we did,” says Doug. “Controlling Hannah’s sugar is really an art, not a science, and there are days I wish we didn’t have to go through all of this,” adds Doug.

As a result of such diligence, Hannah’s hemoglobin A1c (HbA1c) tests have nearly always been good, between 6.9 and 7.1, which lowers Hannah’s risk for complications from type 1 diabetes. These tests are administered by her endocrinologist and are a good indicator of average blood sugar levels over a 3-month period.

It’s obvious that Doug and Mary love Hannah dearly. Doug, in particular, has made it his mission to tell everyone he can about Hannah and how special she is. “No one is responsible for Hannah’s having type 1 diabetes. It’s just part of her life, and we love her for who she is,” says Doug, who actively tries to help other parents whose children have this life-threatening disease.

In many ways, Doug is the consummate communicator. The very first night that Hannah was diagnosed, Doug was on the Internet searching for local support groups. Today, their

family attends a support group near their hometown of Plainwell, Michigan. The group consists of families of children with type 1 diabetes who range in age from 2 to 13 years old. Doug also frequently exchanges e-mails with people around the world, from Argentina to Newfoundland. “We are all seeking answers for our children,” says Doug. “We learn a lot through each other’s experiences and mistakes.”

### **What About All of Those Finger Pricks and Shots?**

It is hard enough for adults with type 1 diabetes to take all of the steps necessary to take care of their disease. Therefore, the questions remain: How does a parent convince a small child with type 1 diabetes that enduring finger pricks to test blood sugar levels and shots to administer insulin, several times a day, is necessary in order to stay alive and healthy? How do parents feel about having to administer those finger pricks and shots?

To help the whole family adjust to Hannah’s new health needs, the Beaugards introduced Hannah to a friend—a fluffy brown teddy bear named Rufus. Rufus™, The Bear with Diabetes, was given to Hannah by the organization [Childrenwithdiabetes.com](http://Childrenwithdiabetes.com). Within hours of their meeting, Rufus became Hannah’s fast friend. Rufus is designed so that he, too, needs to have his fingers “pricked” and to be given “shots.” It wasn’t long before Hannah was administering “shots” to Rufus. After finger pricks to test for sugar levels, both Hannah and Rufus would have their fingers wiped and a special Band-Aid® applied. When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

Everyone in Hannah’s family—except 2-year-old Evan—knows how to care for her, including her 14-year-old brother, Ryan. “Ryan is really good with his little sister,” says Mary. “Yes, they fight and can drive us crazy at times, but Ryan and members of his soccer team know how to test Hannah’s blood sugar level,” adds Doug.

The good news is that the older Hannah gets, the more choices she can make for herself to help balance her diet, physical activities, and insulin injections so that she can maintain healthy control of her blood sugar levels. As Hannah becomes more independent, it is becoming easier for her parents. Doug recounted an experience in which he encouraged Hannah in learning about the foods she needs to eat in order to obtain the proper amounts and balance of nutrients she requires at each meal, including carbohydrates. Says Doug, “At dinner the other day, Hannah said she was full. I told her that she needed to eat so she would get her carbs (carbohydrates). Hannah then asked, ‘Dad, does my bread have carbs?’ Yes, I told her. ‘How about my meat?’ No, I said. ‘I guess I will eat my bread then,’ she said.” Hannah recognized the need to have her carbohydrates to stay healthy. The Beaugards try to make Hannah feel in control of her diabetes as much as possible by giving her choices. “We also always have a fallback food just in case Hannah doesn’t want to eat what we have for dinner,” Mary adds.

As much as Doug and Mary sometimes feel they have things pretty much under control, “It’s not easy being a parent of a child with diabetes, and it never will be,” Doug says. The kindergarten Hannah attends, for example, was leery at first about having a student with Hannah’s disease, so the Beaugards had to educate the staff about diabetes and what to do if Hannah’s blood sugar level became too low or too high. “Part of the problem,” says Doug, “is that Hannah isn’t always cooperative when her blood sugar level is low.” The family has shied away from day care. When Hannah was not in pre-school, Doug’s mother, Elizabeth—who is as well trained as Doug and Mary in how to care for Hannah—spent 2 or 3 days a week at the Beaugard home. Doug adds that when he is at work, “my students know that if my cell phone rings, it’s something important.”

## **In Short, Life Is a Constant Vigil**

Hannah is growing up to be an adorable little girl whose life will be in constant jeopardy until a cure is found for her type 1 diabetes. Until then, she will be required to take insulin every day of her life to survive.

“We’re not angry that Hannah has (type 1) diabetes,” says Doug. He and Mary just want to tell everyone they can about their little girl. “Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength.”

“We need to be strong for every child with diabetes,” says Doug, “because without their parents, they won’t make it.”

## **Hope Through Research**

To balance the long-term risks of developing complications associated with hyperglycemia with the short-term dangers of hypoglycemia, patients with type 1 diabetes and their families must perpetually face a chess match of measuring sugar levels and reacting to them with insulin or sugar. The *Special Funding Program* supports multiple avenues of research that are helping patients improve their blood sugar control and avoid hypoglycemia.

As a result of insulin therapy for type 1 diabetes, many patients experience low blood sugar at night during sleep, a phenomenon known as nocturnal hypoglycemia. Sleep can be a particularly dangerous time because it inhibits the normal adrenaline responses that are usually triggered when blood sugar drops below a threshold level; the adrenaline and nervous system responses are needed to warn patients that they are in danger. Nearly half of all episodes of severe hypoglycemia occur during sleep and, in extreme cases, can lead to coma or seizures that can result in fatal cardiac arrhythmia (disturbed heartbeat).

Despite measuring blood sugar levels just before sleep, type 1 diabetes patients often find it difficult to predict the profile of blood sugar during the night. Research that explores the relationships among diet, behavior, insulin therapy, and the nocturnal sugar profile will make it easier to predict and prepare for changes in blood sugar during the night. For example, a DirecNet study has already provided vital information required to adequately manage active adolescents with type 1 diabetes to avoid precipitous declines in blood glucose after exercise, particularly to prevent the dangers of nocturnal hypoglycemia.

## **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).

### **Brain and Peripheral Nervous System Mechanisms of Hypoglycemia**

Define the Mechanisms and Modulators of Metabolic Sensing:

- ▶ Identify and elucidate the mechanisms involved in glucose sensing in the brain.
- ▶ Determine the hormonal and metabolic modulators involved in glucose sensing.

Elucidate Brain Alterations in Response to Hypoglycemia:

- ▶ Determine alterations in brain metabolism and function induced by recurrent hypoglycemia.
- ▶ Prevent hypoglycemia-induced brain injury and promote protective adaptations.
- ▶ Identify potential genes involved in individual susceptibility to hypoglycemia.

Develop New Strategies To Prevent or Reverse Hypoglycemia-Associated Autonomic Failure (HAAF):

- ▶ Elucidate the mechanisms of HAAF.
- ▶ Identify the clinical consequences of HAAF.
- ▶ Develop and test therapies to restore counter-regulation.

### **Clinical Interventions To Prevent or Reduce Hypoglycemia**

Control Hypoglycemia Through Behavioral Therapies:

- ▶ Refine and link behavioral interventions and algorithms that predict risks of hypoglycemia.
- ▶ Evaluate behavioral approaches to preventing nocturnal hypoglycemia.

Close the Loop—Develop the Tools Required for an Artificial Pancreas:

- ▶ Optimize use of continuous glucose monitors.
- ▶ Develop algorithms needed to link glucose monitors with insulin delivery.

# **GOAL V**

**PREVENT OR REDUCE  
THE COMPLICATIONS OF  
TYPE 1 DIABETES**

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**The *Special Statutory Funding Program for Type 1 Diabetes Research* has enabled the establishment of large-scale collaborative research groups and clinical trials networks that seek to understand and treat the complications of type 1 diabetes. The *Special Program* has also enabled the valuable long-term follow-up study of a well-studied cohort of type 1 diabetes patients as they begin to develop complications.**

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Although the discovery of insulin in 1921 has nearly eliminated death from the acute effects of type 1 diabetes, patients can never ignore the looming specter of chronic health complications that affect nearly every organ system in the body. The *Special Funding Program* has created exciting new opportunities to study the basic mechanisms underlying complications and to develop tools and therapies to prevent or reduce them. In diabetes, damage is caused by persistent elevation of blood glucose levels (hyperglycemia) and by cellular stress due to altered metabolism of sugars and fats. Damage to heart tissue and larger blood vessels (macrovascular complications) gives rise to cardiovascular disease and clogged arteries (atherosclerosis), and increases the risk of premature death from heart attacks and strokes. Damage to the networks of small blood vessels embedded in tissues (microvasculature) leads to: eye disease (diabetic retinopathy), the leading cause of new blindness in the U.S.; kidney disease (nephropathy), which can lead to irreversible kidney failure, known as end-stage renal disease (ESRD); and nerve disease (neuropathy), an often painful condition contributing to foot ulcers, which can lead to limb amputation in extreme cases. Diabetes impedes repair pathways necessary for the success of established cardiovascular therapies such as coronary angioplasty and bypass grafting, and lower extremity revascularization. In addition, diabetic individuals are at increased risk of gum disease and other oral complications, pregnancy-related complications, urinary incontinence, nocturnal diarrhea, and erectile dysfunction. Furthermore, type 1 diabetes increases the likelihood of depression and, in some cases, increases family conflict, which may exacerbate problems with metabolic control.

NIH-supported clinical trials dramatically proved that intensive glucose control can reduce the long-term risk for microvascular, cardiac, and neurologic complications of type 1 diabetes. Nonetheless, even with optimal diabetes care, complications constitute a significant burden for people with diabetes and compromise their quality of life. Therefore, uncovering the molecular mechanisms underlying cellular damage and designing novel therapies to reverse this damage remain high research priorities.

Patients with type 1 diabetes vary in their risk of developing specific complications. Risk factors are dependent on duration of disease, control of blood sugar, co-morbid conditions, and genetic background. Large-scale genetic studies supported by the *Special Funding Program* have enabled identification of genes that confer protection from (or susceptibility to) different diabetic complications. The development of new therapies is a long process requiring basic discoveries, reliable animal models, technology development, and extensive clinical trials, particularly for chronic complications that develop years after diagnosis. The *Special Funding Program* has supported efforts in each of these areas, as well as accelerated research progress through various initiatives that: identify and validate biomarkers and surrogate endpoints that facilitate clinical trials; screen libraries of approved drugs for their potential use in diabetes complications; provide drug development resources through the Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID) program (see Goal VI); and establish a clinical trial network to test new therapies. Importantly, the scientific and clinical accomplishments that emerge from the complications research supported by the *Special Funds* may benefit individuals affected with any form of diabetes, including both type 1 and type 2 diabetes.

## 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 prevent or reduce type 1 diabetes complications 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.

### **Sustained Benefit of Intensive Glucose Control on Complications Susceptibility—“Metabolic Memory”:**

The Diabetes Control and Complications Trial (DCCT) revolutionized the management of diabetes. Started in 1983, the multicenter clinical trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of disease complications in over 1,400 people with type 1 diabetes. It proved conclusively that intensive therapy dramatically reduces the occurrence and severity of microvascular (small blood vessel) complications, such as diabetic eye, kidney, and nerve disease. Nearly all patients who participated in the DCCT volunteered for the valuable follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study, which is supported by the *Special Program*.

Upon completion of the DCCT, participants who had received conventional treatment were taught intensive treatment, and all patients were encouraged to use intensive treatment. The post-DCCT glycemic values for both groups have become nearly identical during the approximately 10 years of follow-up in EDIC. Surprisingly, the effects of intensive glucose control during the DCCT on the incidence of retinopathy persisted, and had even become greater over 7 years after the study ended when the glucose control was similar between the two groups. This report by the EDIC investigators in May 2002 was followed by another exciting finding in October 2003 that showed that the former intensive treatment group had a decreased incidence of kidney damage and high blood pressure compared to the former conventional treatment group 8 years after the end of the DCCT. In February 2006, it was reported that the benefits of 6.5 years of intensive therapy

also extended to symptoms and signs of neuropathy for at least 8 years beyond the end of the DCCT.

Analysis showed that these long-lasting differences in development of complications could be explained by the difference in control of glucose levels between the two treatment groups during the DCCT. The phenomenon of long-lasting effects of a period of intensive or nonintensive glucose control has been termed metabolic memory, and provides further impetus for early intensive therapy of diabetes.

### **Delay or Prevention of Large Blood Vessel**

**Complications of Type 1 Diabetes:** While the DCCT proved that glucose control could prevent small vessel damage that causes kidney, eye, and nerve problems, controversy remained about the effect of elevated blood glucose on cardiovascular disease (CVD). Studies had already shown that high glucose levels correlated with CVD, but the effectiveness of intensive glucose control in preventing or delaying CVD had not been proven in a rigorous, randomized clinical trial. The *Special Funding Program* made it possible to follow the valuable DCCT/EDIC study patients as they reached the life stage at which CVD begins to take its toll. In June 2003, the EDIC research group reported that patients in the former intensive therapy group had a decreased progression toward atherosclerosis compared with the patients in the former conventional therapy group. In December 2005, the EDIC researchers reported that during an average follow-up time of 17 years, the patients who had been intensively treated during the trial had fewer than half the number of CVD events—heart attacks, strokes, or death due to CVD—than those in the conventionally-treated group. These results were the first to prove that

intensive control of blood glucose levels has long-term beneficial effects on CVD risk in diabetes patients. These findings are particularly significant because CVD is the cause of death in two-thirds of patients with diabetes.

**Progress in Reducing Diabetic Nephropathy:** Recent reports indicate that prevention efforts are beginning to have dramatic effects on the rates of diabetic nephropathy in people with type 1 diabetes. This devastating complication of diabetes has historically been seen in as many as one-third of diabetic individuals after 20 or 30 years of disease. In the most recent population-based study from Finland, however, only 7.8 percent of patients with type 1 diabetes have renal failure after 30 years of diabetes. Declines in the incidence of end-stage renal disease due to diabetes are being noted for the U.S. population as well, in reports from the United States Renal Data System. The rate of end-stage renal disease in Caucasians under age 30 with diabetes (most of whom have type 1 diabetes) is almost half the rate seen in the late 1980s and early 1990s. Since that time, several clinical strategies have been proven to significantly reduce the progression of diabetic nephropathy. These include angiotensin-converting enzyme inhibitors (ACE-inhibitors) and angiotensin receptor blockers (ARBs), which lower protein in the urine and are thought to directly prevent injury to the kidneys' blood vessels, and careful control of blood glucose and blood pressure. Credit for the recent gains likely goes to implementation in clinical practice of these strategies to prevent disease. Thus, the investment of *Special Funds* in DCCT/EDIC and the National Glycohemoglobin Standardization Program (see Goal II) is already reaping dividends by helping patients with their blood glucose control, which reduces diabetes complications.

**Genetic Influence in Diabetic Nephropathy:** Mounting evidence suggests that some people with diabetes are more genetically vulnerable to certain complications than others. To tease out the genetic contributions, DCCT/EDIC

geneticists are conducting systematic analyses of candidate genes. For example, angiotensin-converting enzyme (ACE) is key to physiologic pathways regulating blood pressure. Elevated ACE activity can increase pressure in the filtering units of the kidney (glomeruli), which ultimately causes permanent injury. Drugs known as “ACE inhibitors” have been proven to help stave off diabetic kidney damage. In a retrospective study of genetic and other data from 1,365 DCCT/EDIC participants, investigators examined specific genetic variants in the ACE gene for two renal outcomes: incidence of persistent microalbuminuria (leakage of small amounts of protein in the urine) and incidence of severe nephropathy. The standardized methods used in DCCT/EDIC to measure renal function, coupled with comprehensive health data collected for over 17 years, provided a unique opportunity to control for variables other than ACE variants that could affect nephropathy onset and severity, such as age, duration of diabetes, and blood pressure levels, as well as glucose control in the DCCT study. As a result, the group was able to confirm that a specific variant of the ACE gene—“extra” DNA inserted in a non-coding region—is associated with reduced risk of microalbuminuria and severe nephropathy. Furthermore, by analyzing “SNPs”—DNA landmarks for genetic variation—they identified a common variant of the ACE gene that conferred a reduced risk of nephropathy when present in two copies. In the Genetics of Kidneys in Diabetes Study (GoKinD), a variant in another candidate gene, TGF-beta-1, was found to increase the risk of nephropathy. The genetic data that has been collected in EDIC, GoKinD, and the Family Investigation of Nephropathy and Diabetes (FIND) studies will enable further studies of the genetic underpinnings of specific complications in type 1 diabetes. Genome-wide studies currently under way will go beyond looking at candidate genes suspected to predispose to complications, and have the potential to identify new pathways involved in complications and open new avenues of therapy. Identification of genes such as ACE



and TGF-beta-1 that modify risk for nephropathy will help identify patients who can benefit most from intensive control of glucose and blood pressure.

### **Role of Reactive Oxygen Species (ROS) in**

**Complications Pathogenesis:** Over the past 35 years, several molecular mechanisms have been implicated in glucose-mediated vascular damage. Each of these mechanisms has been studied independently of the others, and there has been no apparent common element linking them. Recent discoveries have made clear that all of these seemingly unrelated mechanisms may arise from a single, hyperglycemia-induced process: the overproduction of the reactive free radical molecule, superoxide. It now appears that the energy-generating cellular organelles called mitochondria are required for the initiation of hyperglycemia-induced superoxide production, which can, in turn, activate a number of other superoxide production pathways that may amplify the original damaging effect of hyperglycemia. Increased free fatty acid oxidation in mitochondria produces superoxide as well. In diabetic mice genetically engineered to produce high levels of an enzyme that degrades superoxide (called “superoxide dismutase”), the classic hyperglycemia-induced damaging pathways are not activated, and these mice do not develop diabetic kidney disease. This advance points to the central role of a single pathway involved with complications in multiple organs. Several novel pharmacologic approaches based on this unifying mechanism have already prevented diabetic eye, kidney, and nerve pathology in rodent models of diabetes.

### **Impaired Blood Vessel Formation from Bone Marrow**

**Progenitor Cells in Diabetes:** Diabetic complications result not only from damage to cells and tissues, but also from the inadequacy of the repair process. During the acute response to injury, new blood vessel growth rescues “stunned” areas of the heart or central nervous system, reducing morbidity and mortality. With chronic low perfusion, the development of collateral vessels reduces the size and severity of a subsequent infarction. Circulating progenitor cells from the bone marrow promote the regeneration of blood vessels by acting in concert with the cells and extracellular matrix at the site of injury. A major advance is the observation that these endothelial progenitor cells are depleted and dysfunctional in diabetes, and that injection of normal progenitor cells can improve blood supply to the tissues and nerve function in experimental diabetes. Research focused on the diabetes-induced impairment of this process could lead to novel drug- and cell-based therapies for people with diabetes to restore compensatory vessel formation in CVD, stroke, peripheral vascular disease, and wound healing. In the diabetic retina, however, overly exuberant vascular repair processes can result in excessive proliferation of small vessels. Molecular pathways responsible for the new vessel growth have been identified, and this work suggests new molecular targets for drugs that could protect the retina.

# EVALUATION OF MAJOR RESEARCH CONSORTIA, NETWORKS, AND RESOURCES RELATED TO PREVENTING OR REVERSING THE COMPLICATIONS OF TYPE 1 DIABETES

**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.

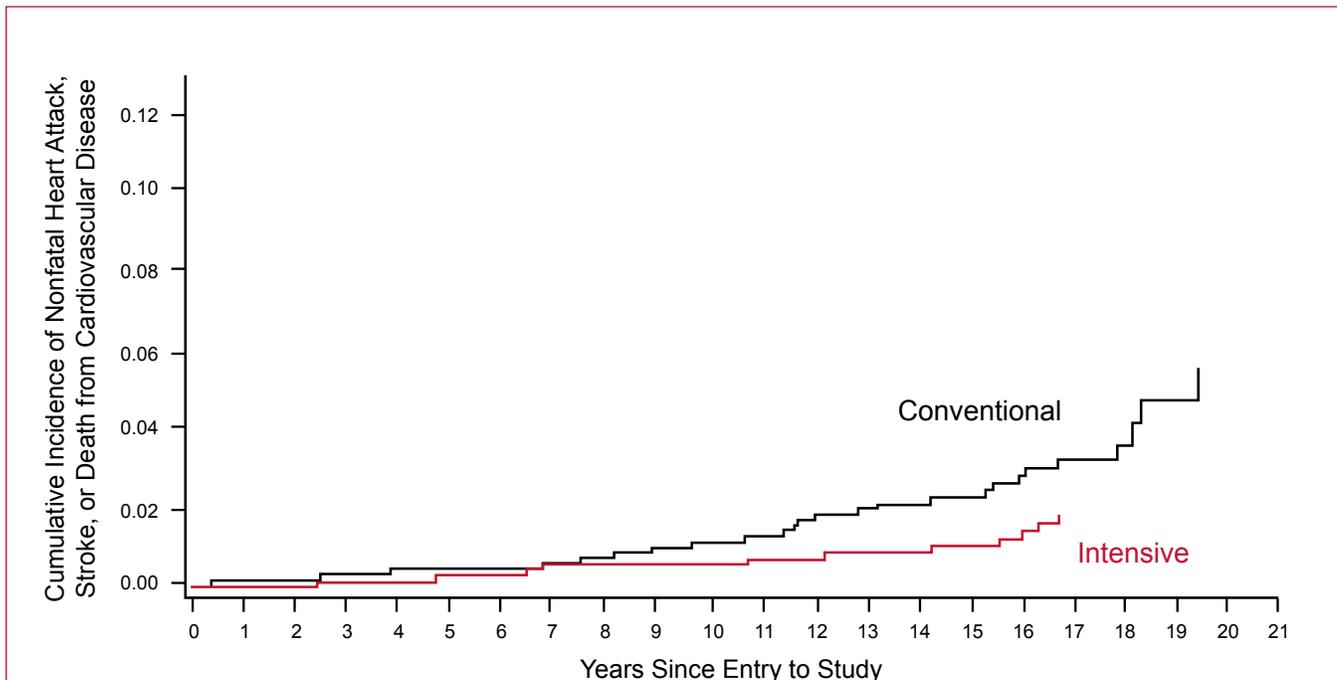
## Epidemiology of Diabetes Interventions and Complications (EDIC)

The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of 1,441 patients who participated in the landmark Diabetes Control and Complications Trial (DCCT). Completed in 1993, the DCCT revolutionized diabetes management by demonstrating the benefit of intensively controlling blood glucose levels with frequent monitoring and insulin injection for preventing or delaying the early complications of the disease. Both the “conventional” and “intensive” treatment groups from the DCCT are being followed observationally, but all participants are now recommended to follow the intensive therapy guidelines. DCCT/EDIC is a prospective study: one of its major strengths is the well-studied cohort of patients in which disease progression has been followed for over 20 years before most complications developed. The *Special Funding Program* support has been pivotal to the success of EDIC. Major findings from the study are described in the Highlights of Research for Goals IV and V. Additional findings below derived from studies to measure the onset and progression of CVD, diseases of the urinary tract (uropathy), and diseases of the nerves that communicate with the internal organs such as the bladder, bowel, and sexual organs (autonomic neuropathy). A separate genetics component is described in the next section entitled “Genetics of Diabetic Complications.”

### Highlights of Progress

The progress that the EDIC studies have made as of March 1, 2006, includes:

- Results show that intensive control of blood glucose levels cut the number of CVD events (heart attacks, strokes, or death) in half relative to the control group in the DCCT. This is the first demonstration of the long-term beneficial effects of intensive diabetes therapy on macrovascular complications in type 1 diabetes patients.
- Results of carotid ultrasonography show significant thickening in arteries of EDIC diabetes patients relative to non-diabetic controls and significantly less progression in the DCCT intensively-treated group compared to the conventionally-treated group.
- Preliminary results show that the DCCT intensively-treated group is associated with reduced coronary calcification (a subclinical progression of CVD).
- Recent, important, and provocative findings are the persistent, long-term benefits of intensive treatment and reduction in glycemia resulting in substantially reduced risk of retinopathy, nephropathy, neuropathy, and CVD in EDIC, termed “metabolic memory.”



Intensive treatment of type 1 diabetes, which includes four or more glucose measurements and three or more insulin injections daily or use of an insulin pump, has previously been shown to dramatically reduce the onset and progression of eye, nerve, and kidney complications. Until recently there was no proof that intensive glucose control reduced cardiovascular disease, the leading cause of premature death in diabetes. Results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study have demonstrated that intensive treatment can reduce the risk of heart attack, stroke, or death from cardiovascular disease by 57 percent compared to conventional treatment. *(Image courtesy of Dr. David Nathan and adapted with permission from Nathan DM et al. DCCT/EDIC Study Research Group. N Engl J Med. 353:2643-2653, 2005. Copyright © 2005 Massachusetts Medical Society. All rights reserved.)*

### Anticipated Outcomes

The dramatic results of the DCCT/EDIC demonstrate the benefits of a long-term prospective study. The DCCT proved conclusively that intensive diabetes therapy reduces the risk and progression of eye disease (retinopathy) by 47 to 76 percent, of kidney disease (nephropathy) by 39 to 54 percent, and of nerve damage (neuropathy) by 60 percent. However, only in the long-term follow-up EDIC study (average 17 years of follow-up) have the benefits for CVD become apparent as well: intensive diabetes therapy reduces non-fatal CVD events by 57 percent. The impact of these findings applies not only to patients with type 1 diabetes, but also is likely to apply to the roughly 19 million people with type 2 diabetes who suffer from the same complications. The research has already been

translated from the clinic into practice as close control of blood glucose levels is now a keystone to the medical management of both forms of diabetes. In addition to reducing the burden of complications, these results have implications for improving the life expectancy in a disease in which heart disease is the leading fatal complication.

Heart disease is a chronic condition, developing over decades. It is difficult to prospectively study a population continuously from a young age before the onset of symptoms through CVD events, such as heart attacks and strokes. Yet as shown in EDIC, therapy early in the course of disease has profound consequences decades later. Because pharmaceutical companies and

the biotechnology industry have a limited willingness to develop products that require years of testing before their clinical effects can be realized, it is therefore important to develop and validate subclinical biomarkers that the FDA will accept as a basis for approval of new drugs for diabetes complications. For example, the DCCT demonstrated that the level of HbA1c—a modified form of hemoglobin that circulates in the blood and correlates to the average blood glucose levels over a 3 month period—can be used as a surrogate endpoint for therapies that seek to reduce complications of diabetes. This test has subsequently become an important outcome measure for future clinical trials of both type 1 and type 2 diabetes. The use of HbA1c as an outcome measure was the basis for FDA approval of improved forms of insulin, as well as many other new drugs for type 2 diabetes.

Comprehensive and meticulous data collection in the DCCT/EDIC cohort for more than 20 years, with participation rates about 95 percent, has created an unparalleled resource of individuals with type 1 diabetes that is ideal for future study of the clinical course of diabetes and its complications and for the validation of surrogate endpoints that can facilitate future drug development. These include assessment of subclinical markers such as testing new imaging techniques to measure the clogging, narrowing, and hardening of major arteries (atherosclerosis), heart muscle function, and other signs of CVD. EDIC has pioneered the use of new noninvasive diagnostic tools such as using ultrasound to measure the thickness of the carotid artery, or use of a “heart scan” (electron beam computed tomography) and multi-detector scanning to determine the extent of coronary calcification. By validating new analytical tools for early detection of CVD complications before events occur, the results of EDIC are paving the way for future trials that are smaller, shorter in duration, and less expensive to conduct.

Longitudinal assessment of the cohort allows analysis of rate-of-change of complications over time, including the interactions among complications and co-occurrence of complications, as well as further evaluation of the longer-term effects of original DCCT interventions on advanced complications. This study also could lead to an examination of the longevity of the metabolic memory phenomenon and whether it applies to all diabetic complications. Important insights will be gained regarding the disease-causing mechanisms that underlie the development and progression of diabetic complications.

#### **External Evaluation by Expert Panel**

To supplement ongoing evaluation and guidance from an External Advisory Committee focused on EDIC, leading scientific and lay experts were asked to evaluate the components of EDIC, such as genetic studies and measures of CVD, supported through the *Special Funding Program* at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ EDIC has been extremely productive over the years with valuable studies, high quality publications, and meaningful bedside applications.
- ▶ These cardiovascular studies address a limitation in the original DCCT studies that examined a young group of patients with few cardiac complications.
- ▶ The relevant question now is to consider the value of continuing these ancillary observational studies versus designing new prospective studies with the latest technology. Despite the lack of baseline data in cardiovascular studies in the DCCT participants, there are still opportunities to capitalize on the long-term investment in resources in this select cohort of patients.

- ▶ The study participants are just beginning to have cardiac events, so this cohort provides a good opportunity to examine subclinical CVD markers (carotid intima-medial thickness, coronary calcification, myocardial function) as predictive of cardiovascular events. The longer-term follow-up just to monitor cardiac events will be less costly than a new prospective study.
- ▶ Neurological manifestations of type 1 diabetes have been less extensively studied than eye and kidney disease in DCCT/EDIC, and plans are under way to redress this with support of the *Special Funding Program*.

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

#### **Recommendations**

EDIC 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 the Study of Neurologic Manifestations of Type 1 Diabetes**

- ▶ In addition to core EDIC neurologic assessment, a neurology protocol is being implemented to assess metabolic memory of intensive glycemic therapy on peripheral and autonomic neuropathy, the impact of neuropathy on health-related quality of life, and the association of autonomic neuropathy with CVD.
- ▶ Preliminary results from an ancillary study have shown that there are no significant differences in neurocognitive function between the two treatment groups, suggesting that the higher rates of hypoglycemia in the intensive-treatment group have not affected cognitive function.

#### **Recommendation: Continue Studies To Verify Surrogates for Cardiovascular Events and Utilize Cardiovascular Data in the Design of Future Prospective Studies**

- ▶ A third carotid ultrasound is being implemented, and comparative studies of surrogates with clinical outcomes are planned.
- ▶ A cardiac magnetic resonance imaging (MRI) study will be funded through the *Special Funding Program*.

#### **Ongoing Evaluation**

To ensure continued and ongoing evaluation of the study design and the progress of the EDIC, the NIDDK has established an External Advisory Committee (EAC). The EAC is composed of investigators with scientific expertise relevant to research conducted by EDIC, but who are not members of the Consortium. The EAC meets annually to:

- ▶ Review activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and performance of clinical centers, data and clinical coordinating centers, central laboratories, and reading centers);
- ▶ Review data to ensure its quality, advise on procedures for analysis and data display, and advise on interpretation and implications of results; and
- ▶ Review proposed major modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

In addition, *ad hoc* advisory groups have been assembled to review new initiatives being proposed in EDIC and to review progress once initiatives have been implemented. Examples of these groups include an *ad hoc* advisory group for the current genetics study, review groups for proposals to obtain EDIC nonrenewable biologic samples, and groups recommending specific measures to be obtained for assessing CVD and autonomic and peripheral neuropathy.

### Coordination with Other Research Efforts

EDIC 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. The coordination of the genetic components of EDIC is described in the subsequent section entitled “Genetics of Diabetes Complications.” For a full description of ongoing collaborative efforts, please see Appendix 2.

### Capitalizing on Research Investment by Collaborating in Ancillary Studies:

- ▶ The EDIC study group has collaborated on studies of CVD, microvascular disease, urology, and neuropathy, thus providing access to this well-characterized patient population and to biosamples derived from the study to talented investigators outside the network.

### Enhancing Data Comparison Among Studies:

- ▶ The National Glycohemoglobin Standardization Program certifies clinical laboratories to use the standard set by DCCT/EDIC for measurements of HbA1c. Nearly all commercial laboratories providing this clinical test in the U.S. are now certified through this program supported by the *Special Funding Program*. This has allowed the National Diabetes Education Program to promulgate a nationwide public health campaign to achieve target HbA1c values based on the DCCT/EDIC.

### EDIC Administrative History

Date Initiative Started	1994
Date <i>Special Program</i> Funding Started	1998
CVD and Urology Components Started	2002
Participating Component	NIDDK

EDIC is a long-term follow-up study to the Diabetes Control and Complications Trial (DCCT) of 1,441 patients with type 1 diabetes conducted between 1983-1993.

## Genetics of Diabetic Complications

The following three consortia were grouped because they all address genetic factors that predispose diabetes patients to, or protect them from, developing complications in various organs. Each has unique attributes that make it highly valuable for genetic studies: EDIC's strength is the careful characterization of the cohort over 20 years of follow-up; FIND has a very large collection of families in which two or more siblings have diabetes; and GoKinD matches patients with type 1 diabetes with and without kidney complications and collects information from their parents.

## Epidemiology of Diabetes Interventions and Complications (EDIC)

The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of 1,441 patients who participated in the landmark Diabetes Control and Complications Trial (DCCT), which showed that intensive glucose control can prevent or delay microvascular (eye, kidney, and nerve) disease complications. For a detailed description of EDIC, please see the previous section. To capitalize on the long-term investment in the select EDIC cohort, the *Special Funding Program* supports a study on the genetics underlying diabetes complications in these patients. The study is analyzing expanded data regarding the progression of complications in EDIC participants and their affected and non-affected family members to identify DNA sequence differences that influence susceptibility to diabetic complications.

### Highlights of Progress

As of March 1, 2006, the progress of the genetics component of EDIC includes:

- Follow-up in over 2,983 relatives of EDIC participants to ascertain presence of diabetes; complications information for 147 diabetic siblings of EDIC participants.
- DNA collection in 1,399 living parents and 1,584 siblings.
- DNA analyzed for association with complications in 1,428 genetic markers (for mapping gene locations on chromosomes).
- Genetic variations in the angiotensin-converting enzyme (ACE) gene are associated with persistent leakage of a small amount of protein in the urine (microalbuminuria) and severe nephropathy in type 1 diabetes.

## Family Investigation of Nephropathy and Diabetes (FIND)

The FIND Consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease (nephropathy) in patients, especially those with diabetes, as well as genetic susceptibility to eye disease (retinopathy) in patients with diabetes. Five to ten percent of the people in FIND have type 1 diabetes. FIND is primarily supported by regularly appropriated NIH funds; however, support from the *Special Funding Program* has permitted expansion of FIND by initiation of a study of the genetic determinants of diabetic retinopathy in persons enrolled in the FIND family study. This component of the study compares the genes in pairs of siblings to identify candidate genes that may influence the development and severity of diabetic eye disease. FIND has also created a resource of genetic samples and data for use by investigators outside the FIND study group, for ancillary or follow-up studies. FIND represents the first large-scale study of the genetic determinants of retinopathy.

### Highlights of Progress

The progress that FIND has made in retinopathy research as of March 1, 2006, includes:

- The family study exceeded recruitment goals, collecting genetic information from 2,367 individuals, who form over 2,000 pairs of siblings from 896 families.
- Preliminary results indicate that sibling correlation for retinopathy is 0.2, indicating that about 40 percent of the severity of the disease can be attributed to genetic causes.
- The entire FIND study, including retinopathy, has recruited over 8,000 individuals, and early genome scan results have identified putative places in the chromosomes contributing to various diabetic conditions, including diabetic eye disease.
- Cell lines have been established for all participants to provide a renewable source of DNA to study.

### Genetics of Kidneys in Diabetes Study (GoKinD)

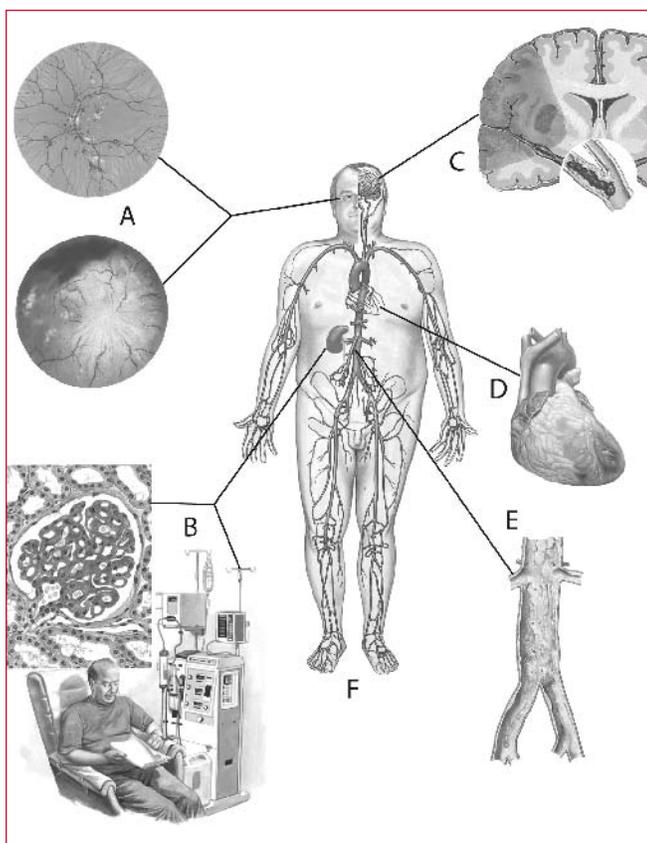
Patients with type 1 diabetes have a high risk of developing kidney disease. The fundamental aim of GoKinD is to facilitate investigator-driven research into the genetic basis of diabetic nephropathy by creating a resource of genetic samples from patients who have both type 1 diabetes and renal disease and “control” patients who have type 1 diabetes but no renal disease. With this design, the genes that confer risk for renal disease can be distinguished from those that are primarily risk factors for type 1 diabetes. Any researcher can apply for access to this collection of samples and data to investigate the role of specific genes.

### Highlights of Progress

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

- Completed collection includes recruitment of 935 patients with both type 1 diabetes and nephropathy; 271 of these include sample collections from parents of the patients. Collections also include samples from 945 diabetes patients without nephropathy; 322 of these collections include parental samples.
- High-resolution genetic data have been analyzed in the most important chromosomal regions for type 1 diabetes (insulin gene; important immune system components known as HLA genes). Because of the design of the collection, very specific information on the genetic risk in a closely inherited block of HLA genes (DRB1, DQA1, and DQB1) will improve the genetic prediction of type 1 diabetes.
- Seven new HLA gene variants (alleles) have been discovered in the study and named; another has been submitted for naming; and several additional new DQB1 alleles have been detected.
- Discovery that a TGF-beta-1 gene variant predisposes type 1 diabetes patients to nephropathy.
- The GoKinD clinical data have provided new information on the potential use of a protein called Cystatin C as an indicator of renal disease.





Type 1 diabetes is associated with serious medical complications. These complications can negatively affect the body in a variety of ways and include: (A) blindness; (B) kidney disease; (C) stroke; (D) heart disease; (E) atherosclerosis (clogged arteries); and (F) nerve damage leading to foot ulcers and amputation. The Epidemiology of Diabetes Interventions and Complications (EDIC), Genetics of Kidneys in Diabetes (GoKinD), and Family Investigation of Nephropathy and Diabetes (FIND) studies are examining the genes that predispose patients to, or protect them from, developing certain complications. (Illustration credit: F. Netter, MD, C. Machado, MD, and ICON Learning Systems. Netter medical illustration adapted with permission of Elsevier. All rights reserved.)

### Anticipated Outcomes

The diagnosis of type 1 diabetes does not automatically predestine a patient to all of the complications associated with the disease. Although the patient may be genetically susceptible to developing the disease itself, he or she may have a genetic composition that possibly confers protection from some dis-

ease complications, while increasing the risk of others. With more complete knowledge of the genetic factors that contribute to different complications, the patient's doctor may be able to intervene early to prevent or delay specific complications. For example, a patient genetically predisposed to diabetic nephropathy could employ clinical strategies such as carefully controlling blood pressure and taking ACE-inhibitors or angiotensin receptor blockers, which lower protein in the urine and are thought to directly prevent injury to the kidney's blood vessels. The synergy of the genetics research in EDIC, FIND, GoKinD, and the Type 1 Diabetes Genetics Consortium (T1DGC) (see Goal I) has promoted significant progress in the effort to identify and predict the natural history of type 1 diabetes and its complications in patients.

In addition to the gene discovery and genetic associations with diabetes complications under way with EDIC, FIND, and GoKinD, each of these consortia also serve as a resource for future efforts: tissue, genetic samples, data, and analytic methods from each Consortium are stored in a repository or database. The large and diverse sample and data collections—with families, cases, and controls—will become a widely-used resource for genetic study of susceptibility to diabetic complications. The availability of immortalized cell lines for each participant provides a renewable source of DNA, allowing future investigators to explore novel hypotheses or analytical approaches (such as whole genome association tests) that may be limited by current technology.

### External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of these three consortia with respect to their components focused on genetics of complications at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ Human genetic studies are extremely challenging because of the difficulty in recruiting a patient with diabetes who has developed complications, as well as two or more family members with type 1 diabetes. These studies would be considered virtually impossible with a standard NIH single-investigator (R01) grant mechanism.
- ▶ These consortia provide extraordinarily valuable collections with strengths in sample size and in heterogeneity. Despite achievement of lower than target recruitment numbers, there is a rich collection of material, including that from one of the largest collections of sibling-paired subjects for genetic analysis of diabetic kidney disease.
- ▶ Enrollment is often an issue in these kinds of studies, and it is not uncommon for genetics studies to have difficulty meeting recruitment goals. The panel noted that the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations and Institutional Review Board (IRB) requirements may have contributed to slower than projected enrollment.
- ▶ The search for genes involved in renal complications is especially promising because of the epidemiology findings: approximately 30 percent of diabetes patients develop nephropathy within 15 years, while patients who have not developed nephropathy in 15 years rarely do so later, suggesting a genetic difference.

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

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

**Recommendation:** Enhance Coordination Among Genetics Consortia Supported by the *Special Funding Program*

- ▶ In July 2005, the consortia supported by the *Special Funding Program* that study the genetics of diabetes complications (EDIC, FIND, and GoKinD) participated in a coordination meeting with the T1DGC. In response to recommendations from this meeting, new initiatives are being developed to coordinate future research efforts among these studies. A summary of this meeting can be accessed at:  
[www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf](http://www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf)

### **Recommendation:** Create a Single, Coherent, Accessible Database Combining the Studies

- ▶ The NIDDK Database Repository has created a single website ([www.niddkrepository.org/niddk/jsp/public/kidney.jsp](http://www.niddkrepository.org/niddk/jsp/public/kidney.jsp)) that summarizes the major characteristics of each of the four genetics studies. It also provides links to relevant study websites and publications, and a table comparing the data collected in the four studies. When data from high-density genotyping of samples in the collection become available, those data will be repositied in a single database at the NIDDK Database Repository.

### **Recommendation:** Share Lessons Learned About Methods for Effectively Addressing Recruiting Limitations

- ▶ A manuscript is in preparation by GoKinD recruiters that presents GoKinD recruitment data and explores the issues that result in barriers to recruitment.

**Recommendation:** Despite Achievement of Lower Than Target Recruitment Numbers, There is a Rich Collection of Material, Including That from One of the Largest Collections of Sibling-Paired Subjects for Genetic Analysis of Diabetic Kidney Disease

- ▶ The FIND family study exceeded recruitment goals, collecting genetic information from 2,367 individuals, who form over 2,000 pairs of siblings from 896 families.

**Recommendation: Use Guidelines Developed by the T1DGC as a Model for Standardizing Release of Materials**

- ▶ All four consortia have agreed to release samples and data by mid-2007 for completed collections.

**Ongoing Evaluation**

To ensure continued and ongoing evaluation of the study design and the progress of FIND and EDIC, the NIH has established External Advisory Committees (EAC). Each EAC is composed of investigators with scientific expertise relevant to research conducted by the Consortium, but who are not members of the Consortium. Please see a full description of “Ongoing Evaluation” of EDIC in the previous section.

The FIND EAC meets semi-annually to review the progress of the study. The advisors comment specifically on activities that affect the operational and methodological aspects of the study (e.g., quality control procedures and performance of clinical centers, data and clinical coordinating centers, and central laboratories and reading centers), review data to ensure its quality, advise on procedures for analysis, and review proposed significant modifications to the protocol or operations of the study for appropriateness, necessity, and impact on overall study objectives.

The GoKinD Executive Committee oversees the day-to-day operation of the study and consists of representatives from academia, government, and voluntary organizations. An external Steering Committee (SC) consisting of scientific and lay reviewers meets once a year to review the study and make recommendations.

**Coordination with Other Research Efforts**

The consortia studying the genetics of complications coordinate their efforts with each other and 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.

**Coordinating Studies of Genetics in Type 1 Diabetes:**

- ▶ EDIC, FIND, and GoKinD participated in a coordination meeting with the T1DGC (see “Actions Taken in Response to Expert Panel Recommendations” for a description of coordination efforts).
- ▶ Key personnel from the FIND study serve in official advisory capacities for GoKinD.

Developing Interoperable Databases for Data Sharing:

- ▶ A series of ongoing database coordination meetings between FIND, EDIC, and GoKinD are seeking to standardize vocabularies allowing investigators to search data across databases.
- ▶ The NIDDK is coordinating an integrated database of the parameters in the genetic studies of kidney disease in diabetes, which will include EDIC, GoKinD, and FIND.

Designing and Creating Animal Models of Disease for Basic Research from Genetics Data:

- ▶ The Animal Models of Diabetic Complications Consortium (AMDCC) semi-annual meeting on March 22-24, 2005, included presentations by FIND, GoKinD, and EDIC to initiate collaborations such that data originating from the genetics consortia will direct the creation of new animal models by the AMDCC, which will in turn validate the findings of the genetics consortia.

**EDIC Administrative History**

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Date Initiative Started	1994
Date <i>Special Program</i> Funding Started	1998
Participating Components	NIDDK

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EDIC is a long-term follow-up study to the Diabetes Control and Complications Trial (DCCT) of 1,441 patients with type 1 diabetes conducted between 1983 and 1993.

**FIND Administrative History**

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Date Initiative Started	1999
Date <i>Special Program</i> Funding Started	2001
Participating Components	NIDDK, NEI, NCMHD
Website	<a href="http://genepi.cwru.edu/FIND">http://genepi.cwru.edu/FIND</a>

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Ten percent of the subjects in the FIND family study have type 1 diabetes. Funds from the *Special Funding Program* have permitted expansion of FIND to support ancillary studies searching for genetic determinants of diabetic retinopathy.

**GoKinD Administrative History**

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Date Initiative Started	1998
Date <i>Special Program</i> Funding Started	1998
Recruitment Ended	2004
Participating Components	CDC, JDRF
Website	<a href="http://www.gokind.org">www.gokind.org</a>

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Saved blood plasma, blood serum, and urine samples are being stored at the CDC repository for use by any investigators in the diabetes research community based on a competitive review process.

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## Diabetic Retinopathy Clinical Research Network (DRCR.net)

The DRCR.net is a collaborative, nationwide network of eye doctors and investigators conducting clinical research of diabetes-induced retinal disorders (diabetic retinopathy, diabetic macular edema, and associated conditions). The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives while incorporating standardization of multiple study procedures, utilization of novel technology, extensive integration of information technology, and the ability to leverage its resources to bring promising new therapies to evaluation that might otherwise not exist. Principal emphasis is placed on clinical trials, but epidemiology, outcomes, and other research approaches may be supported as well. Diabetic retinopathies are complications associated with both type 1 and type 2 diabetes; DRCR.net, which is funded in part by the *Special Funding Program*, enrolls both type 1 and type 2 diabetes patients. In soliciting site participants, involvement of community-based, as well as academic-oriented partners, has been encouraged.

### Highlights of Progress

The progress that DRCR.net has made as of March 1, 2006, includes:

- Establishment of nationwide network including 165 clinical sites spanning 43 states. Community-based clinical sites comprise 61 percent of the network; most major research institution-based programs are also involved.
- An electronic visual acuity test has been distributed to all sites. This FDA-approved test is faster to administer than the standard version, and results are easily incorporated into a database.
- Completed study measuring variability in retinal thickening throughout the day in patients with diabetic macular edema.
- Completed enrollment of trial to evaluate different laser photocoagulation methods for diabetic macular edema.
- Completed enrollment and follow-up (through time of primary outcome) of trial to evaluate peribulbar steroid injection alone and in combination with laser photocoagulation for diabetic macular edema.
- Collaboration with industry on innovative protocol to create a drug that would not otherwise be commercially pursued (preservative-free intraocular steroid); recruitment in this Phase III study is near completion.
- Collaborating with industry on the development of a protocol to evaluate the injection of an anti-VEGF drug for diabetic macular edema.
- Five additional trials for diabetic retinopathy that are either in progress or will be initiated shortly.



A researcher examines a retina with diabetic eye disease. (Photo credit: National Eye Institute, National Institutes of Health.)

### **Anticipated Outcomes**

Diabetes (type 1 and type 2) is the leading cause of new blindness in people 20-74 years old.<sup>1</sup> Laser photocoagulation is an effective technique that uses the heat of a laser beam to seal abnormal leaky blood vessels in the retina. While laser photocoagulation can prevent blindness, the technique itself can lead to impaired vision. Therefore, improved technologies are being developed and tested by DRCR.net. One of the most important DRCR.net priorities for the future is to have a portfolio of ongoing clinical trials that not only encompasses a broad diversity of promising new therapeutic approaches, but also addresses the full spectrum of patients with diabetic eye disease. The Network is actively pursuing identification and design of important clinical trials that complement each other in terms of patient eligibility and therapeutic approach. This approach prevents competition between studies for similar patients and expands the opportunities for patients to participate in these investigations. The goal of the Network is to eventually have any patient with diabetes potentially eligible for a DRCR.net study. As a large-scale multicenter network,

DRCR.net has been successful at leveraging its resources to work with industry in developing therapies that might not have been otherwise pursued. Appreciation of the Network's benefits has prompted numerous inquiries from commercial entities regarding evaluation of new therapies by DRCR.net. These opportunities are being carefully considered to assure that any such study would assess a need judged timely and critical by DRCR.net and would maintain rigorous scientific and ethical guidelines.

DRCR.net contributes to the training and knowledge of the ophthalmologic community with regard to rigorous clinical trials. This is one of the reasons for including a large number of community-based sites, offering them an opportunity to participate and become experienced in these efforts. Such expansion of quality clinical centers helps not only the Network, but patients throughout the country and the overall education of the ophthalmologic community.

### **External Evaluation by Expert Panel**

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

- ▶ DRCR.net successfully met its goals in getting both private- and academic-based retinal practices involved in clinical trials to study epidemiology, therapies, and outcomes of diabetic retinopathy.
- ▶ DRCR.net is a very worthwhile infrastructure, and it is awaiting the emergence of additional innovative therapies to test.
- ▶ The panel was concerned that the Data and Safety Monitoring Committee performs both safety monitoring and protocol review (See "Ongoing Evaluation" section below). However, the panel also recognized that the Steering Committee (SC) provides oversight of protocol conduct.

- ▶ The network incorporated technological innovations such as an electronic visual acuity test to normalize measurements across centers and electronic Clinical Report Forms.
- ▶ DRCR.net could serve as a model for conducting clinical trials for other complications (i.e., kidney, nerve).

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

The expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 did not make any recommendations specific to DRCR.net. However, the panel discussed the dichotomy of consequences from the growth of new blood vessels (angiogenesis). Whereas angiogenesis in the eye leads to development of retinopathy, diabetes complications in other tissues are caused by a loss of blood vessels. Therapies to inhibit angiogenesis in the eye may actually provide a remedy for the development of retinopathy. In 2005, a research solicitation supported by the *Special Funding Program* on angiogenesis in type 1 diabetes (see Appendix 1) generated projects to complement the ongoing DRCR.net efforts in angiogenesis.

### **Ongoing Evaluation**

The DRCR.net Data and Safety Monitoring Committee (DSMC) has a dual role of external monitoring of network protocols and of advising the NEI on the merits of the protocols proposed by the Network as well as the Network's progress. The Committee meets in person at least twice a year and convenes by conference call as needed several times a year. The Network provides monthly data reports for the DSMC to review.

Within DRCR.net, there is an Executive Committee that is involved in policy decisions, as well as SCs that are involved in providing oversight for the development and conduct of each protocol. Each meets via conference call on a monthly basis with face-to-face meetings scheduled as necessary. The NEI has representation on these SCs.

In addition, a Protocol Concept Review Committee reviews ideas for protocols and advises the Executive Committee on whether an idea should be accepted for protocol development. If an idea is accepted, a Protocol Development Committee is created that is responsible for developing the protocol and has representatives from various aspects of DRCR.net. If the protocol involves a large randomized trial, it is presented to an External Protocol Review Committee whose members are assigned by the NEI to be advisory to the Institute regarding the protocol.

Additional committees created by the Executive Committee include a Data Collection Committee whose members advise the Network regarding development of efficient data collection procedures, and a Quality Assurance Committee whose members review detailed information prepared by the Coordinating Center regarding quality of enrollment, follow-up, adherence to protocol, timeliness of response to data queries, and other issues judged critical to maintaining excellent quality of Network clinical center activities. Summary reports are provided twice a year to the sites to strive for continued improvement in quality.

Representation on all of these committees by different clinical center investigators helps to ensure broad representation of investigators on most aspects of Network activities.

### Coordination with Other Research Efforts

The Network also provides funding for small projects judged critical to the development or implementation of its trials. For example, a bioactivity study on bevacizumab was developed to provide necessary data to the FDA regarding shelf life of the compounded drug.

### DRCR.net Administrative History

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Sites (Offices)	Over 150
Participating Physicians	Over 450
Participating Components	NEI, JDRF
Website	<a href="http://www.drcr.net">www.drcr.net</a>

DRCR.net consists of three cooperative agreements; participation is open to all qualified investigators/clinicians whose sites have the requisite equipment to conduct a study protocol.



## Animal Models of Diabetic Complications Consortium (AMDCC)

The AMDCC is an interdisciplinary Consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. Most groups in the Consortium generate mouse models of diabetic complications; however, one site has developed larger animal models by selectively breeding pigs and screening for observable characteristics (phenotypes) of diabetes. In addition to creating animal models, the goals of the AMDCC include defining standards to validate each diabetic complication for its similarity to the human disease, testing the role of candidate genes or chromosomal regions that emerge from genetic studies of human diabetic complications, and facilitating the sharing of animals, reagents, and expertise between members of the consortium and the greater scientific community via its bioinformatics and data coordinating center.

### Highlights of Progress

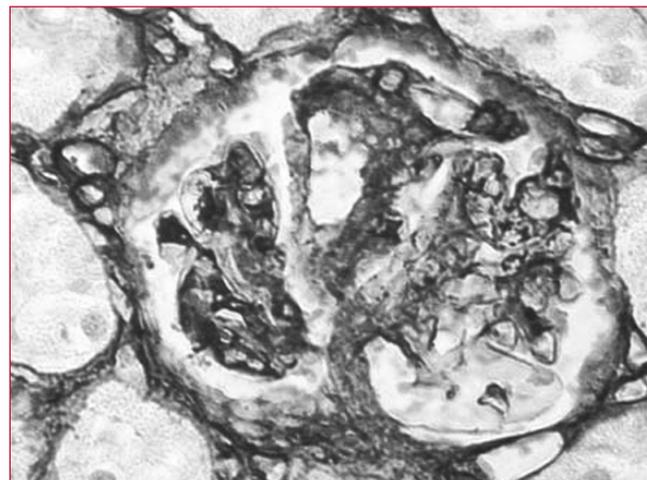
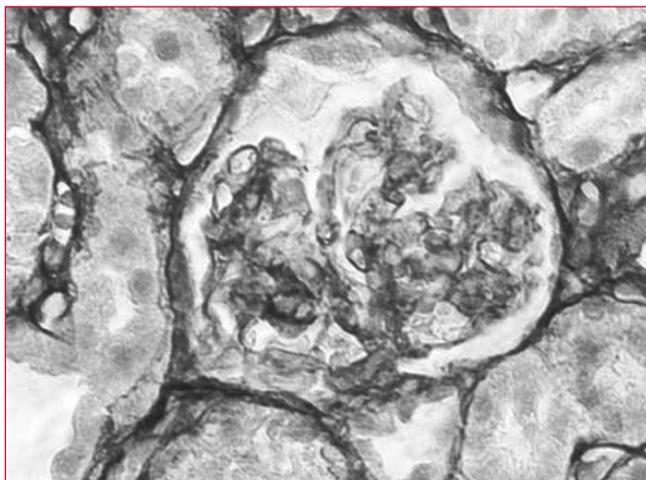
The progress that the AMDCC has made as of March 1, 2006, includes:

- Generated over 60 new mouse models for diabetic complications, including a number of promising models for type 1 diabetic complications of the heart, kidney, and nervous system.
- Generated a new insulin resistant pig model that exhibits hyperglycemia, vascular atherosclerosis, and retinopathy that closely mimics human disease.
- Defined validation criteria for diabetic nephropathy, cardiomyopathy, and micro- and macrovascular disease.
- Developed standardized assays for phenotyping diabetic complications to ensure that data can be easily compared between members of the Consortium and the outside community.
- Built a bioinformatics website featuring a comprehensive laboratory notebook that provides an interoperable phenotype database with statistical and graphical modules. The AMDCC website currently receives about 1,500 hits per month from outside investigators.
- Assembled necessary infrastructure to facilitate sharing of information across the many scientific disciplines involved in complications research and to ensure that animal models developed for one diabetic complication are screened for all relevant complications.

### Anticipated Outcomes

Animal models are an important scientific resource because they enable researchers to investigate underlying disease processes that cannot be studied in humans. For example, the demonstration of the key role of immune cells in the destruction of beta cells in type 1 diabetes would not have been possible without animal models. These models also permit assessment of novel therapeutic interventions before they are tested in people. The creation of the non-obese diabetic (NOD) mouse provided investigators with a critical tool for

pre-clinical testing of new drugs for type 1 diabetes. Just like people with type 1 diabetes, the NOD mouse has genetic susceptibility due to molecules regulating the immune response; the disease is influenced by environmental encounters; the animal produces autoantibodies against beta cell proteins; and the white blood cells infiltrate the pancreatic islets. In the animal model, beta cell destruction can be attenuated through application of agents capable of influencing the immune response.



Studies from the Animal Models of Diabetic Complications Consortium (AMDCC) have shown that diabetic kidney disease is accelerated in mice that lack a protein, called peroxisome proliferator-activated receptor-alpha (PPAR-alpha). To investigate the role of PPAR-alpha in diabetic kidney disease, researchers studied genetically engineered mice that lacked the PPAR-alpha gene. These images show kidney cortical glomeruli stained for type IV collagen, a marker of diabetic kidney disease, in mice that have the PPAR-alpha gene (left panel) or lack it (right panel). The data suggest that kidney damage is accelerated in the mice without the PPAR-alpha gene. AMDCC researchers have also recently demonstrated that activation of PPAR-alpha by the drug fenofibrate improves diabetes and its kidney complications in a mouse model of type 2 diabetes. (Images courtesy of Dr. Matthew Breyer. Copyright © 2006 American Diabetes Association. Adapted from *Diabetes*, Vol. 55, 2006; 885-893. Reprinted with permission from The American Diabetes Association.)

Following this successful approach, the AMDCC is designed to create better animal models of diabetes complications. Because the Consortium has invested in infrastructure to share its resources with the larger scientific community, the impact of its efforts on drug discovery is enormous. For example, a 2006 initiative supported by the *Special Funding Program* is screening compounds already approved by the FDA in cell-based assays for hyperglycemia (please see Appendix 1); compounds identified as potentially useful by a high-throughput screen can then be more intensively investigated in various animal models of diabetes complications to choose the most promising candidates for clinical trials. Animal models also provide an opportunity to identify surrogate markers for diabetic complications. Diagnosing intermediate stages of disease progression is a major challenge inhibiting clinical translation because disease progression is long-term and, at this point, the major focus of the FDA is on endpoints (e.g., death, cardiac events, and stroke). With over 60 new animal models and 50

peer-reviewed scientific publications, the AMDCC has played a critical role in propelling research progress by developing, validating, and distributing animal models with greater fidelity to human type 1 diabetes and its complications.

#### **External Evaluation by Expert Panel**

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

- ▶ The AMDCC's major strengths include the validation criteria and standards that were developed by the very strong phenotyping cores and data coordinating center.
- ▶ The AMDCC fosters research progress by bringing together leaders in the animal model and diabetic complications fields.

- ▶ Strong infrastructure is supported by a functional website for accessing validation criteria and technical methodologies.
- ▶ Although the focus has largely been on mouse models, a promising new large animal model has also been developed.
- ▶ A major resource provided by the AMDCC has been the “standardization” of measurements/endpoints in various diabetic complications.

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

The AMDCC 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: Sustain and Expand the Phenotyping Cores of the AMDCC**

- ▶ The AMDCC will partner with the NIDDK-supported Mouse Metabolic Phenotyping Centers (MMPCs) to ensure standardized phenotyping across all diabetic complications.

#### **Recommendation: Find Correlations Among Mouse Models Across the Spectrum of Different Complications**

- ▶ The AMDCC will share a Coordinating and Bioinformatics Unit with the MMPC to ensure that all phenotyping data generated by both consortia are housed together and easily compared across the spectrum of diabetes and its complications.

#### **Recommendation: Create an Outreach Effort To Provide Animal Models or Breeding Pairs to the Research Community**

- ▶ A Mouse Generation and Husbandry Core will be added to the AMDCC in 2006 to ensure that animal models and

breeding pairs are directly available to the research community.

#### **Recommendation: Emphasize Novel Technologies for Phenotyping for Intermediate Stage Diagnoses**

- ▶ NIDDK recently published a Program Announcement entitled, “Development of Disease Biomarkers” that includes specific language encouraging studies of “diabetes and its complications.” Additionally, a new initiative supported by the *Special Funds* calls for innovative research proposals to find and validate biomarkers for diabetic complications.

#### **Recommendation: Include an Immunologist in Oversight of Complications Models**

- ▶ Immunology expertise will be added to the AMDCC EAC in 2006.

### **Ongoing Evaluation**

The AMDCC is jointly managed by the NIDDK and NHLBI. Program Officers from both Institutes meet every 6 weeks to discuss recent progress and future directions. NIH representatives and AMDCC investigators participate in monthly conference calls; conference calls organized by the nephropathy, cardiovascular, and uropathy subcommittees also occur periodically.

To ensure continued and ongoing evaluation of the study design and the progress of the AMDCC, the NIH has established an EAC. The EAC is comprised of approximately a dozen outside experts who meet with the AMDCC investigators and representatives from the NIH and JDRF for 2 days, every 6 months. The meeting includes an open session where the investigators present their work and a closed session where Program Officers and the EAC evaluate progress and discuss future directions. Following this meeting, the EAC prepares a

written report of its deliberations. This report addresses general progress and productivity within the Consortium, as well as specific strengths and weaknesses of individual projects. The report typically contains a series of critiques prepared by EAC members to which the investigators must provide written responses.

AMDCC investigators must also prepare an Annual Progress Report for submission to the EAC. This document provides a written summary of yearly progress, an appraisal of the interactions between the ongoing projects at each site, and a description of the existing and planned collaborations with other members of the AMDCC.

### Coordination with Other Research Efforts

The AMDCC coordinates its efforts with 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.

Synergism with Genetics Consortia:

- ▶ One promising example of such coordination occurred at the AMDCC semi-annual meeting in March 2005. This meeting included presentations by members of the three existing diabetes genetics consortia (FIND, GoKinD, and EDIC). The collaborations established during this meeting ensure that the genes implicated by these large genetics studies will direct the creation of new animal models by the AMDCC. In turn, the ability of the AMDCC to confirm the role of these genes in animal models of disease will validate the findings of the genetics consortia.

- ▶ Further coordination is evident in the formation of a new partnership between the AMDCC and the NIDDK-supported MMPCs. The mission of the MMPCs is to conduct detailed metabolic phenotyping of genetically-altered mice. Thus, it is a logical extension of both consortia to have all mice generated by the AMDCC shipped to MMPC facilities. This close partnership will not only allow a number of organizational efficiencies, but more importantly, will make certain that all animals generated by the AMDCC are fully phenotyped across each relevant metabolic and diabetic complication.

#### AMDCC Administrative History

Date Initiative Started	2001
Date <i>Special Program</i> Funding Started	2001
Participating Components	NIDDK, NHLBI, JDRF
Website	www.amdcc.org

The AMDCC consists of eight model generation/validation sites, three phenotyping cores, and a bioinformatics/data coordinating center. Most sites are supported by cooperative agreements with the NIH.

## 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 preventing or reversing the complications of type 1 diabetes responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- ▶ "I studied diabetic neuropathy over 25 years using electrophysiological techniques. With this grant, preceded by others, I adopted a morphological approach to attempt to quantify the improvement in diabetic neuropathy after pancreas transplantation that I observed clinically. This new approach using confocal microscopy and immunostaining techniques to study sensory nerves procured by skin biopsy started an international trend to use these methods for diagnosis of several neuropathies. My successful attempt to extend this approach to nerves in internal organs, especially the gastrointestinal tract, has kept me in the field of diabetes research."
- ▶ "This grant was my first R01 and allowed me to justify dedicated research time and laboratory space. Without doubt, it was a factor in early promotion to Associate Professor (after 4 years on faculty) and tenure. Importantly, work funded by the grant was the basis for the development of research collaborations between the Diabetes/Endocrine and Cardiovascular Divisions and helped jumpstart an entire ultrasound microvascular research core. The work on this grant formed the basis for training multiple fellows, and several young investigator awards at national meetings."
- ▶ "This grant was critical for my career, as I am now considered a leading expert in diabetic neuropathy. As a result, diabetes is now the primary focus of my research laboratory, which currently consists of about 30 individuals. I am also now the director of [a clinical diabetes Center of Excellence], overseeing several clinical trials on treatment options for diabetic complications, and have won career achievement awards for my work. Therefore, the success of this NIH grant led to career advancement in both research and the clinic. Diabetic complications will continue to be the main thrust of my work until the end of my career."
- ▶ "It was my first clinical grant after many years of bench research, and it made me eager to continue to maintain a clinical arm to my efforts. I thus applied for another clinical grant from the JDRF, which was funded."

- ▶ “We have started a small company based upon some of the original findings made through this grant.”
- ▶ “Since the initial R21 award, I have transitioned my entire research program, not without substantial pain, into the area of diabetic neuropathy. I believe our ability to use proteomics and generate novel conditional transgenic

mouse models to investigate the contribution of specific genes toward Schwann cell dysfunction in diabetic neuropathy offers novel approaches that have been lacking in the field. Thus, the momentum provided by the initial award has been substantial and aided my securing additional support from the ADA and the NIH.”

### Improving Lives of People with Type 1 Diabetes

Diabetes slowly damages major organs in the body, such as the eyes, kidneys, and heart. Impressive research progress toward combating diabetes complications was achieved through a large clinical trial launched by the NIDDK. The Diabetes Control and Complications Trial (DCCT) was a multicenter clinical trial in over 1,400 people with type 1 diabetes. Completed in 1993, the trial compared the relationship between intensive versus conventional treatment of blood glucose levels and the development of complications affecting the small blood vessels in the eyes, kidneys, and nerves (microvascular complications). Patients on intensive treatment kept their blood glucose levels and hemoglobin A1c (HbA1c) levels (which reflect average blood glucose levels over a 2- to 3-month period) as close to normal as safely possible with frequent monitoring of blood glucose, and at least three insulin injections a day or use of an insulin pump. Conventional treatment consisted of one or two insulin injections a day, with once-a-day urine or blood glucose testing. The result was a large difference in the mean HbA1c levels in the two groups and a striking difference in their development of microvascular complications. The DCCT proved conclusively that intensive therapy reduces the risk of microvascular complications, such as diabetic eye, kidney, and nerve disease, by 35 to 76 percent compared with conventional treatment. This dramatic, positive result has had a profound impact on clinical practice for the management of type 1 diabetes: it led to the development of clinical guidelines by the ADA and other groups; it spurred the creation of the National Diabetes Education Program to disseminate the findings to the public ([www.ndep.nih.gov](http://www.ndep.nih.gov)); and it stimulated multifaceted research efforts to develop tools and therapies that aid patients in achieving close control of blood glucose levels.

Upon completion of the DCCT, participants who had received conventional treatment were taught intensive treatment, and all patients were encouraged to use intensive

treatment. Nearly all patients who participated in the DCCT volunteered for the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which began in 1994. EDIC was established to determine the long-term outcome of reducing exposure of the body's tissues and organs to high blood glucose levels.

Over 10 years after the end of the DCCT, further seminal insights continue to emerge regarding long-term benefits of intensive blood glucose control. In May 2002, EDIC investigators reported that the 6.5-year period of intensive treatment during the DCCT continued to reduce the risk of eye disease as long as 7 years after the study ended. Building on this exciting finding, a study in October 2003 showed that the former intensive treatment group had a decreased incidence of kidney damage and high blood pressure compared to the former conventional treatment group 8 years after the end of the DCCT. These long-term benefits were observed despite nearly identical blood glucose control in the patients after completion of the DCCT. Analysis showed these long lasting differences in development of complications could be explained by the difference in control of glucose levels between the two treatment groups during the DCCT.

While the DCCT proved that glucose control could prevent small vessel damage that causes kidney, eye, and nerve problems, controversy remained about the effect of glucose on cardiovascular disease (CVD). Studies had already shown that high glucose levels correlate with CVD, but the effectiveness of intensive glucose control in preventing or delaying CVD had not been proven. Through support in part by the *Special Statutory Funding Program for Type 1 Diabetes Research*, scientists were able to address this critically important topic. In June 2003, the DCCT/EDIC research group showed that patients in the former intensive therapy group had a decreased progression toward atherosclerosis compared to the patients in the former conventional therapy group. This effect was demonstrated using both ultrasound to measure thickening of the wall of the carotid

artery and also electron beam computed tomography to measure coronary calcification.

In December 2005, the DCCT/EDIC research group reported that, during an average follow-up time of 17 years, the patients who had been intensively treated during the trial had fewer than half the number of CVD events—heart attacks, strokes, or death due to cardiovascular disease—than those in the conventionally-treated group. These results showed for the first time that intensive control of blood glucose levels has long-term beneficial effects on CVD risk in type 1 diabetes patients. These findings are particularly significant because people with type 2 diabetes are 2-4 times more likely to die from CVD than individuals without diabetes,<sup>2</sup> and patients with type 1 diabetes face a 10-fold increased risk of CVD death.<sup>3,4</sup>

The findings of the DCCT/EDIC research team raise interesting questions about the “metabolic memory” that enables the beneficial effect of intensified blood glucose control to persist long after the period of intensive therapy has ended. Researchers are vigorously pursuing possible explanations for the enduring effects of intensive therapy that persist well beyond the period of improved glucose control. Continued efforts by scientists are also beginning to unravel the underlying molecular mechanisms by which elevated glucose levels damage small and large blood vessels and the tissues and organs that are affected.

Even though the results of the DCCT/EDIC studies show that intensive therapy is beneficial for long-term prevention of complications, a severe limitation to the practice of intensive therapy is the potential for acute episodes of hypoglycemia, or low blood sugar. Thus, researchers supported by the *Special Funding Program* are seeking new methods to improve blood glucose monitoring and insulin delivery and to develop new beta cell replacement therapy to cure type 1 diabetes. Researchers supported by the *Special Funding Program* have already been successful in developing continuous glucose monitoring technology that has been

recently approved by the FDA. This technology represents an important current opportunity to help patients implement the recommendations from the DCCT/EDIC that will enable them to achieve significant risk reduction for diabetic complications, while also reducing their risk for episodes of low blood glucose.

The DCCT and EDIC studies have directly and positively affected the manner in which patients and physicians manage diabetes. They have provided conclusive evidence that patients should begin intensive therapy as early as safely possible. By maintaining intensive therapy, patients have significantly reduced development of complications, which directly translates into an improved quality of life. The *Special Funding Program* will continue to support studies to investigate mechanisms by which glucose exerts its devastating effects in the development of complications, with a goal of discovering therapeutic targets to treat or prevent complications.

The DCCT and EDIC studies also demonstrate how the long-term investment in research continues to have a profound impact on the health of patients. Over 20 years after the beginning of the DCCT, researchers are just now demonstrating significant findings that continue to improve the care of type 1 diabetes patients and have implications for type 2 diabetes patients as well. Because the cohort of DCCT patients was too young for examination of cardiovascular complications when the study began, the long-term follow-up was necessary to assess the effect of intensive glucose control on this most life-threatening diabetic complication. Likewise, it is anticipated that the long-term research efforts that have been recently launched with support of the *Special Funding Program* will also result in dramatic and positive benefits for type 1 diabetes patients in the future.



## ANGIOGENESIS: A NEW FRONTIER IN DIABETES RESEARCH

Angiogenesis is a process in which new blood vessels grow from existing ones. This process is critically important to the development and growth of a healthy embryo. It is also important in some cases in a healthy adult. For example, angiogenesis is triggered at the site of a wound to help speed the repair process. However, aberrant angiogenesis can contribute to disease states, and over 70 diseases have been identified in the last two decades which depend on angiogenesis.<sup>5</sup> These diseases include cancer, heart disease, many eye disorders, psoriasis, rheumatoid arthritis, and some diabetic complications. Historically, angiogenesis is most commonly studied in relation to its role in cancer. Cancer research has resulted in significant new insights regarding the underlying molecular mechanisms that control angiogenic processes. Research supported by the *Special Statutory Funding Program for Type 1 Diabetes Research* is building upon and applying this knowledge to study angiogenesis as it relates to diabetes complications, with the ultimate goal of identifying new prevention and treatment strategies.

### Angiogenesis and Cancer: From Hypothesis to Therapeutic Agent

In 1971, Dr. Judah Folkman proposed a novel view of the importance of blood vessels in the cancer field when he suggested that tumor growth is dependent on angiogenesis. Subsequent research has confirmed this hypothesis, and scientists have demonstrated that primary tumor growth, as well as the spread of cancer to other parts of the body (metastasis), is dependent on new blood vessel formation. Without new blood vessels, the tumors lack the blood, oxygen, and other nutrients needed for growth.

Dr. Folkman further postulated that inhibiting angiogenesis was a reasonable approach for cancer therapy. He reasoned that if a therapeutic intervention could stop tumors from promoting angiogenesis, then it would in essence “starve” the tumor and inhibit its growth. Since Dr. Folkman’s initial observations and hypotheses, researchers have vigorously studied angiogenesis as it relates to cancer. In February

2004, the FDA approved the first cancer drug that works by inhibiting angiogenesis. The drug was approved for treating colorectal cancer. The approval of this therapeutic agent demonstrates how basic research to understand angiogenesis ultimately led to a therapy to treat some cancer patients.

### Applying Angiogenesis Research To Reduce the Burden of Diabetic Complications

Although research on angiogenesis has primarily focused on cancer, it is crucial to apply the lessons learned, as well as to expand upon this knowledge base, to benefit research on other diseases which depend on angiogenesis. Research has shown that angiogenesis plays a key role in the development of diabetic complications. Both type 1 and type 2 diabetes share the same disease complications, which include blindness, kidney failure, lower limb amputations, heart disease, and stroke. Even with recent advances in treatment, type 1 diabetes is estimated to lower average life expectancy by 15 years due to the development of these life-threatening and serious complications.<sup>6</sup> Because type 1 diabetes patients develop the disease so early in life, the complications can also develop earlier, be more serious and costly, and dramatically reduce patients’ quality-of-life.

The role of angiogenesis varies in different diabetic complications. For example, in diabetic eye disease (retinopathy), blood vessel growth in the eye directly leads to blindness because the new blood vessels are leaky and prone to bleeding. Likewise, research has suggested a role for excessive angiogenesis in the early phase of diabetic kidney disease (nephropathy). Therefore, a therapeutic agent to inhibit angiogenesis could potentially be used to treat these complications. However, in a diabetic wound, the blood vessels at the wound edge are abnormal, and studies in animal models have shown reduced angiogenesis in healing of skin wounds. Thus, an agent to promote angiogenesis selectively may be therapeutically useful to treat this complication. Because there is not a “one size fits all” strategy for treating diabetic complications, additional

research is needed to further elucidate the pathways that lead to abnormal angiogenesis in the different complications of diabetes.

### **Angiogenesis Research Supported by the Special Statutory Funding Program for Type 1 Diabetes Research**

To take advantage of the strong angiogenesis research base that has been realized by studying cancer, the *Special Funding Program* has propelled studies on angiogenesis related to diabetic complications, as described below.

#### **Collaborative Studies on Angiogenesis and Diabetic Complications**

The *Special Funding Program* has supported an initiative to stimulate research on the abnormal angiogenesis observed in type 1 diabetes and the mechanisms that lead to these abnormalities. The research supported under the initiative could ultimately lead to the development of therapies, biomarkers, and imaging tools to improve the diagnosis and treatment of diabetic complications. Ongoing studies include those to: elucidate the molecular pathways regulating angiogenesis in diabetic kidney disease; develop strategies to restore normal angiogenesis in type 1 diabetes patients to prevent the poor outcome of cardiovascular events (e.g., heart attack, stroke); understand the mechanisms that underlie the impaired function of endothelial precursor cells (cells that have been found to be involved in angiogenesis) in animal models of type 1 diabetes; and study the progression of diabetic retinopathy. Although these studies are still in their infancy, they have potential to provide insights regarding the aberrant angiogenesis observed in the development and progression of diabetic complications. This knowledge could be used to develop novel prevention and treatment strategies which could, in turn, improve morbidity and mortality associated with type 1 diabetes.

#### **Diabetic Retinopathy Clinical Research Network**

The NEI-led Diabetic Retinopathy Clinical Research Network (DRCR.net) facilitates the conduct of multicenter clinical

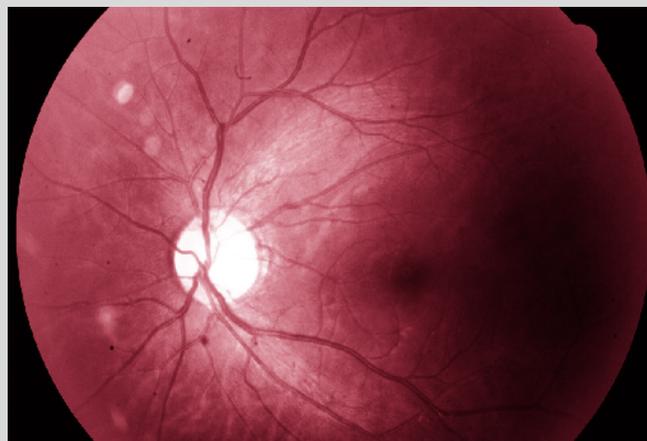


Image of human retina. Excessive angiogenesis (new blood vessel growth) in diabetic eye disease can lead to blindness; therapies to inhibit angiogenesis could possibly be used to prevent or treat this complication. (Image courtesy of Dr. Ray Gariano.)

research of diabetic retinopathy, diabetic macular edema, and associated conditions. The Network provides the infrastructure to permit the conduct of multiple concurrent and consecutive studies while retaining the ability to rapidly develop and initiate new protocols.

Because excessive angiogenesis in the eye leads to blindness, identifying a therapeutic agent that inhibits angiogenesis can tremendously benefit type 1 diabetes patients. Investigators in DRCR.net are currently collaborating with industry on the development of a protocol to evaluate an injected anti-VEGF drug as a therapy for diabetic macular edema. VEGF, or vascular endothelial growth factor, is associated with promoting angiogenesis in the eye; agents that block its action, such as anti-VEGF drugs, could possibly be used to inhibit angiogenesis. For example, a drug that can bind VEGF has already been approved by the FDA for treating age-related macular degeneration. Further clinical research studies are needed to determine if anti-VEGF drugs are effective on other eye diseases, including diabetic eye disease.

#### **NIH Trans-Institute Angiogenesis Research Program**

The potential for angiogenesis research to improve so many lives prompted the formation of the NIH Trans-Institute

Angiogenesis Research Program (TARP) in early 2004. The overall goal of this program is to apply a multidisciplinary approach to research in order to accelerate the discovery of new interventions for a variety of diseases and conditions. Importantly, advances in one disease area may fuel advances in others. The NIH TARP will ensure that discoveries in one disease area are rapidly applied to other disease areas so as to maximize the NIH's investment in angiogenesis research.

### **Angiogenesis Research in the Future**

The angiogenesis research supported by the *Special Funding Program* has the potential to not only

benefit type 1 diabetes patients, but also type 2 diabetes patients, who share similar disease complications. Scientific knowledge gained from this research can also help patients suffering from other diseases in which angiogenesis plays a role. Just as angiogenesis research has benefited some cancer patients, it is hoped that similar benefits for type 1 diabetes patients could be realized and that research will uncover novel ways to prevent or treat the devastating and life-threatening disease complications. It is only through continued research that this goal can be realized.

### At Age 18, a World-Class Ambassador for Diabetes Awareness

Eighteen-year-old college freshman Dana Lewis of Huntsville, Alabama, always considered herself a good talker. She's put that skill to very good use by helping to raise diabetes awareness not only throughout the U.S., but also throughout the world.

Dana was diagnosed with type 1 diabetes at age 14, and shortly thereafter began speaking at American Diabetes Association (ADA) events on behalf of people with the disease. At age 16, she was ADA's Alabama State Ambassador. A year later, Dana was crisscrossing the U.S. as ADA's National Youth Advocate, regularly meeting with policy makers to increase awareness about type 1 diabetes, and reaching out to her peers, as well as to adults, encouraging them to become involved in the fight against diabetes.

Today, Dana is reaching beyond America's borders, helping to make the entire world more aware of diabetes and its impact on people and society.

### International Diabetes Foundation Youth Ambassador

In 2006, the International Diabetes Foundation (IDF) selected 25 youth ambassadors from around the globe, "and I was chosen as one of them," Dana says proudly. Last December, she and her fellow youth ambassadors were invited to participate in the World Diabetes Congress held in South Africa, where they helped pass a United Nations Resolution that proclaims every November 14th, starting in 2007, as World Diabetes Day.

"This U.N. Resolution is one of the biggest and most important things that's happening to make the world more aware of diabetes and its consequences," says Dana. She is proud to be a part of this global effort



Dana Lewis

that is encouraging nations from around the world to develop national policies for the prevention, treatment, and care of diabetes. But when she was first diagnosed with type 1 diabetes 4 years ago, her initial reaction was quite different.

### Taking Good Care of Herself—and Others

Except for telling a few very close friends, Dana kept the fact that she had type 1 diabetes a secret from others for 4 or 5 months after her diagnosis. "I was scared of diabetes because my grandmother had been diagnosed with the type 2 form of the disease when I was 9 or 10 years old. Diabetes was a curse word to me," she says. "It took me a while to get used to being 'different,' and I didn't want to tell anyone that I had it."

Then one day, sitting in an advanced geometry class in high school, Dana suddenly made a complete turnaround. "I just all of a sudden said to myself that I want to get an insulin pump; I want to find a cure for this disease; I want to do whatever I can."

And given all of her diabetes-related activities, she's made good on that promise to herself.

Not only does Dana talk the talk; she walks the walk. She is acutely aware that tight regulation of blood sugar levels helps to prevent or delay the development of life-threatening complications related to diabetes, which include eye, kidney, nerve, and heart disease. Therefore, exercise, eating the right foods, and frequently testing her blood sugar levels are part of her daily routine.

"I take good care of myself," says Dana, "and I don't have any complications from my diabetes." Dana has two older brothers, but she is the only one in her family who has type 1 diabetes. "My mom keeps a close watch on my brothers for any symptoms, but so far they are both diabetes-free," she says.

Diabetes also has put Dana very much in touch with her body and herself. "I find that when I get stressed, my blood sugar goes up." To help prevent this problem, she spends part of every day by herself, just relaxing, perhaps reading or writing, which are two of her favorite things. To control her blood sugar levels, Dana also uses an insulin pump and is meticulous about checking her blood sugar levels at least 12 times a day.

In addition to taking care of herself, Dana is a strong advocate for finding ways to help others with their diabetes. "No matter what you do," she says, "doing something for someone else is better for you than anything. Volunteering is what puts diabetes in perspective for me."

To help teens like herself, Dana, when she was still in high school, created a support group, called "Teen

Team," which served as a venue for members to share their experiences. "Support groups provide an opportunity to meet other teens who have diabetes and to learn how they are managing and juggling the disease with everything else that's going on in their busy lives," she says. She encourages young people to contact a local diabetes education center or doctor's office to help get a support group up and running in their school or community.

"I feel strongly that young people with diabetes not only need to take good care of themselves, but they also need to advocate for research that will one day cure us of this disease," says Dana. She believes that her double major in public relations and political science at the University of Alabama will help her in her advocacy work on behalf of people with diabetes. She continues to speak at ADA events and encourages people to participate in America's Walk for Diabetes and the Tour de Cure to help find a cure for the disease.

Thankfully, Dana is healthy and active right now. "I live my life the way I do in spite of having diabetes, not because of it! I plan to make a difference in the fight against diabetes, and I'm working very hard to encourage as many young people as I can to get involved and to advocate for more research."

With all the improvements in research and technology, Dana has high hopes that a cure for diabetes will be found in her lifetime. In the meantime, she will do whatever she can to manage her disease, as well as advocate on behalf of others with diabetes.

## 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).

### Molecular Mechanisms of Common Pathways in Diabetic Complications

Identify Molecular Pathways of Hyperglycemia Damage:

- ▶ Discover the factors controlling hyperglycemia-induced reactive oxygen species (ROS) formation and adaptive and maladaptive cellular responses to increased ROS.
- ▶ Identify the molecular events controlling receptor for advanced glycation endproducts (RAGE) expression and endogenous soluble RAGE production.
- ▶ Discover the mechanisms by which hyperglycemia impairs bone marrow progenitor cell function, especially vascular cell progenitors needed to repair wounds and revascularize ischemic heart muscle, peripheral nerves, and lower limbs.
- ▶ Identify the mechanisms of vascular proliferation in diabetic retinopathy.
- ▶ Discover the mechanisms leading to diabetic neuropathy that can occur through impaired blood vessel function and other causes, such as advanced glycation endproducts (AGE) formation and alterations in nerve growth factor signaling.

Clarify Mechanisms Linking Fuel Utilization and Heart Disease:

- ▶ Characterize the factors controlling increased fatty acid accumulation and mitochondrial oxidation in the development of diabetic cardiomyopathy and accelerated atherosclerosis, as well as the mechanisms by which this cellular lipotoxicity induces cell damage.

Understand the Systems Biology of Diabetic Complications:

- ▶ Apply a systems biology approach to research on diabetic complications.

### Metabolic Memory

Discover the Molecular Mechanisms of Metabolic Memory:

- ▶ Study epigenetic factors involved in metabolic memory.
- ▶ Investigate the role of mitochondria in metabolic memory.
- ▶ Understand the regulation of the antioxidant response element.

### Genetic Factors

Identify Genes Conferring Susceptibility and Resistance to Diabetic Complications:

- ▶ Determine the genes that increase susceptibility to diabetic complications.
- ▶ Discover genetic modifiers for diabetic complications.

### Animal Models

Develop More Human-like Animal Models of Diabetic Complications:

- ▶ Develop human-like mouse models for diabetic complications.
- ▶ Utilize large animal models of diabetic complications.

### Biomarkers and Surrogate Endpoints to Facilitate Clinical Trials

Identify Biomarkers or a Combination of Biomarkers for Earlier Detection of Cell and Tissue Damage:

- ▶ Validate newly developed biomarkers.
- ▶ Discover specific molecular targets and innovative technologies for early biomarker development.

Validate Surrogate Endpoints for Assessing the Progression of Complications in Clinical Trials:

- ▶ Develop surrogate endpoints for clinical trials in diabetic complications.

### **Therapies To Improve Patient Health**

Identify Therapeutics That Prevent or Reverse the Development and Progression of Diabetic Complications:

- ▶ Use high-throughput screening of molecular libraries to find new therapeutics for diabetic complications.
- ▶ Improve the high-throughput assays for diabetic complications.
- ▶ Apply the latest advances in drug development technology to diabetic complications.
- ▶ Encourage the translation to human application of promising new therapies.

Mitigate Psychosocial Complications and Comorbidities of Diabetes To Improve Quality of Life:

- ▶ Clarify the bidirectional influences of depression as a complication and potentially modifiable risk factor for type 1 diabetes complications.

Combine New Technology for Diabetes Management with Behavioral and Translational Research:

- ▶ Design family-based interventions to improve patient management of diabetes.
- ▶ Identify strategies to improve adherence to therapy in adolescents and young adults with type 1 diabetes.

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# **GOAL VI**

**ATTRACT NEW TALENT AND  
APPLY NEW TECHNOLOGIES TO  
RESEARCH ON TYPE 1 DIABETES**



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**The *Special Statutory Funding Program for Type 1 Diabetes Research* has expanded the research opportunities in type 1 diabetes and its complications by harnessing cutting edge tools and technologies in addition to attracting creative and skilled scientists with diverse backgrounds.**

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New and emerging technologies, coupled with a cadre of talented scientists, have the potential to generate breakthroughs in the understanding, prevention, treatment, and cure of type 1 diabetes. The *Special Funding Program* has facilitated the creation of multiple research consortia to tackle specific challenges that will impact the health of people with type 1 diabetes. These efforts have brought together clinical and basic researchers—linking scientists investigating the pathogenesis and therapy of type 1 diabetes and its complications with new technologies needed to pursue evolving areas of opportunity. In addition, the strategies used to study type 1 diabetes have expanded through interdisciplinary research approaches. This increased collaboration will be essential as type 1 diabetes research evolves.

The tools of biomedical research have changed rapidly due to the biotechnology revolution. Many technologies that were used 20 years ago have been replaced by technologies that permit scientists to conduct research more efficiently and to ask and answer new research questions. Imaging advances now afford researchers the ability to track cells in the body by means never before possible. Advances in genetics and molecular biology provide researchers with new insights into cellular processes. New animal models provide more realistic test systems in which to study disease onset and progression. These new and emerging technologies hold promise for advancing the type 1 diabetes research field.

The pace of discovery is accelerating, and, as in the past, future research advances should directly translate into improvements in the health and quality of life of patients. The *Special Funding Program* has enabled scientists to study biologic processes in ways that were once not possible. The *Special Funding Program* has allowed researchers to harness new technologies and information that have emerged in order to optimize progress. A talented workforce of researchers is being mobilized to apply their expertise to overcome current barriers. Pursuing novel research directions and attracting new research talent are key elements in conquering type 1 diabetes.

## 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 attract new talent and apply new technologies to research on type 1 diabetes 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.

### **Novel Imaging Technologies To Monitor Type 1 Diabetes Disease Progression and Islet Transplantation:**

Type 1 diabetes is typically diagnosed very late in disease progression, when most of the insulin-producing beta cells of the pancreas have already been destroyed. Imaging technologies are needed that can detect the first signs of beta cell destruction, monitor therapy against immune attack, or look for possible regeneration of beta cells. Scientists have recently developed a new, noninvasive imaging technology to monitor infiltration of inflammatory cells into the pancreas in an animal model of type 1 diabetes. This project was initiated with a small pilot and feasibility award supported by the *Special Funding Program*, which helped unite imaging and immunology experts. Under another pilot award from the *Special Funding Program*, scientists are exploring the use of positron emission tomography (PET) imaging to see radiolabeled ligands targeted to the insulin-producing beta cells within the pancreas. If such an approach proves successful, it would permit physicians to estimate the number or mass of a patient's own endogenous beta cells, as well as to monitor the fate of transplanted islets. These approaches are now being tested in people. If successful, they could dramatically improve the ability of researchers to perform type 1 diabetes clinical trials. They could also permit physicians to detect beta cell loss in people prior to onset of symptoms, facilitating earlier attempts to intervene in the disease process.

Another important advance is the successful labeling of isolated human and mouse islets, and mouse T cells, with non-toxic imaging probes that can be detected with magnetic resonance imaging (MRI), fluorescence, or nuclear imaging. The islets have been imaged quantitatively over time after implantation in the liver or under the kidney capsule in mice. T cells have been seen as they infiltrate the pancreas of a non-obese diabetic (NOD) mouse. Although such molecular imaging approaches are still very new, trials are beginning to test them in human patients, and it is hoped that these will soon include studies in type 1 diabetes.

### **Reducing Gut Permeability To Block Triggers of**

**Autoimmune Diseases:** Researchers funded by the *Special Funding Program* determined that a protein, called zonulin, is expressed at very high levels in the intestines of diabetic rats. Zonulin is involved in regulating intestinal tight junctions, which are gates through which molecules may cross into the intestine. When the tight junctions are not working properly, it becomes easier for foreign molecules to enter and possibly trigger the immune system. Increased intestinal permeability has been observed in numerous autoimmune diseases, including type 1 diabetes. Researchers have found that the increased level of zonulin correlates with an increase in intestinal permeability and the progression toward development of type 1 diabetes. When the rats were treated with an agent

that blocks zonulin from binding to its cellular receptor, the incidence of progression to type 1 diabetes was decreased by 70 percent. These findings suggest that zonulin is involved in the development of type 1 diabetes, and inhibition of zonulin may be a possible therapeutic approach to prevent or treat the disease. Based on these exciting discoveries and a Small Business Innovation Research (SBIR) grant, pharmaceuticals that target zonulin are being developed by academic and industry researchers.

**Generation of a Pipeline for Novel Therapeutic Agents:**

The *Special Funding Program* has created the infrastructure for investigators to translate research discoveries through the drug development process, ultimately resulting in therapeutic agents. For example, researchers have recently demonstrated that, in a mouse model of type 1 diabetes, treatment with an

anti-inflammatory drug, called lisofylline (LSF), after islet transplantation protected against recurrent autoimmunity (destruction of the transplanted cells by the autoimmune process that initially led to type 1 diabetes). Because recurrent autoimmunity is a major clinical barrier in human islet transplantation (CIT), LSF is a promising therapeutic agent to test in humans. Building upon these results, the Clinical Islet Transplantation (CIT) Consortium (see Goal III) will be testing LSF in humans. The LSF that will be used in the trial is being manufactured through the Type 1 Diabetes Rapid Access to Intervention Development (T1D-RAID) program. This example demonstrates how the *Special Funding Program* is supporting the discovery, manufacture, and testing of promising therapeutic agents, thereby creating a pipeline of agents that can potentially improve the health of patients.

## EVALUATION OF MAJOR EFFORTS TO BRIDGE DISCIPLINES, ATTRACT NEW TALENT, AND APPLY NEW TECHNOLOGIES TO RESEARCH ON TYPE 1 DIABETES

**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.

### Bench to Bedside Research on Type 1 Diabetes and Its Complications

The “bench to bedside” research initiatives have stimulated translational diabetes research by fostering interactions between basic and clinical scientists to move discoveries from a laboratory setting to pre-clinical or clinical testing of new therapies that could improve the health of people with type 1 diabetes. The goal of the program is for the basic and clinical scientists to use their combined expertise to foster the development of a basic research finding to the point where the underlying hypothesis can be tested in a clinical trial or an animal model to assess its value in the treatment and/or prevention of type 1 diabetes or its complications. Applicants are encouraged to propose pilot studies to evaluate a potential therapeutic approach with pre-specified milestones to determine feasibility of the approach. If the milestones are met, the novel R21/R33 grant mechanism allows for rapid transition from the first pilot phase (R21) to a possible second extended phase (R33) with more substantial support. Five of eight R21/R33 grants from the 2002 and 2003 “bench to bedside” initiative awards achieved their milestones and transitioned directly to the second phase R33. Those with evidence of feasibility could apply directly for the R33 exploratory/developmental awards. Two grants awarded as R21 alone successfully applied for 3-year R33 grants from a subsequent “bench to bedside” solicitation. R21 awards from the third solicitation in 2004 are still in progress.

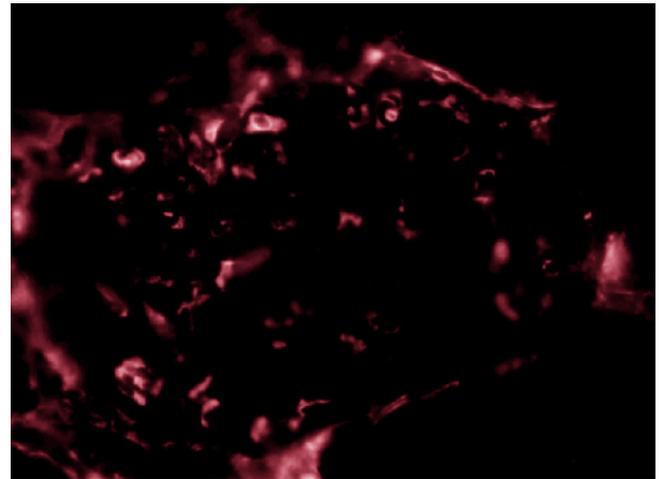
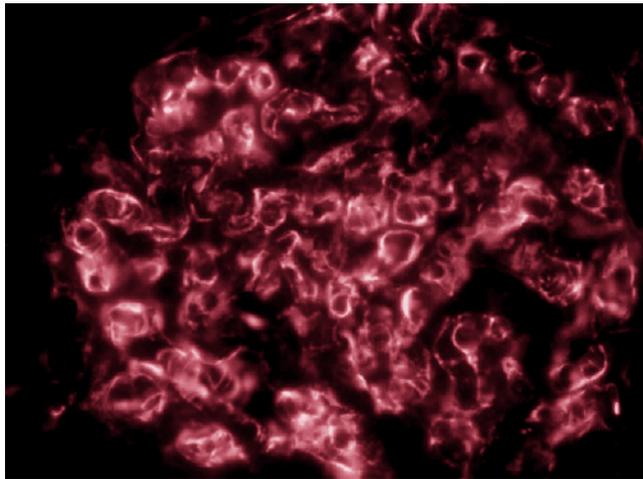
#### Highlights of Progress

Highlights of progress made by researchers supported through the “bench to bedside” initiative as of March 1, 2006, include:

- Demonstrated that the incidence of diabetes could be significantly delayed in a mouse model of type 1 diabetes. Researchers treated NOD dendritic cells (DCs) *ex vivo* with a mixture of antisense oligonucleotides and injected these engineered DCs one time into NOD mouse recipients. This single injection was sufficient to significantly delay the incidence of diabetes in the animal model. The protection was due to an increase in regulatory T cells. Previously, the investigators had tried this approach with DCs treated with NF-kappaB-specific oligodeoxyribonucleotide (ODN) *in vitro* and demonstrated that administration of these treated DCs into NOD mice aged 6-7 weeks effectively prevented the onset of diabetes. Thus, genetically engineering DCs to express “designer” immunosuppressive molecules suggest that gene therapy may be a viable method for preventing the onset of type 1 diabetes in genetically at-risk people.
- Demonstrated that, in a mouse model of type 1 diabetes, treatment with an anti-inflammatory drug, called lisofylline (LSF), after islet transplantation protected against recurrent autoimmunity. Because recurrent autoimmunity is a major clinical barrier in human islet transplantation, LSF is a promising therapeutic agent to test in humans. Building upon these results, the CIT Consortium (see Goal III) will be testing LSF in humans. The LSF that will be used in the trial is being manufactured through the T1D-RAID program (see additional information later in this chapter).
- Demonstrated that kidneys of diabetic mice have reduced levels of a protein that blocks blood vessel formation, called pigment epithelium-derived factor (PEDF). Furthermore, the researchers found evidence, in studies of cultured kidney cells, that increased glucose levels significantly decreased PEDF secretion. Subsequent studies showed that

increasing PEDF expression in diabetic mice using gene therapy reduced several factors associated with the development or progression of diabetic kidney disease including urine albumin, a marker of diabetic kidney disease. PEDF is therefore a potential therapeutic target for preventing or treating this devastating disease complication.

- Determined that a protein, called “zonulin,” is expressed at very high levels in the intestines of diabetic rats. Zonulin is involved in regulating intestinal tight junctions, which are gates through which molecules may cross into the intestine. When the tight junctions are not working properly, which can lead to increased intestinal permeability, it may be easier for molecules to enter into the intestine. Increased intestinal permeability has been observed in numerous autoimmune diseases, including type 1 diabetes. Researchers have found that the increased level of zonulin correlates with an increase in intestinal permeability and the progression toward development of type 1 diabetes. When the rats were treated with an agent that blocks zonulin from binding to its cellular receptor, the incidence of progression to type 1 diabetes was decreased by 70 percent. These findings suggest that zonulin may be involved in the development of type 1 diabetes, and inhibition of zonulin may be a possible therapeutic approach to prevent or treat the disease.



Analysis of the protein expression of pigment epithelium-derived factor (PEDF) in the kidneys of wild-type rats (left image) and diabetic rats (right image), is depicted by the red color. Less PEDF protein is expressed in the kidneys of diabetic rats. This study suggests that PEDF is a possible therapeutic target for diabetic kidney disease. (Images courtesy of Dr. Jian-xing Ma. Copyright © 2005 American Diabetes Association. From *Diabetes*, Vol. 54, 2005; 243-250. Reprinted with permission from The American Diabetes Association.)

### Anticipated Outcomes

The “bench to bedside” initiatives were developed to address a major barrier in clinical research—moving promising therapeutic agents from a laboratory setting to testing in actual type 1 diabetes patients. Although the full benefits of the program may not be realized for several years, the program has

already facilitated the conduct of clinical trials. For example, through research supported by this initiative, a therapeutic agent was found to prevent recurrent autoimmunity after islet transplantation in an animal model of type 1 diabetes. The agent will be tested to see if it has the same beneficial effects in a clinical trial of islet transplantation in humans. The

translation of a potentially beneficial therapeutic agent from bench to bedside is a key example of how the continuum of research supported by the *Special Funding Program* is making a significant impact on the lives of type 1 diabetes patients. Other potential therapeutic targets have also been identified through research supported by the *Special Program*—and additional targets and therapeutic agents are expected to be identified in the future—which can pave the way to more clinical trials to test promising agents. Another major strength of the program is the research partnerships that it has fostered. Partnerships between basic and clinical scientists enable both types of researchers to use their expertise to accelerate the movement of agents from bench to bedside. It is critically important to continue these types of translational research efforts so that there is a constant pipeline of therapeutic agents to test in future clinical trials. Such trials will propel the pace by which real improvements are made in the prevention and treatment of type 1 diabetes and its complications.

### External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of the “bench to bedside” initiatives 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 type of program is important and should continue. It is an excellent way to stimulate investigators to propel their laboratory research into a clinical or pre-clinical phase.
- ▶ One strength of this program is that it creates synergies between basic scientists and physicians at the same or different institutions.
- ▶ The critical juncture of research supported under this initiative is the transition from the R21 phase (the “bench”) to the R33 phase (the “bedside”).
- ▶ It is premature to judge success of this program; its impact will be realized in the next several years.

### Actions Taken in Response to Expert Panel Recommendations

The NIDDK took the following action in response to a recommendation of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

#### Recommendation: Continue To Support Bench to Bedside Research on Type 1 Diabetes and Its Complications

- ▶ R33 phase support continues through conversions from the R21 phase.

### Ongoing Evaluation

A trans-NIH committee, consisting of representatives from the NIDDK, NIAID, NHLBI, NINDS, and NEI, was established to oversee the transition from the R21 phase to the R33 phase for grants supported through this initiative. In some cases, external reviewers are convened to review the formal application requesting transition to the R33 phase; the reviewers make recommendations to the trans-NIH committee regarding whether the transition should occur.

#### Bench to Bedside Research Administrative History

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NEI, NHLBI, NINDS, ODS

In September 2002, 11 awards were made (5 R21 grants and 6 R21/R33 awards). In September 2003, 10 awards were made (7 R21 grants; 1 R33 grant; and 2 R21/R33 awards). In September 2004, 11 awards were made (6 R21 grants; 2 R33 grants; and 3 R21/R33 awards).

## Innovative Partnerships in Type 1 Diabetes Research

The overall objective of this research program is to support collaborations between investigators who focus their research efforts on type 1 diabetes or its complications and researchers from other research areas with relevant expertise. The intent is to attract new talent to type 1 diabetes research; strengthen the ongoing efforts of type 1 diabetes researchers by providing access to specialized expertise or technologies relevant to their research; and facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes. Through this program, type 1 diabetes researchers are encouraged to act as “talent scouts” by identifying and recruiting leading scientists with expertise relevant to the field of type 1 diabetes research. Using this mechanism, researchers with expertise in areas such as cell-based screening, imaging, genomics, and systems engineering are now pursuing research on type 1 diabetes. While awards issued under the program in 2002 provided only limited pilot support to initiate collaborations, it is noteworthy that 6 of 12 of those who applied for continued support to pursue these projects through regular research grants (R01s) were successful; this is substantially higher than the general R01 success rate.

### Highlights of Progress

The progress that has been accomplished through the Innovative Partners initiative as of March 1, 2006, includes:

- After analyzing pancreatic sections from persons with and without type 1 diabetes, researchers demonstrated that 88 percent of type 1 diabetes patients still had insulin-producing beta cells. Furthermore, the number of remaining beta cells was unrelated to duration of disease or age at death. The data suggest that most patients with the disease continue to make new beta cells throughout their lives, and these cells continue to be destroyed by the immune system. The source of these beta cells is unknown. Further research is needed to uncover the mechanism by which the body continues to make beta cells throughout the lifespan (such as research that is being pursued by the Beta Cell Biology Consortium [BCBC] [see Goal III]), so that new therapies could be developed to “coax” beta cell formation, together with halting the destruction of existing beta cells.
- Scientists have demonstrated that a cytokine, called stromal cell derived factor-1 (SDF-1), plays a key role in the development of diabetic retinopathy (eye disease). SDF-1 levels were found to be increased in eyes of patients with severe diabetic retinopathy. SDF-1 is thought to attract cells derived from bone marrow that are involved in response to injury, a process that goes awry in diabetic eye disease with excessive formation of leaky new blood vessels. Importantly, blocking SDF-1 function in the eyes of a rodent model of diabetic retinopathy prevented the formation of abnormal blood vessel growth—a hallmark of this disease complication. Therefore, SDF-1 is a promising target for preventing diabetic retinopathy, which is a serious and debilitating complication of type 1 diabetes.
- Lack of appropriate recognition of all partners is a serious deterrent to collaboration. Through this initiative, the NIDDK pioneered a novel solicitation mechanism so that all partners funded under this initiative were named as co-equal “Principal Investigators.” Previously, the standard policy at the NIH was to award an actual grant to only one principal investigator, while the partner was listed as a co-investigator. The new mechanism provided an important incentive to collaboration and attracted experts from diverse fields. The new awards benefited both partners, who receive equal recognition

for their contributions to the research study. This recognition can be beneficial to investigators, who may be evaluated by their home institution in terms of the number of grant awards they have received. The “co-principal investigator” mechanism—first employed by the NIDDK with this initiative—has now been implemented by the NIH as a whole.

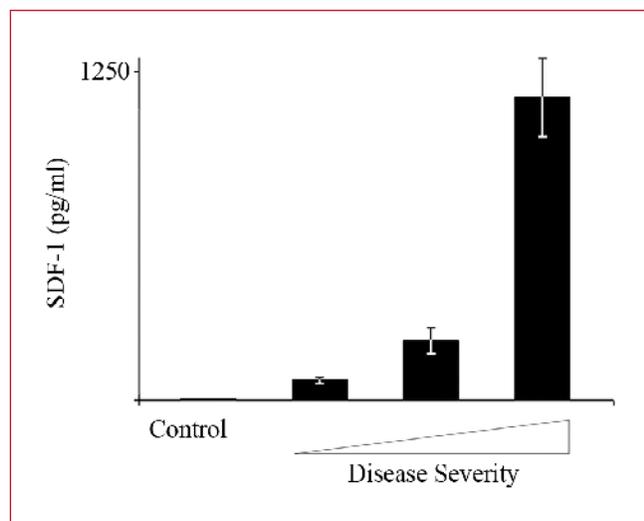
### Anticipated Outcomes

Because type 1 diabetes affects so many different organ systems (e.g., pancreas, eyes, kidneys, heart, nervous system), and involves such diverse areas of science (e.g., immunology, stem cell and developmental biology, bioengineering) and medicine (e.g., pediatrics, transplant surgery), it is imperative to attract new talent to pursue research in this complex disease field.

Type 1 diabetes will also benefit from the application of new and emerging technologies, such as imaging, proteomics, and metabolomics. As these types of new technologies are revolutionizing the biomedical research field, it has become increasingly important to build “teams” of researchers with diverse expertise. For example, researchers who study islet transplantation most likely do not have expertise in the specialized field of imaging. However, imaging techniques can greatly enhance the islet transplant field by allowing researchers to “see” the transplanted islets. This ability would permit them to determine if the islets are being rejected by the immune system and possibly intervene earlier to prevent graft rejection and the need for patients to resume insulin administration. Researchers with expertise in these two areas must partner to make real advances in this field, and the Innovative Partners program has supported just this type of partnership. The *Special Funding Program* has enabled the NIH to facilitate these and other types of important research partnerships that are necessary for attracting new talent to type 1 diabetes research, as well as taking advantage of new technologies to accelerate research progress.

### External Evaluation by Expert Panel

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



Researchers supported by the *Special Funding Program* measured the levels of a cytokine, SDF-1, in samples from the eyes of human patients with differing severity of diabetic eye disease, compared to non-diabetic control patients. They found that levels of SDF-1 increased with increasing severity of disease. The results of the study suggest that inhibiting SDF-1 could be a therapeutic approach for preventing diabetic eye disease. (Figure courtesy of Dr. Edward Scott [*J Clin Invest.* 115: 86-93, 2005]. Adapted from the *Journal of Clinical Investigation* by Butler, JM. Copyright 2005 by American Society for Clinical Investigation. Reproduced with permission of American Society for Clinical Investigation in the format Other Book via Copyright Clearance Center.)



- ▶ The program is an important way to attract new research talent and it should be continued. It is difficult for researchers in fields outside of diabetes to successfully apply for grant support if this partnership mechanism is not employed.
- ▶ The program's progress has been very good.
- ▶ A possible way of funding this program is by supporting competitive supplements to existing NIH type 1 diabetes research grants in order to enhance and broaden the roles of non-diabetes collaborators.
- ▶ A strength of the program is defining both partners as co-Principal Investigators (PI) rather than having a single PI and a collaborator. This co-equal distribution of leadership helps to incentivize the investigators.
- ▶ The program may be strengthened by increasing the award duration, which is currently 2 years. This increase would permit more time for researchers to build productive partnerships and perform collaborative research.

### Ongoing Evaluation

The NIH continually seeks input from the external scientific community regarding future research directions and emerging

research opportunities. The Innovative Partnership initiatives have been informed and enhanced by external input. For example, the repeat issuance of this initiative was recommended in 2002 by an *ad hoc* expert panel convened by the NIDDK to evaluate progress of the *Special Funding Program*. In addition, external experts encouraged the NIDDK to recognize both research partners as PIs. This mechanism was employed when the initiative was reissued. These are just a few examples of how the NIH solicits broad external input to evaluate ongoing programs and inform future research directions.

#### Innovative Partnerships Administrative History

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NEI, NHLBI, NINDS, NINR, ODS

The solicitation for investigator-initiated research grants was issued twice. In September 2002, 16 awards were made using the R21 grant mechanism for 2 years of support. The second initiative was issued in July 2004, using the R01 grant mechanism such that both of the research partners would receive recognition as the Principal Investigator on an NIH grant. In 2004, 23 R01 grants (supporting 11 research projects) were awarded.

## Research Training and Career Development in Pediatric Diabetes

Management of diabetes in children is particularly arduous and requires an exceptional level of effort from the children, their families, and their health care providers. These extraordinary clinical care demands make it challenging for pediatric endocrinologists involved in diabetes care to also pursue research careers. The purpose of this research program is to support research training and career development in pediatric diabetes at institutions with environments, mentors, and programs that will make them particularly effective in enhancing the number of independent investigators contributing to research in pediatric diabetes. The training program uses the T32 (Institutional National Research Service Awards) and the K12 (Mentored Clinical Scientist Development grants) mechanisms of support. In combination, the T32 and K12 programs provide an opportunity for continuous training from the clinical fellowship years to emergence as a fully trained independent investigator.

### Highlights of Progress

Highlights of progress made by trainees supported through the Pediatric Diabetes Research Training Program as of March 1, 2006, include:

- Fifty-nine pediatric endocrinologists have received training and career development to foster careers in pediatric diabetes research through this program.
- Eighteen of the trainees have attained faculty positions at universities (e.g., Stanford University, University of Iowa, Children's Hospital of Buffalo, Children's Hospital of South Carolina, The Ohio State University, University of Alabama, and University of Pennsylvania).
- Trainees have published over 200 peer-reviewed papers, editorials, book chapters, and reviews (published or in press) and over 200 scientific abstracts.
- The T32/K12 trainees have obtained numerous other prestigious grants to support their research and training (e.g., Lawson-Wilkens Pediatric Endocrine Fellowships and Clinical Scholar Awards, Juvenile Diabetes Research Foundation (JDRF) regular research grants, Centers for Disease Control and Prevention (CDC) grants, awards through the NIH Loan Repayment Program, pilot and feasibility awards through NIH/NIDDK Center grants, and private foundation awards).
- The T32/K12 trainees have been involved in numerous significant scientific activities, such as: mentoring summer research students; giving invited scientific lectures; preparing invited reviews of publications for scientific journals; and completing Certificates in Clinical Science or Public Health.

### Anticipated Outcomes

Several of the trainees who have been supported by this program have already moved forward in their career path to secure their own research funding and/or begin their own independent research program studying pediatric diabetes (for example, see "Investigator Profile" in this chapter). This program provides critical support to incentivize persons to enter the pediatric diabetes research field—and, importantly,

to continue to pursue research in this area after their training ends. For example, the K12 award could provide "bridge" funding between a fellowship and finding an independent faculty position; the award permits recipients to continue their research endeavors while securing independent funding. Because pediatric endocrinologists have such specialized knowledge about diabetes in children, applying their expertise



The *Special Funding Program* supports research training and career development in pediatric diabetes. Training a workforce of talented individuals to pursue diabetes research is essential to accelerating and maintaining research progress. (Photo credit: Getty Images.)

to research is truly critical to advancing research progress on type 1 diabetes. Furthermore, their combination of research and clinical experience is extremely beneficial to translational research efforts. The *Special Funding Program* has spurred the expansion of a workforce of these specialists to tackle research on type 1 diabetes in children. As more of the trainees leave their training institutions and begin their own independent research programs, the beneficial effects of this program will be realized for many years to come.

### External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of the pediatric endocrinology training program 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 program is extremely important to attracting new investigators to research on pediatric diabetes, and it should be continued.

- ▶ It is important to continue to follow the trainees after they receive their awards to determine if they remain in the pediatric diabetes research field.

### Actions Taken in Response to Expert Panel Recommendations

The NIDDK 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: Follow Trainees After They Receive Their Awards to Determine if They Remain in the Pediatric Diabetes Research Field

- ▶ NIDDK program staff track the career path of T32 and K12 trainees.

#### Recommendation: Maintain Communication with Trainees in Order To Hear their Concerns To Help Retain New Investigators

- ▶ K12 trainees are invited to NIDDK K awardees meetings. In this setting, the trainees have an opportunity to meet the NIH staff members who will most likely be the program directors for their independent R01 grants. The goal of the meetings is to assist the researchers in their transition from being trainees to independent investigators. In addition, the meetings provide an opportunity for the NIH to receive feedback from the trainees.
- ▶ T32 trainees are invited to JDRF-sponsored fellows meetings. This venue also allows trainees to give feedback on their training experiences.

### Ongoing Evaluation

The T32/K12 program directors from each institution and NIDDK staff meet at least annually to discuss the overall progress of the training programs. Plans to collaborate in the training of the T32/K12 trainees have been discussed. The institutions also submit annual progress reports, which are

reviewed by NIDDK staff to ensure that sufficient progress is being made. Nearly all of the K12 trainees attended the NIDDK New Investigators' Workshop held in September 2004. In 2005, the JDRF hosted a forum that included the T32 trainees. Another NIDDK New Investigators' Workshop was held in April 2006, and new K12 trainees were invited to participate.

**Research Training and Career Development in Pediatric Diabetes  
Research Administrative History**

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, ADA, JDRF

Five combined research training/career development programs were established in FY 2002 for periods up to 5 years. Two additional programs were launched in FY 2003. Each program supports up to 5 pediatric endocrinologists (fellows or junior faculty) on either the T32 training grant or the K12 Mentored Clinical Scientist Development grant. In addition, each program was offered the opportunity to support the training of medical students during a summer research experience each year.

## **Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID)**

Promising ideas for novel therapeutic interventions can encounter roadblocks in movement from bench to bedside testing. Many investigators who have discovered a promising therapeutic agent in the laboratory do not have the resources or the background knowledge, for example, to “scale up” production of the agent for use in clinical trials. The T1D-RAID program was established to help overcome this major barrier to development of potential new therapeutics for type 1 diabetes and its complications. The program provides resources for pre-clinical development of drugs, natural products, and biologics that will be tested in clinical trials. The goal of T1D-RAID is to facilitate translation from the lab to the clinic of novel, scientifically meritorious therapeutic interventions for type 1 diabetes and its complications. T1D-RAID is not a grant mechanism and it does not sponsor clinical trials. Rather, it sponsors the work needed to get ready to do clinical trials. The program will assist investigators by providing pre-clinical development steps, the absence of which may impede clinical translation.

### **Highlights of Progress**

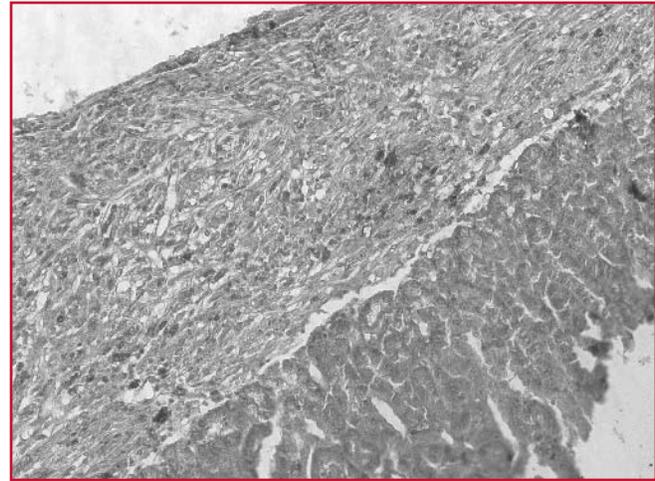
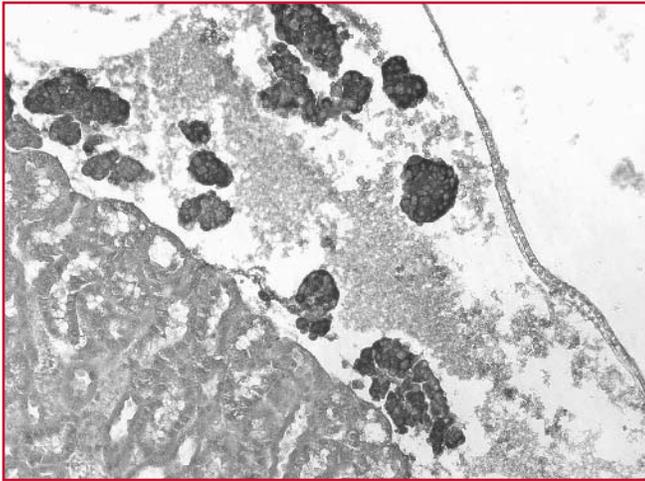
The progress that T1D-RAID has made as of March 1, 2006, includes:

- Approved five requests for use of pre-clinical drug development resources: (1) lisofylline, which is an anti-inflammatory compound that has a unique spectrum of activity to improve beta cell function and viability; (2) Starch-Deferoxamine, which is an iron-binding drug that will be tested in the treatment of diabetic neuropathy; (3) hOKT3-Gamma-1 (Ala-Ala) monoclonal antibody, which is a molecule that prevents the progression of type 1 diabetes in newly-diagnosed patients and may be useful in slowing onset of disease and in islet transplantation; (4) IL-2/Fc and mutant IL-15/Fc to be used in combination with rapamycin for treatment of new onset type 1 diabetes and for islet protection after islet transplantation; and (5) recombinant site-inactivated Factor VIIa (ASIS) to protect islets after islet transplantation.
- hOKT3-Gamma-1 (Ala-Ala) monoclonal antibody is being tested in a clinical trial in the Immune Tolerance Network (ITN) (see Goal II) to determine if it can halt the progression of type 1 diabetes in new onset patients and may also be studied for its ability to prevent type 1 diabetes in the Type 1 Diabetes TrialNet (TrialNet) (see Goal II);
- Lisofylline will be tested in a clinical trial supported by the CIT (see Goal III) to determine if it can help to prevent recurrent autoimmunity after islet transplantation.
- Recombinant site-inactivated Factor VIIa will be tested in a clinical trial supported by the JDRF to determine if it can help to prevent recurrent autoimmunity after islet transplantation.

### **Anticipated Outcomes**

Because clinical trials of agents to prevent, reverse, or treat type 1 diabetes and its complications are so important to realizing real improvements in the health and quality of life of patients, it is crucial to have a research continuum from the laboratory, where therapeutic agents are identified and initially tested, to the clinic, where agents are tested in patients. T1D-RAID provides a necessary resource that permits

researchers to overcome the major barrier to moving promising agents from bench to bedside. This type of resource has also been identified as critically important for propelling translational research efforts through the NIH Roadmap for Medical Research, and an initiative supporting an NIH-RAID pilot project has been released. T1D-RAID is already manufacturing agents for testing in type 1 diabetes clinical trials and



Scientists supported by the *Special Funding Program* demonstrated that an agent, lisofylline, prevented the recurrence of type 1 diabetes after islet transplantation in a mouse model. The islets were engrafted into the mouse's kidney capsule. To assess islet survival and insulin production, the kidneys were stained with an antibody to detect insulin. The grafts of mice treated with lisofylline (left panel) made insulin (depicted by the dark circles), while insulin could not be detected in untreated mice (right panel). Overall, the study suggested that lisofylline protected transplanted islets from autoimmune rejection. The Type 1 Diabetes—Rapid Access to Intervention Development program supported the manufacture of lisofylline for human studies that will be undertaken through the Clinical Islet Transplantation Consortium. (Images courtesy of Dr. Jerry Nadler and reprinted with permission from Yang Z, et al. *The novel anti-inflammatory agent lisofylline prevents autoimmune diabetic recurrence after islet transplantation*. *Transplantation*. 77 (1): 55-60, 2004.)

is expected to produce several more. As more knowledge is gained about the underlying mechanisms of disease development, including genes and environmental factors that cause disease (see Goal I), as well as key immune system players (see Goal II), researchers could use this information to develop additional targets for disease prevention and treatment. Therefore, having the T1D-RAID resource in place will help to translate these new discoveries from the laboratory to the clinic, thereby accelerating the pace at which therapeutic agents can be used to prevent or treat type 1 diabetes.

### External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of T1D-RAID at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ T1D-RAID is extremely important and should be continued.

- ▶ Although the program is relatively new, investigators have already begun to submit requests to use T1D-RAID resources, suggesting that there is a need for this type of program.
- ▶ The program should support pre-clinical development of therapeutic agents that span the type 1 diabetes research field, including complications.
- ▶ The monetary resources that support T1D-RAID must be sufficient to support the breadth of necessary research and resource development.

### Actions Taken in Response to Expert Panel Recommendations

The following actions were taken 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 the T1D-RAID Program

- ▶ Funding for T1D-RAID is being continued.

**Recommendation:** Create Initiatives Which Support Pre-Clinical Studies of New Therapeutic Agents To Prevent or Treat Type 1 Diabetes or Its Complications in Animal Models

- ▶ Two RFPs were issued in March 2005 to support performance of pre-clinical studies in animal models of potential new therapeutics for the prevention or treatment of type 1 diabetes or its complications.

**Recommendation:** The Program Should Support Pre-clinical Development of Therapeutic Agents That Span the Type 1 Diabetes Research Field, Including Complications

- ▶ The T1D-RAID program is supporting the production of Starch-Deferoxamine, which is an agent that will be tested for treating diabetic neuropathy—a devastating complication of type 1 diabetes.

**Ongoing Evaluation**

To determine which submitted requests are scientifically meritorious, the NIDDK convenes qualified external reviewers who make recommendations to the Institute regarding whether a project should receive support. Investigators whose projects are supported are invited to present their project to a joint NIDDK/NCI T1D-RAID team, at which time questions can be asked and decisions made regarding the exact next steps. Milestones for progression of the project are then set by the NIDDK, NCI, and the PI. Monthly meetings of the NIDDK/NCI T1D-RAID team review the progress and roadblocks on each project to ensure that projects are progressing and that information is widely disseminated.

**Coordination with Other Research Efforts**

T1D-RAID is supporting the pre-clinical development of therapeutic agents that will be tested in clinical trials supported by the *Special Funding Program*. Therefore, this resource has been critically important in facilitating the translation of agents from bench to bedside, where they will be tested in type 1 diabetes patients.

Facilitating Type 1 Diabetes Clinical Trials:

- ▶ T1D-RAID is supporting the manufacture of lisofylline, which will be tested in the CIT Consortium to determine if it can help reduce islet autoimmune destruction after islet transplantation.
- ▶ T1D-RAID is assisting in the manufacture of the hOKT3-Gamma-1 (Ala-Ala) monoclonal antibody, which will be tested in a clinical trial conducted by the Immune Tolerance Network to determine if it can halt further destruction of beta cells in new-onset type 1 diabetes patients.

**T1D-RAID Administrative History**

Date Initiative Started	2003
Date <i>Special Program</i> Funding Started	2004
Participating Components	NIDDK, NCI
Website	<a href="http://www.T1Diabetes.nih.gov/T1D-RAID/index.shtml">www.T1Diabetes.nih.gov/T1D-RAID/index.shtml</a>

The T1D-RAID program was modeled after the NCI's RAID program and is a collaboration between the NIDDK and NCI. The sponsors of approved requests to T1D-RAID gain access to the pre-clinical drug development contract resources of NCI's Developmental Therapeutics Program.

## EVALUATION OF INVESTIGATOR-INITIATED RESEARCH

**T**he Special Funding Program has supported pediatric diabetes research training and career development, as well as 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 attracting new talent and applying new technologies to research on type 1 diabetes responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- ▶ "The T32 diabetes training program has been extremely helpful in increasing the number of fellow trainees we have been able to accommodate. The K12 mentor-based program has, likewise, allowed us to train young pediatric endocrinologists in diabetes research producing excellent clinical investigators. An added bonus has been an increased clinical research productivity of our faculty as a byproduct of training our fellows and junior faculty in clinical research techniques."
- ▶ "The fellowship has produced exactly the type of candidate [highly ranked University Pediatric Endocrine programs are] looking for: a well-trained clinician with skills in clinical investigation who will be capable of collaborating in and initiating clinical research in their institution. Parenthetically, the availability of many excellent job opportunities for a well-trained pediatric endocrinologist attests to the continued significant shortage of pediatric endocrinologists across the United States."
- ▶ "The R21 was an invaluable way for me to establish independence as a clinician-scientist. I was the recipient of a K08 award as a junior faculty member. I received a small R03 grant, as a supplement to my K08, prior to my R21. The R21 began the day my K08 ended—enabling me to stay in diabetes-related research. As a pulmonologist doing cross-disciplinary research, it would have been nearly impossible to continue doing diabetes-related research without this support."
- ▶ "This program was a creative solution to increase the number of investigators in the area of type 1 diabetes, and to bring new ideas to bear on the problem. The people who developed the program should be complimented for that. I believe that collaborative research and generation of global resources will accelerate our ability to translate findings into new strategies for prevention and clinical cures."
- ▶ "This has been a very valuable source of funding for me and has allowed me, an active clinician-scientist, to remain in biomedical research. We have made some exciting discoveries, which I believe will have an immediate and positive impact on the field of human islet transplantation."



- ▶ “This grant has had a tremendous impact on my career. Because this was my first grant as a Principal Investigator, it greatly contributed in establishing my independent research project. In addition, it played an important part in my ability to keep focusing on type 1 diabetes and its complications in my research program.”
- ▶ “Before this grant I had never worked on diabetes. This grant gave me the opportunity to apply tools and concepts from tissue engineering and gene therapy to engineer potential solutions for this devastating disease. In this respect, this was a highly valuable grant that resulted in development of a project that would not have been pursued otherwise.”

## Research in Pediatric Endocrinology: Road to Independence

### A Lifelong Ambition

Dr. Andrew Norris always knew that he wanted to be a researcher. “Going into research was a lifelong ambition,” recalls Dr. Norris, an Assistant Professor at the University of Iowa. “Beginning in second grade, I read every science book in the library of my elementary school.”

Dr. Norris also developed an interest in medicine, so in order to pursue both medicine and research, he enrolled in a combined M.D. and Ph.D. training program at the Washington University School of Medicine in St. Louis. He entered the program intending to pursue medical research, with a particular interest in nutrition and the role that carbohydrates and lipids play in the development of human disease. He also enjoyed working with children. After receiving his degrees, he completed a pediatrics residency program. During that time, more and more children were being diagnosed with type 2 diabetes, and this sparked his interest in studying diabetes, an endocrine disease, in the pediatric population.

For further training as a sub-specialist in pediatric endocrinology, Dr. Norris applied to and was accepted into a combined fellowship program at the Children’s Hospital Boston and the Joslin Diabetes Center. “The fellowship program was an extremely wonderful experience for me,” recalls Dr. Norris, “and I went there with the intention of doing diabetes research.” During the first year of his fellowship, he worked directly with children with diabetes.

“I found that I really enjoyed working with children with diabetes and their families. This positive experience also synergized with my interest in research,” states Dr. Norris. During the next 2 years of his fellowship, he pursued research in the laboratory of Dr. C. Ronald Kahn, a prominent diabetes researcher. Dr. Norris recalls, “While working in Dr. Kahn’s lab, my goal was always to become an independent



Dr. Andrew Norris

investigator studying pediatric diabetes.” However, making the transition from being a research trainee to an independent investigator can be a daunting task.

### Transition to Independence

At the end of his fellowship, Dr. Norris would transition from being a “fellow” to a faculty member, at which time he would be expected to find his own source of funding to support his research program. In preparation for this transition, approximately 1 year before his fellowship ended, he applied for an NIH “Mentored Clinical Scientist Development Award” (K08) to support his research. Two months before becoming a faculty member, he found out that his application was, as he states, “good, but not good enough” to receive funding. Therefore, he was facing the prospect of having to put research on hold until he could find funding support.

Fortunately for Dr. Norris, the Children’s Hospital Boston/Joslin Diabetes Center was one of seven sites participating in the *Special Funding Program*-supported “Pediatric Diabetes Research Training and Career Development Program.”

Dr. Norris was familiar with this program because, earlier in his fellowship, he was supported by an institutional research training grant (T32) under this umbrella program. In addition to T32 training grants, the program also awards K12 grants (Clinical Scientist Career Development Program), which provide funding for investigators as they transition to independent faculty positions. "Fortunately," says Dr. Norris, "a K12 slot was available when I needed funding to bridge time between completing my fellowship and receiving my own grant. Without the K12 award, I would not have had professional time to pursue diabetes research, and might have instead had no choice but to spend the majority of my time in the clinic. This award mechanism allowed me to have 'protected time' so that I could resubmit my K08 grant application and still focus on diabetes research and building my own research program." While receiving support from the K12 training grant for 1 year, Dr. Norris resubmitted his K08 application and was awarded funding. Importantly, there was no disruption to his diabetes research endeavors.

Dr. Norris recently joined the faculty at the University of Iowa, where he directs his own independent research program. His research focuses on how the events early in life affect later risk of diabetes and diabetic complications. As an example, a person's blood sugar level today has a strong effect on his or her risk of complications years down the line, even if the individual feels healthy in the interim. In other words, as Dr. Norris states, "The immediate effect is subtle and unnoticed, but over time can lead to significant problems." To this end, he is developing new mathematical models to better identify the early subtle effects of diabetes on gene expression. These tools will help determine how these barely noticeable effects eventually lead to such devastating complications. The hope is to develop improved strategies enabling doctors to better prevent or delay the development of complications, which affect patients with both type 1 and type 2 diabetes. Dr. Norris is also studying the ways that abnormal buildup of fat contributes to the complications of diabetes as well as the development of insulin resistance. This research could provide insights

into additional means to prevent or delay certain diabetic complications.

Dr. Norris stresses that, "Because of the shortage of pediatric endocrinologists throughout the country, the pediatric endocrinology research training program is of incredible importance to attracting talented individuals to pursue research in this area." Furthermore, he notes, "It is difficult to secure funding for independent research by the end of a fellowship. The K12 grant mechanism is a necessary tool to bridge the gap between completing research training and pursuing independent research."

### **Pediatric Diabetes Training Program**

To enlarge the pool of pediatric endocrinologists conducting diabetes research, the NIH, in partnership with the ADA and the JDRF and with support by the *Special Funding Program*, awarded institution-wide research training and career development grants to seven medical centers with strong research programs in childhood diabetes: Children's Hospital Boston/Joslin Diabetes Center, where Dr. Norris received his training; Baylor College of Medicine; University of Colorado; University of Pennsylvania; University of Pittsburgh; Washington University; and Yale University. More information on the program can be found at: [www.niddk.nih.gov/fund/diabetesspecialfunds/train\\_peddiab.htm](http://www.niddk.nih.gov/fund/diabetesspecialfunds/train_peddiab.htm).

The awards, through the T32 (institutional research training) and K12 (Clinical Scientist Career Development Program) grant mechanisms of the NIH, provide for 2-3 years of fellowship training, as well as 2-3 additional years of support for junior clinical investigators, for a total of 5-6 years of continuous, uninterrupted research training in diabetes. The funding supports up to five positions at each medical center; each center was free to decide how many of the five slots were to be reserved for pediatric endocrinology fellows or investigators who were transitioning from fellow to independent scientist.

## INNOVATIVE PARTNERSHIPS IN TYPE 1 DIABETES RESEARCH: A NOVEL CO-PRINCIPAL INVESTIGATOR MECHANISM

Because research on type 1 diabetes spans a broad range of scientific disciplines, propelling research progress requires a cadre of scientists with diverse research training and expertise. To attract new research talent to study type 1 diabetes and its complications, the NIH has supported an initiative on “Innovative Partnerships in Type 1 Diabetes Research.” The overall objective of the initiative was to support collaborations between investigators who focus their research efforts on type 1 diabetes or its complications and investigators from other research areas with expertise relevant to type 1 diabetes. Type 1 diabetes researchers therefore acted as “talent scouts” by identifying and recruiting leading scientists with expertise relevant to the field of type 1 diabetes research. Using this mechanism, researchers with expertise in areas such as cell-based screening, imaging, genomics, and systems engineering are now pursuing research on type 1 diabetes.

The intent of the initiative was to encourage true partnerships in which two or more investigators with complementary expertise tackled a common problem. However, the standard policy at the NIH was to award a grant to only one principal investigator, while the partner was listed as a co-investigator—an

arrangement that did not recognize both partners as being equal and thus posed a barrier to collaboration. Based on feedback received from the external scientific community, the NIH pioneered a novel solicitation so that both partners were named as co-equal principal investigators. This arrangement was first used under the *Special Statutory Funding Program for Type 1 Diabetes Research*. It provided an important incentive to collaboration and attracted expertise from diverse fields. For example, one project brought together diabetes complications investigators with experts in angiogenesis (small blood vessel formation), thereby helping to move therapeutics currently used for cancer toward applications for diabetes complications. The new awards benefited both partners, who have now received equal recognition for their contributions to the research study. This recognition can be beneficial to investigators, who may be evaluated by their home institution in terms of the number of grant awards they have received. The “co-principal investigator” mechanism—first employed by the NIDDK with this initiative—is now being considered for broader implementation by the NIH as a whole, under the NIH Roadmap for Medical Research.

## 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).

### Engaging Talented Scientists

Recruit Expertise from Diverse Fields:

- ▶ Encourage interdisciplinary collaborations.

Design Incentives That Reward Research Innovation:

- ▶ Promote high-risk, high-impact research.
- ▶ Create an environment conducive to innovation and collaboration.

Train New Scientists in Clinical Type 1 Diabetes Research:

- ▶ Attract and train new diabetes investigators.

### Development and Application of New Technologies

Develop Noninvasive Imaging Technologies To Monitor Type 1 Diabetes:

- ▶ Develop imaging for pancreatic beta cell mass, function, and inflammation.
- ▶ Develop brain imaging techniques to use in understanding hypoglycemia.

Promote Application of Advances in Bioengineering to Type 1 Diabetes:

- ▶ Develop novel drug delivery methods.
- ▶ Develop noninvasive glucose monitoring technologies.
- ▶ Integrate tissue engineering and regenerative medicine to develop tissues and organs to replace those destroyed by diabetes and its complications.
- ▶ Apply nanomedicine to drug delivery, islet encapsulation, noninvasive imaging, and glucose-sensing technologies.

Foster Application of Gene Delivery and Gene Silencing Technology To Develop New Therapies for Type 1 Diabetes and Its Complications:

- ▶ Develop technology for gene delivery to cells and tissues that are therapeutic targets for type 1 diabetes.
- ▶ Create siRNA vectors for gene silencing in target tissues.

Apply New and Emerging Technologies in Functional Genomics, Proteomics, and Metabolomics to Type 1 Diabetes Research:

- ▶ Use “omics” technologies to identify interactions among genes, proteins, and metabolites in type 1 diabetes and its complications.
- ▶ Utilize proteomic and metabolomic technologies to identify and validate surrogate markers that predict risk, rate of progression, or response to therapy for type 1 diabetes and its complications.

Improve the Power of Diabetes Research by Utilizing Computational Biology and Bioinformatics:

- ▶ Enhance type 1 diabetes research efforts by incorporating bioinformatics at the inception of the research effort.
- ▶ Apply computational biology to the complex systems in type 1 diabetes.
- ▶ Integrate information technology into type 1 diabetes self-care and medical management.

Apply New Technology to the Development of Improved Animal Models for the Study of Type 1 Diabetes:

- ▶ Develop models needed to identify cellular and molecular pathways influencing beta cell formation and function.
- ▶ Develop animal systems with greater fidelity to human disease to enhance pre-clinical testing and biomarker development.

# APPENDIX 1: ALLOCATION OF THE SPECIAL STATUTORY FUNDS FOR TYPE 1 DIABETES RESEARCH

The complete budget allocation of the *Special Statutory Funding Program for Type 1 Diabetes Research* from FY 1998 through FY 2005 is provided in this Appendix. It is important to note that the six overarching goals of type 1 diabetes research are interdependent. For example, “Attracting New Talent and Applying New Technologies” (Goal VI) is important for every area of type 1 diabetes research. Furthermore, the scientific aims of many of the initiatives coincide with multiple Goals. However, to facilitate management of this program, most initiatives have been assigned to a single, specific Goal.

## BUDGET OF THE SPECIAL FUNDING PROGRAM

The expenditure of funds from the *Special Statutory Funding Program for Type 1 Diabetes Research* is detailed in Table A1. Budget figures for FY 1998 through FY 2005 represent actual spending levels. Some of the projects have received additional support from funds provided to the National Institutes of

Health (NIH) or the Centers for Disease Control and Prevention (CDC) through the regular appropriations process or through non-governmental sources. Scientific descriptions of each funded or planned initiative are located in the main text and this Appendix.

**Table A1: Detailed Budget by Goal of the Special Statutory Funding Program for Type 1 Diabetes Research (FY 1998-2005)**

	1998	1999	2000	2001	2002	2003	2004	2005
<b>GOAL I: IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES</b>								
Type 1 Diabetes Genetics Consortium (T1DGC) (NIDDK, NIAID, NHGRI, JDRF, Diabetes UK)	0	0	0	1,536,000	5,047,330	8,958,898	13,000,000	17,541,724
Repository Services for T1DGC (NIDDK)	0	0	0	0	0	0	0	1,000,000
13th International Histocompatibility Working Group (NIAID, NIDDK, NCI, NHGRI, JDRF)	0	0	0	3,000,000	1,000,000	0	0	0
Search for Diabetes in Youth (SEARCH) (CDC, NIDDK)	0	0	0	4,200,000	3,000,000	3,000,000	4,000,000	2,000,000
The Environmental Determinants of Diabetes in the Young (TEDDY) (RFA DK02-029) (NIDDK, NIAID, NICHD, NIEHS, CDC, JDRF, ADA)	0	0	0	0	5,000,000	7,568,300	17,500,000	24,542,679
Type 1 Diabetes Mouse Repository (NCR, NIDDK)	0	0	0	4,000,000	0	0	0	0
Bioinformatics Integration Support Contract (RFP AI-DAIT02-16) (NIAID)	0	0	0	0	1,000,000	0	0	0
Mammalian Gene Collection (NCI, NIDDK)	0	0	0	500,000	0	0	0	0
Sequence the NOD Mouse for Immune System Genes for Type 1 Diabetes (NIAID)	0	0	0	4,500,000	0	0	0	0
Biotechnology Resource Centers (RFA DK00-002) (NIDDK)	0	0	454,575	693,750	502,250	0	0	0
Functional Genomics of the Developing Endocrine Pancreas (RFA DK99-007) (NIDDK)	0	1,500,000	3,241,602	3,081,250	0	0	0	0
Public Health Pilot Programs in Newborn Screening (CDC)	246,718	301,544	548,261	804,826	609,652	0	0	0
Proficiency Testing for Laboratory Assays of Dried Blood Spots (CDC)	0	0	0	0	0	190,256	0	0
High-Throughput, High-Sensitivity Methods for Measuring Markers of Type 1 Diabetes (CDC)	246,718	268,648	219,305	219,305	219,305	0	0	0
Cadaveric Pancreata of Autoantibody Positive Individuals (NIDDK)	0	0	0	0	0	0	308,000	0
<b>Total—Goal I<sup>1</sup></b>	<b>493,436</b>	<b>2,070,192</b>	<b>4,463,743</b>	<b>22,535,131</b>	<b>16,378,537</b>	<b>19,717,454</b>	<b>34,808,000</b>	<b>45,084,403</b>

Table A1: continued

	1998	1999	2000	2001	2002	2003	2004	2005
<b>GOAL II: PREVENT OR REVERSE TYPE 1 DIABETES</b>								
Type 1 Diabetes TrialNet (RFA DK01-004) (NIDDK, NIAID, NICHD, JDRF, ADA) and Immune Tolerance Network (RFP-AI-99-30) (NIAID, NIDDK, JDRF) <sup>2</sup>	0	0	0	17,320,000	15,489,174	12,920,894	11,242,933	7,350,382
Recruitment for Clinical Research Studies (Matthews Media)	0	0	0	0	0	0	943,215	716,010
Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID) (Prevention Projects) (NIDDK, NCI)	0	0	0	0	0	0	105,000	1,575,503
Cooperative Study Group for Autoimmune Diseases Prevention (RFA AI00-016) (NIAID, NICHD, NIDDK, ORWH, JDRF)	0	0	0	2,154,000	2,318,796	2,336,681	2,354,595	2,392,355
Trial To Reduce IDDM in the Genetically-At-Risk (TRIGR) (NICHD, CIHR, EFSO, EU, JDRF, Mead Johnson, NDF)	0	0	0	2,000,000	500,000	500,000	3,000,000	1,799,998
Diabetes Autoantibody Standardization Program (DASP) (CDC, IDS)	816,680	746,014	438,609	778,609	755,199	1,158,101	675,000	566,000
C Peptide Standardization (CDC, NIDDK)	0	0	0	0	0	57,225	64,301	34,854
Data and Biosample Repository (RFP DK02-04) (NIDDK)	0	0	0	0	0	3,000,000	0	0
Gene Therapy Approaches for Diabetes and Its Complications (RFA DK01-006) (NIDDK, NHLBI, NIAID)	0	0	0	993,000	1,112,600	0	0	0
Innovative Grants on Immune Tolerance (RFA AI00-006) (NIAID, NIDDK)	0	0	0	2,443,000	1,658,523	1,658,523	982,665	741,765
Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013) (NIDDK, NIAID)	0	1,146,742	1,170,524	0	0	0	0	0
Immunopathogenesis of Type 1 Diabetes (RFA DK98-010) (NIDDK, NIAID, NICHD)	4,086,215	4,124,050	3,806,447	0	0	0	0	0
Autoantibodies in Type 1 Diabetes (NIDCR)	0	100,000	200,344	200,000	100,000	0	0	0
Diabetes Prevention Trial for Type 1 Diabetes—Supplements (NIDDK, NIAID, NICHD, NCRR)	3,350,000	95,000	0	0	0	0	0	0
One-Year Supplements to Ongoing Projects (NIDDK, NIAID, NCRR)	994,340	0	0	0	0	0	0	0
<b>Total—Goal II<sup>3</sup></b>	<b>9,247,235</b>	<b>6,211,806</b>	<b>5,615,924</b>	<b>25,888,609</b>	<b>21,934,292</b>	<b>21,631,424</b>	<b>19,367,709</b>	<b>15,176,867</b>



Table A1: continued

	1998	1999	2000	2001	2002	2003	2004	2005
<b>GOAL III: DEVELOP CELL REPLACEMENT THERAPY</b>								
Beta Cell Biology Consortium (RFA DK01-014) (NIDDK)	0	0	0	7,250,000	7,589,779	6,790,240	6,126,956	583,095
Beta Cell Biology Consortium (RFA DK04-017; RFA DK04-018) (NIDDK)	0	0	0	0	0	0	0	8,308,561
Clinical Islet Transplantation Consortium (RFA DK04-005; RFA DK04-004) (NIDDK, NIAID)	0	0	0	0	0	0	24,569,188	14,977,134
Comprehensive Programs in Beta Cell Biology (RFA DK02-014) (NIDDK)	0	0	0	0	3,154,850	3,055,850	2,393,922	1,942,751
Non-Human Primate Transplantation Tolerance Cooperative Study Group (RFA AI01-006) (NIAID, NIDDK)	0	0	0	518,000	1,822,876	1,772,003	4,979,323	4,156,398
Immune Tolerance Network—Islet Transplantation (RFP AI99-30) (NIAID, NIDDK, JDRF)	0	0	0	3,500,000	0	0	1,417,000	0
Immunobiology of Xenotransplantation Cooperative Research Program (RFA AI04-042) (NIAID, NIDDK)	0	0	0	0	0	0	0	1,929,129
NIDDK Intramural Program (NIDDK)	0	492,458	0	1,370,000	0	0	0	0
Islet Cell Resource Centers (ICR) (RFA RR01-002) (NCR, NIDDK)	0	0	0	5,000,000	1,999,998	5,000,000	5,000,000	5,000,000
Collaborative Islet Transplant Registry (CITR) (RFP DK00-02) (NIDDK)	0	0	0	3,964,000	0	0	0	336,988
Pilot and Feasibility Program in Human Islet Biology (RFA DK03-021) (NIDDK)	0	0	0	0	0	0	2,010,158	3,830,341
Islet Encapsulation Research (NIDDK)	0	0	0	0	894,471	0	0	0
Gene Transfer Approaches To Enhance Islet Transplantation (RFA DK02-020) (NIDDK, NIAID)	0	0	0	0	1,744,423	1,727,771	0	0
Imaging Pancreatic Beta Cell Mass, Function, Engraftment, or Inflammation (RFA DK02-002) (NIDDK)	0	0	0	0	1,258,302	1,356,106	651,723	651,723
New Strategies for Treatment of Type 1 Diabetes (RFA DK00-001) (NIDDK)	0	0	1,135,749	1,107,681	882,200	0	0	0
Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013) (NIDDK)	0	779,293	783,039	0	0	0	0	0
Cellular and Molecular Approaches to Achieving Euglycemia (RFA DK98-007) (NIDDK, NIAID, NICHD)	4,883,944	4,921,491	3,962,434	0	0	0	0	0
Beta Cell Proteomics (NIDDK, NHGRI)	0	0	0	2,495,000	0	0	0	0
Glucagon-like Peptide as a Differentiation Factor for Pancreatic Beta Cells (NIA)	94,379	99,995	0	0	0	0	0	0
One-Year Supplements to Ongoing Projects (NIDDK, NIAID, NICHD)	1,401,654	0	0	0	0	0	0	0
<b>Total—Goal III</b>	<b>6,293,237</b>	<b>5,881,222</b>	<b>25,204,681</b>	<b>19,346,899</b>	<b>19,701,970</b>	<b>47,148,270</b>	<b>41,716,120</b>	

Table A1: continued

	1998	1999	2000	2001	2002	2003	2004	2005
<b>GOAL IV: PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES</b>								
Diabetes Research in Children Network (DirecNet) (RFA HD01-009) (NICHD, NIDDK)	0	0	0	2,000,000	3,148,071	1,886,158	2,500,000	2,499,994
Standardization Program To Improve the Measurement of Blood Glucose (CDC)	0	148,284	188,931	231,526	101,319	209,282	0	0
Hypoglycemia in Patients with Type 1 Diabetes (RFA DK03-017) (NIDDK, NINDS)	0	0	0	0	0	0	2,475,590	2,532,821
Effects of Hypoglycemia on Neuronal and Glial Cell Function (RFA NS02-008) (NINDS, NIDDK, JDRF)	0	0	0	0	1,454,310	1,438,495	646,480	645,090
Sensor Development and Validation (RFA EB02-002) (NIBIB, NIDDK)	0	0	0	0	2,091,949	2,073,237	1,405,465	641,154
Understanding Hypoglycemia Unawareness in Patients with Diabetes (RFA DK01-031) (NIDDK, NINDS, JDRF)	0	0	0	0	2,055,648	2,036,527	1,362,001	1,361,842
Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013) (NIDDK)	0	141,408	130,216	0	0	0	0	0
Glucose Sensors in the Treatment of Diabetes (RFA DK98-008) (NIDDK, NCRN)	3,298,740	3,239,772	2,117,998	0	0	0	0	0
Developing New Tools for Detecting and Monitoring Low Blood Glucose (CDC)	0	142,548	142,548	142,548	142,548	0	0	0
Development of Surrogate Markers for Clinical Trials: Supplements (NIMH, NIDDK)	0	0	0	300,000	0	0	0	0
One-Year Supplements to Ongoing Projects (NIDDK, NCRN)	172,000	0	0	0	0	0	0	0
<b>Total—Goal IV</b>	<b>3,470,740</b>	<b>3,672,012</b>	<b>2,579,693</b>	<b>2,674,074</b>	<b>8,993,845</b>	<b>7,643,699</b>	<b>8,389,536</b>	<b>7,680,901</b>
<b>GOAL V: PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES</b>								
Genetics of Kidneys in Diabetes (GoKinD) Study (CDC, JDRF)	921,792	872,114	974,809	1,315,827	1,315,827	1,247,536	1,500,000	1,019,150
Epidemiology of Diabetes Interventions and Complications (EDIC): Genetics Study and Measurement of Cardiovascular Disease, Uropathy and Autonomic Neuropathy <sup>a</sup>	1,000,000	0	0	7,000,000	3,807,082	290,000	0	2,021,077
Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID) (Complications Projects) (NIDDK, NCI)	0	0	0	0	0	0	75,000	344,728
Family Investigation of Nephropathy and Diabetes (FIND) (NIDDK, NEI, NCMHD)	0	0	0	500,000	500,000	500,000	500,000	500,000
Diabetic Retinopathy Clinical Research Network (DRCR.net) (RFA EY01-001) (NEI)	0	0	0	0	2,000,000	2,000,000	2,000,000	1,000,000

Table A1: continued

	1998	1999	2000	2001	2002	2003	2004	2005
Animal Models of Diabetic Complications Consortium (RFA DK01-009 and HL01-010) (NIDDK, NHLBI)	0	0	0	3,982,000	4,135,862	4,055,585	4,252,287	4,296,778
Improving the Clinical Measurement of HbA1c (CDC)	768,092	520,848	487,537	466,649	384,903	534,825	600,000	600,000
Collaborative Studies on Angiogenesis and Diabetic Complications (RFA DK04-022) (NIDDK, NINDS, NHLBI, NEI)	0	0	0	0	0	0	0	1,736,225
Progression of Cardiovascular Disease in Type 1 Diabetes (RFA HL04-013) (NHLBI, NIDDK)	0	0	0	0	0	0	3,258,309	3,470,479
Feasibility Projects To Test Strategies for Preventing or Slowing the Progression of Diabetic Nephropathy (RFA DK02-025) (NIDDK)	0	0	0	0	1,325,273	1,190,190	0	0
Surrogate Markers for Diabetic Microvascular Complications (RFA DK02-016) (NIDDK, NEI, NINDS)	0	0	0	0	3,427,339	3,468,856	2,731,380	2,031,157
Imaging Early Markers of Diabetic Microvascular Complications in Peripheral Tissue (RFA DK02-001) (NIDDK)	0	0	0	0	1,282,371	1,288,444	729,250	729,250
Oral Microbiology/Immunology of Type 1 Diabetes (RFA DE01-001) (NIDCR)	0	0	0	645,000	500,000	0	0	0
Neurobiology of Diabetic Complications (RFA NS00-002) (NINDS, NIDDK, JDRF) <sup>5</sup>	0	0	907,406	895,971	610,916	442,485	712,852	0
Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013) (NIDDK, NHLBI, NEI)	0	1,174,221	1,159,255	0	0	0	0	0
Neurological Complications of Diabetes (RFA NS99-005) (NINDS, NIDDK)	0	2,243,319	2,193,073	2,007,389	1,603,619	0	0	0
Pathogenesis and Therapy of Complications of Diabetes (RFA DK98-009) (NIDDK, NEI, NHLBI, NICHD, NINDS)	6,713,260	6,914,914	5,622,671	440,431	452,086	0	0	0
Development of Clinical Markers for Kidney Disease (NIDDK)	0	0	0	834,000	0	0	0	0
Advanced Glycation Endproducts (CDC)	0	0	0	280,710	57,567	0	0	0
Development of Surrogate Markers for Clinical Trials: Supplement (NIEHS, NIDDK)	0	0	0	318,000	0	0	0	0
One-Year Supplements to Ongoing Projects (NIDDK, NEI, NIDCR, NICHD, NHLBI)	936,150	0	0	0	0	0	0	0
Functional Genomics Approaches to Diabetic <sup>6</sup> Complications—IHWG SNPs (NHGRI, NIDDK) <sup>6</sup>	0	0	0	750,000	0	0	0	0
<b>Total—Goal V<sup>7</sup></b>	<b>10,339,294</b>	<b>11,725,416</b>	<b>11,344,751</b>	<b>19,435,977</b>	<b>21,402,845</b>	<b>15,017,921</b>	<b>16,359,078</b>	<b>17,748,844</b>

Table A1: continued

	1998	1999	2000	2001	2002	2003	2004	2005
<b>GOAL VI: ATTRACT NEW TALENT AND APPLY NEW TECHNOLOGIES TO RESEARCH ON TYPE 1 DIABETES</b>								
Training Programs in Diabetes Research for Pediatric Endocrinologists (RFA DK02-024) (NIDDK, JDRF, ADA)	0	0	0	0	2,571,342	3,472,772	3,274,907	3,169,415
Innovative Partnerships in Type 1 Diabetes Research (RFA DK02-023) (NIDDK, NEI, NIAID)	0	0	0	0	5,778,702	5,620,843	4,337,638	4,258,939
Bench to Bedside Research on Type 1 Diabetes and Its Complications (RFA DK02-022) (NIDDK, NIAID)	0	0	0	0	3,443,507	3,587,082	392,500	1,236,677
Bench to Bedside Research on Type 1 Diabetes and Its Complications (RFA DK03-001) (NIDDK, NIAID, NEI, NHLBI)	0	0	0	0	0	3,449,975	3,415,870	1,629,440
Bench to Bedside Research on Type 1 Diabetes and Its Complications (RFA DK03-019) (NIDDK, NIAID, NEI, NHLBI, NINDS, ODS)	0	0	0	0	0	0	4,376,639	4,184,253
Proteomics and Metabolomics in Type 1 Diabetes and Its Complications (RFA DK03-024) (NIDDK, NIAID, NEI, NHLBI, NINDS, NICHD)	0	0	0	0	0	0	3,789,400	3,410,294
Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) RFA in Type 1 Diabetes and Its Complications (RFA DK03-020) (NIDDK, NEI, NIAID, NHLBI, NINDS, NICHD, NINR) and SBIR: Measurement Tools for Altered Autonomic Function in Spinal Cord Injury and Diabetes (RFA HD04-018) (NICHD, NIDDK)	0	0	0	0	0	0	4,202,727	4,167,000
Phased Innovation Partnerships (NIDDK)	0	0	0	4,049,000	0	0	0	0
<b>Total—Goal VI<sup>a</sup></b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>4,049,000</b>	<b>11,793,551</b>	<b>16,130,672</b>	<b>23,789,681</b>	<b>22,056,018</b>
Conferences and Other Expenses	69,318	27,337	114,667	212,528	150,031	156,860	137,726	536,847
<b>TOTALS:</b>	<b>30,000,000</b>	<b>30,000,000</b>	<b>30,000,000</b>	<b>100,000,000</b>	<b>100,000,000</b>	<b>100,000,000</b>	<b>150,000,000</b>	<b>150,000,000</b>

Footnotes for Table A1: In some instances, the funding levels reported in this table are different from those reported in the April 2003 Report on Progress and Opportunities of the *Special Funding Program* (accessed at: [www.niddk.nih.gov/federal/planning/type1\\_specialfund](http://www.niddk.nih.gov/federal/planning/type1_specialfund)). The following footnotes explain the differences.

1. The total funding for Goal I in FY01 has decreased because: (1) the EDIC Genetics Study was combined with the other EDIC funding in Goal V; (2) the TrialNet Epidemiology Study was combined with TrialNet funding in Goal II; and (3) Functional Genomics Approaches to Diabetic Complications was recategorized to Goal V because of its relevance to complications. The total funding for Goal I in FY02 has also decreased due to combining of TrialNet Epidemiology Study with TrialNet funding in Goal II.
2. The funding for TrialNet and ITN studies relevant to Goal II has been combined into a single line item. As noted in footnote 1, the TrialNet Epidemiology Study that was previously categorized in Goal I was also combined with TrialNet funding in FY01-02.
3. The total funding for Goal II in FY01-02 has increased because the TrialNet Epidemiology Study that was previously categorized in Goal I was combined with TrialNet funding in Goal II.
4. All EDIC funding has been combined into this line item. This total includes the FY01 funding for the EDIC Genetics Study that was previously categorized in Goal I.
5. The funding levels for FY01-03 were incorrectly reported in the April 2003 "Report on Progress and Opportunities." The adjusted numbers are reported here.
6. This item was previously listed in Goal I.
7. The total funding levels for Goal V are adjusted based on changes described in footnotes 4-6.
8. Prior to FY 2001, Goal VI was addressed by solicitations for research projects that encouraged the participation of new investigators and the submission of applications for pilot and feasibility awards. These early efforts relative to Goal VI are thus embedded in other goals during the FY 1998-2000 period of the program. Starting in FY 2001, specific initiatives were launched relative to Goal VI.

## EXTRAMURAL RESEARCH GRANTS

Extramural NIH grants, cooperative agreements, contracts, and supplements, which were awarded through the *Special Statutory Funding Program for Type 1 Diabetes Research* between FY 1998-2005, are listed in Table A2. Some initiatives supported additional awards with regularly appropriated funds; some awards were supported by both *Special Funds* and

regularly appropriated funds. Abstracts describing research topics pursued through these grants are available through the NIH CRISP (Computer Retrieval of Information on Scientific Projects) database at <http://crisp.cit.nih.gov>. Bibliometric analysis of publications resulting from these awards as of January 1, 2006, is found in the Assessment chapter.

**Table A2: Research Grants and Contracts Awarded with Special Program Funds**

	Year*	Project No.	Project Title
<b>GOAL I: IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES</b>			
<b>Type 1 Diabetes Genetics Consortium (T1DGC)</b>			
Donald Bowden, Wake Forest University <sup>†</sup>	2001	R01 DK056289	ID of Diabetes Genes on Human Chromosome 20Q12-Q13.1
Patrick Concannon, Virginia Mason Research Center	2001	R01 DK046635	Susceptibility Genes in Type 1 Diabetes
Stephen Rich, Wake Forest University Health Sciences	2002	U01 DK062418	Type 1 Diabetes Genetics Consortium
Johns Hopkins University	2002	N01 HG065403	Center for Inherited Disease Research
<b>Repository Services for T1DGC</b>			
Rutgers University	2005	N01 DK032610	Repository Services for T1DGC
<b>13th International Histocompatibility Working Group</b>			
John Hansen, Fred Hutchinson Cancer Research Center	2001	U24 AI049213	13th International Histocompatibility Working Group
<b>The Environmental Determinants of Diabetes in the Young (RFA DK02-029)</b>			
William Hagopian, Pacific Northwest Research Institute	2002	U01 DK063829	Diabetes Evaluation in Washington (DEW-IT) Clinical Center
Jeffrey Krischer, Moffitt Cancer Center and Research Institute	2002	U01 DK063790	Data Coordinating Center
Ake Lernmark, University of Washington	2002	U01 DK063861	Diabetes Prediction in Skane (DiPiS)
Marian Rewers, University of Colorado Health Sciences Center	2002	U01 DK063821	Environmental Causes of Type 1 Diabetes
Jin-Xiong She, Medical College of Georgia	2002	U01 DK063865	Consortium for Identification of Environmental Triggers
Olli Simell, Turku University Central Hospital	2002	U01 DK063863	Environmental Triggers of Type 1 Diabetes
Anette Ziegler, Diabetes Research Institute	2002	U01 DK063836	Type 1 Diabetes Triggers: Diet Modification in Neonates

\*The first year that the project received support from the *Special Funds*.

<sup>†</sup> Institutional affiliations at the time of the grant award are listed. Some Principal Investigators (PIs) have moved to new institutions.

Table A2: continued

	Year	Project No.	Project Title
<b>Uniform Population-based Approach to Case Ascertainment, Typology, Surveillance and Research on Childhood Diabetes: SEARCH for Diabetes in Youth Study (PA 00097)</b>			
Lawrence Dolan, Children's Hospital Medical Center, Cincinnati	2001	U48 CCU919219	Search for Diabetes in Youth
Richard Hamman, University of Colorado Health Sciences Center	2001	U48 CCU81924	Search for Diabetes in Youth
Elizabeth Mayer-Davis, University of South Carolina	2001	U48 CCU419249	Search for Diabetes in Youth
Diana Pettiti, Kaiser Permanente Southern California	2001	U48 CCU919219	Search for Diabetes in Youth
Catherine Pihoker, Children's Hospital and Regional Medical Center, Seattle	2001	U58 CCU019235	Search for Diabetes in Youth
Beatriz Rodriguez, Pacific Health Research Institute	2001	U58 CCU019235	Search for Diabetes in Youth
<b>Incidence, Natural History, and Quality of Life of Diabetes in Youth (SEARCH for Diabetes in Youth Study) (RFA DP05-069)</b>			
Ronny Bell, Wake Forest University Health Sciences	2005	U01 DP000250	SEARCH for Diabetes in Youth Coordinating Center
Dana Dabelea, University of Colorado at Denver Health Sciences Center	2005	U01 DP000247	SEARCH for Diabetes in Youth 2: Colorado Center
Lawrence Dolan, Children's Hospital Medical Center, Cincinnati	2005	U01 DP000248	SEARCH for Diabetes in Youth 2: Ohio Center
Jean Lawrence, Kaiser Permanente Southern California	2005	U01 DP000246	SEARCH for Diabetes in Youth 2: California Center
Elizabeth Mayer-Davis, University of South Carolina	2005	U01 DP000254	SEARCH for Diabetes in Youth 2: South Carolina Center
Catherine Pihoker, Children's Hospital and Regional Medical Center, Seattle	2005	U01 DP000244	SEARCH for Diabetes in Youth 2: Washington Site
Beatriz Rodriguez, Pacific Health Research Institute	2005	U01 DP000245	Search for Diabetes in Youth 2: Hawaii Center
<b>Type 1 Diabetes Mouse Repository</b>			
Muriel Davison, The Jackson Laboratory	2001	P40 RR009781	Transgenic and Targeted Mutant Preservation
<b>Cadaveric Pancreas of Autoantibody Positive Individuals</b>			
John Hutton, Barbara Davis Center for Childhood Diabetes	2004	P30 DK057516	UCHSC Diabetes and Endocrinology Research Center
<b>Bioinformatics Integration Support Contract (RFP NIAID-DAIT-02-016)</b>			
Northrop Grumman	2002	N01 AI025487	Bioinformatics Integration Support Contract
Research Triangle Institute	2002	N01 AI025486	Bioinformatics Integration Support Contract
<b>Mammalian Gene Collection</b>			
Science Applications International Corporation	2001	N01 CO012400	Mammalian Gene Collection
<b>Sequence the NOD Mouse for Immune System Genes for Type 1 Diabetes</b>			
University of California, San Francisco	2001	N01 AI015416	Collaborative Network for Clinical Research on Immune Tolerance
<b>Biotechnology Resource Centers (RFA DK00-002)</b>			
Jin-Xiong She, University of Florida	2000	U24 DK058778	NIDDK Biotechnology Center at the University of Florida
<b>Functional Genomics of the Developing Endocrine Pancreas (RFA DK99-007)</b>			
Klaus Kaestner, University of Pennsylvania	1999	R24 DK056947	Functional Genomics of the Developing Endocrine Pancreas
Marshall Permutt, Washington University	1999	R24 DK056954	Functional Genomics of the Developing Endocrine Pancreas

Table A2: continued

	Year	Project No.	Project Title
<b>GOAL II: PREVENT OR REVERSE TYPE 1 DIABETES</b>			
<b>Type 1 Diabetes TrialNet (RFA DK01-004)</b>			
John Lachin, George Washington University	2001	U01 DK061055	Type 1 Diabetes TrialNet: Operations Coordinating Center
Jay Skyler, University of Miami	2002	U01 DK061041	Type 1 Diabetes TrialNet
<b>Type 1 Diabetes TrialNet: Clinical Centers (RFA DK01-003)</b>			
Dorothy Becker, Children's Hospital of Pittsburgh	2005	U01 DK061058	Prediction and Prevention of Type 1 Diabetes
Jennifer Marks, University of Miami	2005	U01 DK061037	Diabetes TrialNet
Antoinette Moran, University of Minnesota	2005	U01 DK061036	Type 1 Diabetes—A Proposal for Prevention & Intervention
Tihamer Orban, Joslin Diabetes Center	2005	U01 DK061040	Type 1 Diabetes TrialNet: Clinical Centers
Henry Rodriguez, Indiana University School of Medicine	2005	U01 DK061038	Type 1 Diabetes TrialNet Indiana University Clinical Center
Darrell Wilson, Stanford University	2005	U01 DK061042	Type 1 Diabetes TrialNet at Stanford
<b>Immune Tolerance Network - Immunomodulation (RFP NIAID-99-30)</b>			
University of California, San Francisco	2001	N01 AI015416	Collaborative Network for Clinical Research on Immune Tolerance
<b>Recruitment for Clinical Research Studies</b>			
Matthews Media	2004	N02 DK032625	
Matthews Media	2004	N02 DK042680	
<b>Type 1 Diabetes—Rapid Access to Intervention Development Projects Relevant to Prevention)</b>			
Jeffrey Bluestone, Tolerance Therapeutics, Inc.	2005	N01 CO12400	GMP Manufacturing of hOKT3gamma1 (Ala-Ala) Monoclonal
Jerry Nadler, DiaKine Therapeutics, LLC	2005	N02 CM27005/ N02 CM37005	Purification of Lisofylline Drug Substance and Manufacture of Lisofylline Drug Product
Terry Strom, Beth Israel Deaconess Medical Center	2005	N01 CO12400	IL-2/Fc-IL15/Fc Fusion Proteins Components of the "Power Mix" Immune Modulator
<b>Cooperative Study Group for Autoimmune Disease Prevention (RFA AI00-016)</b>			
Teodor-Doru Brumeanu, Mount Sinai School of Medicine	2001	R01 DK061927	Prevention of Type 1 Diabetes by Soluble, MHC-II Peptide
George Eisenbarth, University of Colorado Health Sciences Center	2001	U19 AI050864	Virginia Mason/UCHSC Autoimmune Prevention Center
C.G. Fathman, Stanford University	2001	U19 DK061934	Strategies for Prevention of Autoimmunity
C.G. Fathman, Stanford University	2001	U01 DK061925	CD25+ Regulator CD4+ T Cells
David Hafler, Brigham and Women's Hospital	2001	U01 DK061926	Role of Regulatory CD4+/CD25+ T Cells in Diabetes
Matthias Von Herrath, La Jolla Institute for Allergy/Immunology	2001	U19 AI051973	How Does Blockade of CD40/CD40L Prevent Autoimmunity?
<b>Trial To Reduce the Incidence of Type 1 Diabetes in the Genetically-At-Risk (TRIGR)</b>			
Hans Akerblom, University of Helsinki	2001	U01 HD040364	Trial To Reduce IDDM in the Genetically At-Risk Study
Dorothy Becker, Children's Hospital (Pittsburgh)	2001	U01 HD042444	Nutritional Primary Prevention of Type 1 Diabetes
<b>Gene Therapy Approaches for Diabetes and Its Complications (RFA DK01-006)</b>			
George Christ, Yeshiva University	2001	R21 DK060204	Gene Therapy for Bladder Hyperactivity in Diabetic Rats
Chih-Pin Liu, Beckman Research Institute	2001	R21 DK060190	Regulation of Type 1 Diabetes Using Ribozymes
William Osborne, University of Washington	2001	R21 AI051637	Autoantigen Delivery to Induce Tolerance in Diabetes
Manikkam Suthanthiran, Weill Medical College	2001	R21 DK060186	Gene Therapy for Islet Transplantation
Jide Tian, University of California, Los Angeles	2001	R21 DK060209	Genetic Modification of DCs as Immunotherapy for IDDM
Roland Tisch, University of North Carolina, Chapel Hill	2001	R21 AI051638	The Use of VEE Replicons Encoding GAD65 to Treat IDDM
Keith Webster, University of Miami	2001	R21 HL069812	Therapeutic Angiogenesis To Treat Ischemic Disorders

Table A2: continued

	Year	Project No.	Project Title
<b>Innovative Grants in Immune Tolerance (RFA AI00-006)</b>			
Adam Adler, University of Connecticut School of Med/Dnt	2001	R21 AI049813	Comparing Toleragenic Versus Immunogenic APC Function
Lin Chen, University of Colorado	2001	R21 AI049905	Develop Peptide Inhibitors of the NFAT/AP-1 Complex
Mark Crew, University of Arkansas	2001	R21 AI049885	Tolerated Xenografts Using Virus Stealth Technology
Joanna Davies, Scripps Research Institute	2001	R21 DK061334	Transplantation Tolerance Induced by Linked Suppression
Nicholas Gascoigne, Scripps Research Institute	2001	R21 DK061329	Real-Time Molecular Interactions in Tolerance Induction
Irving Goldschneider, University of Connecticut School of Med/Dnt	2001	R21 AI049882	Induction Acquired Thymic Tolerance by Regulatory APCs
Hidehiro Kishimoto, Scripps Research Institute	2001	R21 DK061332	Tolerance in NOD Mice
Mark Poznansky, Massachusetts General Hospital	2001	R21 AI049858	Movement of Recipient T-Cells Away from an Allograft
Haval Shirwan, University of Louisville	2001	R21 DK061333	Apoptosis: A Means of Immune Regulation To Treat Diabetes
Luk Van Parijs, Massachusetts Institute of Technology	2001	R21 AI049897	Specificity and Fate of Autoreactive CD4+ T-cells
Dario Vignali, St. Jude's Children's Research Hospital	2001	R21 DK061330	Tolerance Induction by Targeted Expression of GAD
<b>Innovative Grants in Immune Tolerance (RFA AI03-010)</b>			
Andrea Sant, University of Rochester	2004	R21 AI059898	Selective Presentation of Autoantigens by B Cells
Matthias Von Herrath/ Douglas Green, La Jolla Institute for Allergy & Immunology	2004	R21 AI059850	Immune Tolerance Induction By Apoptotic Bodies
Chen Dong, University of Texas, MD Anderson Cancer Center	2004	R21 DK069278	Costimulatory Regulation of CD8 T Cell Tolerance
<b>Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013)</b>			
Steinunn Baekkeskov, University of California, San Francisco	1999	R21 DK055977	Generation of a Non-Human Primate Model of Type 1 Diabetes
Kevin Breuel, East Tennessee State University	1999	R21 DK057115	NF-Kappa B as a Therapeutic Target for IDDM
Alan Escher, Loma Linda University	1999	R21 DK057113	APC-Targeting Vaccine for Prevention of Type 1 Diabetes
Daniel Kaufman, University of California, Los Angeles	1999	R21 AI047773	Rational Design of Antigen-Based Immunotherapeutics
William Langridge, Loma Linda University	1999	R21 DK057206	A Targeted Plant-Based Vaccine for Type 1 Diabetes
Jon Mabley, Inotek Corporation	1999	R21 DK057239	Poly(ADP) Ribose Synthetase and Autoimmune Diabetes
Noel MacLaren, Louisiana State University Medical Center	1999	R21 DK057122	A Vaccine for Immune Mediated Diabetes
James Thomas, Vanderbilt University	1999	R21 AI047763	Selection and Regulation of B Lymphocytes in IDDM
<b>Immunopathogenesis of Type 1 Diabetes Mellitus (RFA DK98-010)</b>			
Cheong-Hee Chang, University of Michigan, Ann Arbor	1998	R21 AI044454	Tolerance and Autoreactivity by Self Antigen
Patrick Concannon, Virginia Mason Research Center	1998	R01 DK055970	Immunological Candidate Genes for IDDM Susceptibility
John Corbett, St. Louis University	1998	R01 AI044458	Mechanisms of Viral-Induced Beta Cell Damage
George Eisenbarth, University of Colorado Health Sciences Center	1998	R01 DK055969	<i>In Vivo</i> NOD Evaluation of a Pathogenic Insulin Peptide
Christopher Goodnow, Australian National University	1998	R01 AI044392	Mechanisms Regulating Islet Destruction by CD4 T cells
David Hafler, Brigham and Women's Hospital	1998	R01 AI044447	The Role of Invariant T Cells and IL-4 in Type 1 Diabetes
Kathryn Haskins, University of Colorado Health Sciences Center	1998	R01 AI044482	Immunoregulation in the NOD Mouse
Jonathan Katz, Washington University	1998	R01 AI044416	Role of I-AG7 on Selecting Autoreactive T Cells
William Kwok, Virginia Mason Research Center	1998	R01 AI044443	Structure and Immunobiology of an IDDM-Protective Molecule
Paul Lehmann, Case Western Reserve University	1998	R21 AI044484	Human/Humanized T Cell Response to Islet Cell Antigens
Chih-Pin Liu, Beckman Research Institute	1998	R21 AI044429	Regulatory Mechanisms in Type 1 Diabetes
Ali Naji, University of Pennsylvania	1998	R01 HD037754	Autoimmune Diabetes-Maternal Immunoglobulin
Alberto Pugliese, University of Miami	1998	R01 AI044456	Proinsulin Expression in the Immune System
Eric Simone, University of Colorado Health Sciences Center	1998	R01 AI044466	NOD T Cell Receptors for Specific Islet Autoantigens
Grete Sonderstrup, Stanford University	1999	P01 DK055364	Autoimmune T and B Cell Responses in Type 1 Diabetes
Matthias Von Herrath, Scripps Research Institute	1998	R01 AI044451	Regulation and Immunotherapy of IDDM
Li Wen, Yale University	1998	R01 AI044427	Development of a Novel Humanized Animal Model of IDDM



Table A2: continued

	Year	Project No.	Project Title
<b>Diabetes Prevention Trial for Type 1 Diabetes - Supplements</b>			
Nathaniel Clark, University of Vermont	1998	M01 RR000109	General Clinical Research Center: Diabetes Prevention Trial
George Eisenbarth, University of Colorado Health Sciences Center	1998	R01 AI039213	Antibodies to Recombinant Autoantigens- Prediction/ Immunogenetics
Richard Jackson, Joslin Diabetes Center	1998	U01 DK046601	Diabetes Prevention Trial -Type 1
Noel MacLaren, Children's Hospital (New Orleans)	1998	U01 DK046636	Diabetes Prevention Trial -Type 1
Alvin Powers, Vanderbilt University	1998	M01 RR000095	General Clinical Research Center: Diabetes Prevention Trial
Susan Ratzan, University of Connecticut Health Center	1998	M01 RR006192	General Clinical Research Center: Diabetes Prevention Trial
David Schade, University of New Mexico	1998	M01 RR000997	General Clinical Research Center: Diabetes Prevention Trial
Desmond Schatz, University of Florida	1998	M01 RR000082	General Clinical Research Center: Diabetes Prevention Trial
Stuart Weinzimer, Children's Hospital (Philadelphia)	1998	M01 RR000240	General Clinical Research Center: Diabetes Prevention Trial
<b>One-Year Supplements to Ongoing Projects</b>			
Mark Atkinson, University of Florida	1998	P01 AI042288	Immune Function and Low Risk Genotypes in IDD
Mark Atkinson, University of Florida	1998	R01 AI039250	Mechanisms of Immunotherapy in IDD Prevention Trials
William Hagopian, Pacific Northwest Research Institute	1998	P51 RR000166	Controlled Transfer Model for Autoimmune Diabetes
Laurence Turka, University of Pennsylvania	1998	P01 AI041521	Costimulation and Cytokines in Tolerance
Don Wiley, Children's Hospital (Boston)	1998	P01 AI039619	MHC Linked Susceptibility to Autoimmunity - Structure and Biology
<b>GOAL III: DEVELOP CELL REPLACEMENT THERAPY</b>			
<b>Beta Cell Biology Consortium (RFA DK01-014)</b>			
Michael German, University of California, San Francisco	2001	U19 DK061245	Molecular Control of Pancreatic Islet Development
Joel Habener, Massachusetts General Hospital	2001	U19 DK061251	Restoration of Endocrine Pancreas Function
John Hutton, University of Colorado Health Sciences Center	2001	U19 DK061248	Development and Regeneration of the Endocrine Pancreas
Mark Magnuson, Vanderbilt University	2001	U19 DK042502	Genes of Pancreas Function and Development
Catherine Verfaillie, University of Minnesota	2001	U19 DK061244	Characterization of Beta Cell Stem Cells
<b>Beta Cell Biology Consortium (U19) (RFA DK04-017)</b>			
Mark Magnuson, Vanderbilt University	2005	U19 DK042502	Mechanisms of Pancreas Development
Palle Serup, Hagedorn Research Institute	2005	U19 DK072495	Pancreatic Endocrine Development and Regeneration
<b>Beta Cell Biology Consortium (U01) (RFA DK04-018)</b>			
Markus Grompe, Oregon Health Sciences University	2005	U01 DK072477	Novel Reagents for Beta Cell Biology
Pedro Herrera, University of Geneva	2005	U01 DK072522	Transgenic Model of Inducible Diabetes
Gordon Keller, Mount Sinai School of Medicine	2005	U01 DK072513	Endoderm Induction and Pancreatic Specification from ES Cells
Douglas Melton, Harvard University	2005	U01 DK072505	Mechanisms of Pancreatic Beta Cell Regeneration
Lori Sussel, University of Colorado Health Sciences Center	2005	U01 DK072504	Defining the Roles of Nkx2.2 and NeuroD in Regulating Islet Cell Fate
Kenneth Zaret, Institute for Cancer Research, Fox Chase Cancer Center	2005	U01 DK072503	Gene Regulatory Signals for Beta Cell Development
<b>Beta Cell Biology Consortium (Coordinating Center) (RFA DK04-501)</b>			
Mark Magnuson, Vanderbilt University	2005	U01 DK072473	Coordinating Center for Beta Cell Biology Consortium
<b>Cooperative Clinical Islet Transplantation Consortium (Data Coordinating Center) (RFA DK04-004)</b>			
William Clarke, University of Iowa	2004	U01 DK070431	Clinical Islet Transplantation: Data Coordinating Center

Table A2: continued

	Year	Project No.	Project Title
<b>Cooperative Clinical Islet Transplantation Consortium (Clinical Centers) (RFA DK04-005)</b>			
Bernhard Hering, University of Minnesota	2004	U01 AI065193	Advancing Islet Transplants for Type 1 Diabetes Care
Olle Korsgren, Uppsala University	2004	U01 AI065192	Innate Immunity in Clinical Islet Transplantation
Ali Naji, University of Pennsylvania	2004	U01 DK070430	B-Lymphocyte Immunotherapy in Islet Transplantation
Camillo Ricordi, University of Miami	2004	U01 DK070460	Strategies To Improve Long Term Islet Graft Survival
Andrew Shapiro, University of Alberta	2004	U01 AI065191	Islet Transplant - Costimulatory Blockade with LEA29Y
<b>Pilot and Feasibility Program in Human Islet Biology (RFA DK03-021)</b>			
John Corbett, St. Louis University	2004	R21 DK068839	Unfolded Protein Response as a Regulator of Human Beta-Cell Viability
Peter Drain, University of Pittsburgh	2004	R21 DK068833	Human Beta Cell Parameters for Islet Engraftment Success
Adolfo Garcia-Ocana, University of Pittsburgh	2004	R21 DK068836	Protein Kinase B/Akt in the Human Islet
Regina Kuliawat, Albert Einstein College of Medicine	2004	R21 DK068843	Beta-Cell Granule Protein Profile by Split Reporter Assay
Alvin Powers, Vanderbilt University	2004	R21 DK068854	Pdx-1 and Maf Proteins in Human Islets
Michael Roe, University of Chicago	2004	R21 DK068822	Real-Time Analyses of Apoptosis in Human Beta Cells
Rupangi Vasavada, University of Pittsburgh	2004	R21 DK068831	Parathyroid Hormone Related Protein in the Human Islet
Juan Contreras, University of Alabama-Birmingham	2005	R21 DK071300	Effects of Brain-Death on Islet Recovery and Functionality
Luis Fernandez, University of Wisconsin	2005	R21 DK071218	Donation After Cardiac Death for Isolated Pancreatic Islet Transplantation: Biology and Predicting Factors for Success
Klaus Kaestner, University of Pennsylvania	2005	R21 DK071216	Expression Profiling of Human Islets
Charles King, University of California, San Diego	2005	R21 DK071228	Proteomic Analysis of PI 3-Kinase Signaling in Islet
Brad Marsh, University of Queensland	2005	R21 DK071236	3D Structural Biology of the Human Islet
Anna Moore, Massachusetts General Hospital	2005	R21 DK071225	Labeling Human Pancreatic Islets for Multi-Modal Imaging
<b>Comprehensive Programs in Beta Cell Biology (RFA DK02-014)</b>			
Vincenzino Cirulli, University of California, San Diego	2002	R01 DK063443	Role of Connexins in Beta Cell Development and Function
Roger Davis, University of Massachusetts Medical School	2002	R01 DK063368	Functional Analysis of the Beta Cell
Peter Dempsey, Pacific Northwest Research Institute	2002	R01 DK063363	Endogenous Betacellulin Signaling in Beta Cell Biology
Kathleen Dunlap, New England Medical Center Hospitals	2002	R01 DK063344	GABA-B Receptors as Regulators of Islet Biology
Claudia Kappen, University of Nebraska Medical Center	2002	R01 DK063336	Genome-Wide Discovery of Beta Cell Gene Control Elements
Jeffrey Pessin, University of Iowa			
Fredric Wondisford, University of Chicago	2002	R01 DK063349	Control of Beta Cell Function by Co-Activators
<b>Non-Human Primate Transplantation Tolerance Cooperative Study Group (RFA AI01-006)</b>			
Hugh Auchincloss, Massachusetts General Hospital	2001	U01 AI051706	Tolerance Induction for Primate Islet Transplantation
Bernhard Hering, University of Minnesota	2001	U01 DK062932	Mixed Chimerism in Haploidentical Non-Human Primates
Christian Larsen, Emory University	2001	U19 AI051731	Transplant Tolerance
Judith Thomas, University of Alabama, Birmingham	2001	U19 DK057958	Preclinical Models of Organ and Cell Transplantation Tolerance
Greg Westergaard, Alpha Genesis	2004	U01 AI049916	Specific Pathogen Free Rhesus Macaque Breeding Program
<b>Immune Tolerance Network - Islet Transplantation (RFP-NIAID-99-30)</b>			
University of California, San Francisco	2001	N01 AI015416	Collaborative Network for Clinical Research on Immune Tolerance

Table A2: continued

	Year	Project No.	Project Title
<b>Islet Cell Resource Centers (RFA RR01-002)</b>			
A. Osama Gaber, University of Tennessee Health Sciences Center	2001	U42 RR016602	Standardization and Procedure on Islet Isolation
Ronald Gill, University of Colorado Health Sciences Center	2001	U42 RR016599	Islet Cell Resources Facility at the University of Colorado
Mark Hardy, Columbia University of Health Sciences	2001	U42 RR016629	New York Regional Islet Isolation Facility
Bernhard Hering, University of Minnesota	2001	U42 RR016598	Human Pancreatic Islet Cell Resources (ICRs)
Thalachallour Mohanakumar, Washington University	2001	U42 RR016597	Human Islet Isolation Program at Washington University
Ali Naji, University of Pennsylvania	2001	U42 RR016600	Isolation/Distribution of Human Pancreatic Islets
Jo Reems, Puget Sound Blood Center	2001	U42 RR016604	Human Islet Isolations in Seattle
Camillo Ricordi, University of Miami	2001	U42 RR016603	Islet Cell Resources for Diabetes Research and Treatment
Arthur Riggs, Beckman Research Institute	2001	U42 RR016607	Islet Cell Resources of Southern California
Gordon Weir, Joslin Diabetes Center	2001	U42 RR016606	Human Pancreatic Islet Cell Resource
<b>Islet Cell Resource Centers: Administrative and Bioinformatics Coordinating Center (RFA RR02-002)</b>			
Joyce Niland, City of Hope National Medical Center	2002	U42 RR017673	National Islet Cell Consortium Coordinating Center
<b>Collaborative Islet Transplant Registry (RFP NIDDK-00-002)</b>			
EMMES Corporation	2001	N01DK012472	Islet/Beta Cell Transplant Registr
<b>Immunobiology of Xenotransplantation (RFA AI04-042)</b>			
Judith Thomas, University of Alabama, Birmingham	2005	U19 AI067151	Pig to Non-Human Primate Islet Xenografts
Simon Robson, Beth Israel Deaconess Medical Center	2005	U01 AI066331	Thromboregulatory Strategies to Prolong Xenografts
<b>Islet Encapsulation Research - Pilot and Feasibility Supplements to Existing Centers</b>			
John Hutton, University of Colorado Health Sciences Center	2002	P30 DK057516	Diabetes Endocrinology Research Center
Jerry Palmer, University of Washington	2002	P30 DK017047	Diabetes Endocrinology Research Center
Robert Sherwin, Yale University	2002	P30 DK045735	Diabetes Endocrinology Research Center
Donald Steiner, University of Chicago	2002	P60 DK020595	Diabetes Research and Training Centre
<b>Gene Transfer Approaches To Enhance Islet Transplantation (RFA DK02-020)</b>			
Mark Cattral, Toronto General Hospital	2002	R21 AI055024	Immunomodulation of Pancreatic Islets by Adenoviral Genes
Lieping Chen, Mayo Clinic, Rochester	2002	R21 AI055028	Novel Strategies to Prevent Islet Transplantation Rejection
Christiane Ferran, Beth Israel Deaconess Medical Center	2002	R21 DK062601	Gene Transfer with A20 To Improve Islet Transplantation
Donald Kohn, Children's Hospital (Los Angeles)	2002	R21 DK062649	Gene Expression in Beta Cells by Lentiviral Vectors
Joseph LeDoux, Georgia Institute of Technology	2002	R21 DK062616	Induction of Stem Cells To Adopt an Endocrine Fate
Adrian Morelli, University of Pittsburgh	2002	R21 AI055027	Dendritic Cells with Galectin-1 To Enhance Islet Grafts
Alvin Powers, Vanderbilt University	2002	R21 DK062641	Gene Transfer and Revascularization of Transplanted Islets
Paul Robbins, University of Pittsburgh	2002	R21 AI055026	Inhibition of NF-KB to Facilitate Islet Transplantation
Daniel Salomon, Scripps Research Institute	2002	R21 DK062598	Lentiviral-Transduced Endothelium for Islet Transplants
Sihong Song, University of Florida	2002	R21 DK062652	Anti-Inflammatory Serpin (AAT and Elafin) Gene Transfers
Jide Tian, University of California, Los Angeles	2002	R21 AI055025	Genetic Modification of Mouse Islets for Transplantation
Zandong Yang, University of Virginia, Charlottesville	2002	R21 DK062610	Induction of Suppression for Islet Transplantation
<b>Imaging Pancreatic Beta Cell Mass, Function, Engraftment, or Inflammation (RFA DK02-002)</b>			
Paul Harris, Columbia University Health Sciences	2002	R01 DK063567	Human Islet Antigen Discovery and Imaging
Dixon Kaufman, Northwestern University	2002	R01 DK063565	Bioluminescent Imaging of Pancreatic Islet Transplants
Wen-Hong Li, University of Texas SW Medical Center	2002	R01 DK063525	Image Beta Cell Mass and Function in Implants and Pancreas
Anna Moore, Massachusetts General Hospital	2002	R01 DK063572	<i>In Vivo</i> Imaging of Autoimmune Attack in Type 1 Diabetes
Louis Philipson, University of Chicago	2002	R01 DK063493	Imaging Beta Cell Function with Biosensors
Massimo Trucco, Children's Hospital (Pittsburgh)	2002	R01 DK063335	Optical Imaging of Beta Cell Function and Engraftment

Table A2: continued

	Year	Project No.	Project Title
<b>New Strategies for Treatment of Type 1 Diabetes Mellitus (RFA DK00-001)</b>			
Paul Gores, Carolinas Medical Center	2000	R01 DK059070	Islet Transplantation in Non-Uremic Diabetic Patients
Peter Gottlieb, University of Colorado Health Sciences Center	2000	R01 DK059097	Immunotherapy Trial in New-onset Type 1 Diabetes
A. Shapiro, University of Alberta	2000	R01 DK059101	Trial of Anti-TNFalpha in Islet Transplantation
<b>Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013)</b>			
Geoffrey Block, University of Pittsburgh	1999	R21 DK057143	Bioengineered Primary Islets for Transplantation
George Gittes, New York University School of Medicine	1999	R21 DK057224	Mesenchymal Inducers of Beta Cell Differentiation
Lawrence Olson, Michigan State University	1999	R21 DK057173	Pluripotent Human Pancreatic Ductal Cells
Vijayakumar Ramiya, Ixion Biotechnology, Inc.	1999	R21 DK057121	Islets from Islet Progenitor/Stem Cells for Implantation
Raymond Steptoe, Walter and Eliza Hall Institute	1999	R21 DK057228	Proinsulin Gene Transfer Via Bone Marrow To Prevent IDDM
Hei Sul, University of California, Berkeley	1999	R21 DK057217	Pref-1 Function in Islet Growth and Differentiation
<b>Cellular and Molecular Approaches for Achieving Euglycemia (RFA DK98-007)</b>			
Kenneth Brayman, University of Pennsylvania	1998	R21 DK055353	Adenoviral Mediated Islet Gene Transfer
Michael Brownlee, Albert Einstein College of Medicine	1998	R01 DK055299	Genetic Engineering of Beta Cells for Transplantation
Sylvia Christakos, University of Med/Dnt of New Jersey	1998	R21 DK055050	Preservation of Beta Cell Function by Calbindin-D28K
Joanna Davies, Scripps Research Institute	1998	R01 AI045488	Allograft Induced IL-4 in Pancreas Graft Protection
Herbert Gaisano, University of Toronto	1998	R21 DK055160	SNARE Regulation of B-Cell KCA and SUR Potentiates Secretion
Lakshmi Gaur, Puget Sound Blood Center and Program	1998	R01 AI045487	Induction of Tolerance to Islet Allografts in Primates
Ivan Gerling, University of Tennessee	1998	R21 DK055263	Human Leukocyte Response To Human Islets in SCID mice
Marvin Gershengorn, Weill Medical College of Cornell University	1998	R21 DK055087	Dynorphin and Beta Cell Sensitization
Ronald Gill, University of Colorado Health Sciences Center	1998	R01 DK055333	T Cell Mediated Injury to Islet Allografts
Suzanne Ildstad, Allegheny University of Health Sciences	1998	R01 AI045486	Hematopoietic Stem Cell Chimerism To Treat Diabetes
Karen Kover, University of Kansas Medical Center	1998	R21 AI045490	The Effects of Anti-Rat CD40L on Islet Allograft Survival
Fred Levine, University of California, San Diego	1998	R01 DK055065	Inhibition of Apoptosis in Pancreatic Beta Cells
Andreas Martin, Mount Sinai School of Medicine	1998	R21 DK055277	An <i>In Vivo</i> Model of Pancreatic Islet Organoids
Albee Messing, University of Wisconsin Madison	1998	R21 DK055309	New Method for Purifying Islets from Transgenic Pancreas
Christopher Newgard, University of Texas SW Medical Center	1998	R01 DK055188	Engineering of Immunoprotection in Beta Cell Lines
Colin Nichols, Washington University	1998	R01 DK055282	Genetic Engineering of Glucose Regulation
Camillo Ricordi, University of Miami	1998	R01 DK055347	Immunomodulation for Islet Transplantation in Diabetes
David Rothstein, Yale University	1998	R01 AI045485	Role of CD45 in Generation of Islet Allograft Tolerance
Thomas Steinberg, Washington University	1998	R01 HD037799	P2 Receptors, Extracellular ATP, and Islet Function
<b>Beta Cell Proteomics (PAR-00-101)</b>			
Joshua LaBaer, Harvard University Medical School	2001	R01 DK061906	Manipulating the Proteome
<b>One-Year Supplements to Ongoing Projects</b>			
Hugh Auchincloss, Massachusetts General Hospital	1998	R01 AI038397	Pathways of Alloreactivity
Jeffrey Bluestone, University of Chicago	1998	P01 AI029531	Immunomodulation of Transplant Rejection
Kenneth Polonsky, University of Chicago	1998	P01 DK044840	Molecular Mechanisms/Beta Cell Dysfunction in Diabetes
Daniel Salomon, Scripps Research Institute	1998	R01 AI042384	Importance of Islet Structure in Islet Transplantation
Nora Sarvetnick, Scripps Research Institute	1998	R01 HD029764	Model of Islet Regeneration and Neogenesis
Ming-Jer Tsai, Baylor College of Medicine	1998	R37 HD017379	<i>In Vitro</i> Expression of Hormone-Regulated Genes

Table A2: continued

	Year	Project No.	Project Title
<b>GOAL IV: PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES</b>			
<b>DirecNet: A Network To Test Glucose Sensors in Children with Type 1 Diabetes (RFA HD01-009)</b>			
Roy Beck, Jaeb Center for Health Research, Inc.	2001	U01 HD041890	Coordinating Center - Glucose Sensors in Type 1 Diabetes
Peter Chase, University of Colorado Health Sciences Center	2001	U10 HD041919	Glucose Sensors in Children with Type 1 Diabetes
William Tamborlane/Stuart Weinzimer, Yale University	2001	U10 HD041906	Yale's Center in the Children's Glucose Sensor Network
Eva Tsalikian, University of Iowa	2001	U10 HD041915	Glucose Sensors and Hypoglycemia in Children with DM
Darrell Wilson/Bruce Buckingham, Stanford University	2001	U10 HD041908	Near-Continuous Glucose Monitoring in Pediatrics
Tim Wysocki, Nemours Children's Hospital	2001	U10 HD041918	Continuous Glucose Sensors in Youth: a Biobehavioural Study
<b>Hypoglycemia in Patients with Type 1 Diabetes (RFA DK03-017)</b>			
Stephen Davis, Vanderbilt University	2004	R01 DK069803	Hypoglycemia Associated Autonomic Failure in Type 1 DM
Rory McCrimmon, Yale University	2004	R01 DK069831	Role of AMPK in Hypoglycemia-Sensing in the VMH
Charles Mobbs, Mount Sinai School of Medicine	2004	R01 DK070057	Adenosine Receptors and Hypoglycemic Responses
Douglas Rothman, Yale University	2004	R01 NS051854	MRS Studies of Brain Metabolic Adaptations in Diabetes
Raymond Swanson, University of California, San Francisco	2004	R01 NS051855	Hypoglycemic Neuronal Death
Cornelis Tack, University Medical Center, St. Radboud	2004	R21 DK069881	Brain Glucose Metabolism and Hypoglycemia Unawareness
Dennis Turner, Duke University Medical Center	2004	R01 NS051856	Lifespan Metabolic Neuroprotection During Hypoglycemia
<b>Effects of Hypoglycemia on Neuronal and Glial Cell Function (RFA NS02-008)</b>			
James Mandell, University of Virginia, Charlottesville	2002	R21 NS045300	Hypoglycemic Signaling Targets in Astrocytes
Jullie Pan, Yeshiva University	2002	R21 DK064565	Cerebral Activation in Hypoglycemia and Hyperketonemia
Scott Rivkees, Yale University	2002	R21 NS045310	The Role of Adenosine in Hypoglycemic Brain Injury
Vanessa Routh, University of Med/Dnt of New Jersey	2002	R01 DK064566	Glucosensing Neurons in Euglycemia, Hypoglycemia, and HAAF
Stephen Salton, Mount Sinai School of Medicine	2002	R01 NS045305	Mechanisms of Neuronal Hypoglycemic Injury
Dennis Turner, Duke University	2002	R21 NS045304	Lifespan Neuronal/Glial Metabolism During Hypoglycemia
<b>Sensor Development and Validation (RFA EB02-002)</b>			
Mark Arnold, University of Iowa	2002	R01 DK064569	Continuous Near Infrared Glucose Sensor
David Gough, University of California, San Diego	2002	R01 DK064570	Validation of Long-Term Glucose Sensor in Tissues
Myra Lipes, Joslin Diabetes Center	2002	R01 DK064568	A Cell-Based Glucose Sensing and Insulin Delivery System
Garry Steil, Medtronic Minimed	2002	R01 DK064567	Long Term Glucose Sensing and Physiologic Insulin Delivery
<b>Understanding Hypoglycemia Unawareness in Patients with Diabetes (RFA DK01-031)</b>			
Casey Donovan, University of Southern California	2002	R01 DK062471	Portal Vein Glucose Sensors in Hypoglycemia
Rolf Gruetter, University of Minnesota	2002	R21 NS045519	NMR Measurements of Human Brain Glycogen Metabolism
Lauren Jacobson, Albany Medical College	2002	R21 DK062442	Role of Glucocorticoids in Hypoglycemia Unawareness
Dianne Lattemann, University of Washington	2002	R21 DK062446	CNS Stress Pathways and the Development of Acute HAAF
Yijun Liu, University of Florida	2002	R21 NS045518	Dynamic fMRI Analyses of Hypoglycemia Unawareness
S. Ritter, Washington State University	2002	R01 NS045520	Hindbrain Mechanisms of Hypoglycemia Unawareness
Elizabeth Seaquist, University of Minnesota	2002	R01 DK062440	Cerebral Responses to Insulin-Induced Hypoglycemia
Harry Shamoon, Yeshiva University	2002	R01 DK062463	Modulation of Hypoglycemic Counterregulatory Responses
<b>Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013)</b>			
David Gough, University of California, San Diego	1999	R21 DK057109	Key Parameters for Artificial Pancreas Controller

Table A2: continued

	Year	Project No.	Project Title
<b>Glucose Sensors in the Treatment of Diabetes (RFA DK98-008)</b>			
Mark Arnold, University of Iowa	1998	R21 DK055255	Solid-State Optics for Non-Invasive Glucose Monitors
Sanford Asher, University of Pittsburgh	1998	R01 DK055348	Development of (Non) Invasive Real-Time Glucose Sensors
Katherine Crothall, Animas Corporation	1998	R01 DK055246	An Implantable Near IR Glucose Sensor
Casey Donovan, University of Southern California	1998	R01 DK055257	Portal Glucosensors in Hypoglycemic Detection
Dale Drueckhammer, State University of New York, Stony Brook	1998	R21 DK055234	New Approaches to Fluorescence-Based Glucose Sensors
Johannes Everse, Texas Tech University	1998	R21 RR014174	Enzyme-Thermistors as Glucose Sensors
David Gough, University of California, San Diego	1998	R01 DK055064	Tissue Response to Implanted Glucose Sensor
Joseph Izatt, Case Western Reserve University	1998	R21 RR014172	Pathlength-Resolved Non-Invasive Optical Glucose Sensors
John Mastrototaro, Minimed, Inc.	1998	R01 DK055242	Transdermal Glucose Sensing with Optical Amplification
Francis Moussy, University of Connecticut	1998	R01 RR014171	Control of Sensor/Tissue Interact for Extended Lifetime
Govind Rao, University of Maryland	1998	R01 RR014170	Protein Engineered Glucose Sensor
Kerstin Rebrin, Minimed, Inc.	1998	R01 DK055337	Interstitial Glucose Dynamics Using a Glucose Sensor
Christopher Saudek, Johns Hopkins University	1998	R01 DK055132	Clinical Research Toward Closed-Loop Insulin Delivery
Gary Saylor, University of Tennessee	1998	R21 RR014169	Eukaryotic Bioluminescent Integrated Circuit Sensors
Binghe Wang, North Carolina State University	1998	R21 DK055062	Glucose-Sensitive Artificial Receptors for Insulin
Joseph Wang, New Mexico State University, Las Cruces	1998	R01 RR014173	Oxygen-Independent Interference-Free Glucose Sensors
George Wilson, University of Kansas, Lawrence	1998	R01 DK055297	Evaluation of a Continuous Glucose Monitoring System
<b>Developing New Tools for Detecting and Monitoring Low Blood Glucose for People with Diabetes (CDC PA 99151)</b>			
Robert Langer, Massachusetts Institute of Technology	1999	R08/CCR117792	Ultrasound Mediated Transdermal Glucose Monitoring
Kenneth Ward, National Applied Science	1999	R08/CCR017796	Development of a Continuous Hypoglycemia Monitor
Suzanne Gebhart, SpectRx, Inc.	1999	R08/CCR417812	Continuous Interstitial Fluid Glucose Monitoring
<b>Development of Surrogate Markers for Clinical Trials: Supplements</b>			
University of Iowa	2001	N01 MH120006	Brain Molecular Anatomy Project (BMAP)
<b>One-Year Supplements to Ongoing Projects</b>			
Peter Havel, University of California, Davis	1998	R01 DK050129	ANS Hypoglycemia Induced Glucagon Secretion in Diabetes
Govind Rao, University of Maryland	1998	R01 RR010955	Minimally Invasive Glucose Monitoring
<b>GOAL V: PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES</b>			
<b>Epidemiology of Diabetes Interventions and Complications: Measurement of Cardiovascular Disease</b>			
William Dahms, Case Western Reserve University	1998	N01 DK062203	Coordinating Center - Diabetes Interventions/Complications
John Lachin, George Washington University	1998	N01 DK062204	Epidemiology of Diabetes Interventions and Complications
<b>Epidemiology of Diabetes Interventions and Complications: Uropathy and Autonomic Neuropathy</b>			
William Dahms, Case Western Reserve University	1998	N01 DK062203	Coordinating Center - Diabetes Interventions/Complications
<b>Epidemiology of Diabetes Interventions and Complications: Genetics Study</b>			
William Dahms, Case Western Reserve University	2001	N01 DK062203	Coordinating Center - Diabetes Interventions/Complications
John Lachin, George Washington University	2001	N01 DK062204	Epidemiology of Diabetes Interventions and Complications

Table A2: continued

	Year	Project No.	Project Title
<b>Family Investigation of Nephropathy and Diabetes Study (FIND)</b>			
EMMES Corporation	2001	N01 EY062112	Clinical Trials and Statistical Study Monitoring and Coordination
Hanna Abboud, University of Texas Health Sciences Center	2001	U01 DK057295	Genetics of Diabetic Nephropathy in Mexican Americans
Sharon Adler, Harbor-UCLA Research and Education Institute	2001	U01 DK057249	Identification of Diabetic Nephropathy Risk Genes
Robert Elston, Case Western Reserve University	2004	U01 DK057292	Linkage Consortium for End-Stage Renal Disease
Barry Freedman, Wake Forest University	2001	U01 DK057298	Renal Failure Genes in the Southeastern U.S.
Susanne Nicholas/Mohammed Saad, University of California, Los Angeles	2001	U01 DK057303	Genetics of Diabetic Nephropathy in Hispanics
John Sedor, Case Western Reserve University	2001	U01 DK057329	Genetic Regulation of Renal Disease Progression
Philip Zager, University of New Mexico, Albuquerque	2001	U01 DK057300	Zuni Kidney Project- Family Studies
<b>Diabetic Retinopathy Clinical Research Network (RFA EY01-001)</b>			
Roy Beck, Jaeb Center for Health Research, Inc.	2002	U10 EY014231	Diabetic Macular Edema Clinical Research Network
<b>Animal Models of Diabetic Complications Consortium (RFA DK01-009 and HL01-010)</b>			
Erwin Bottinger, Yeshiva University	2001	U01 DK060995	Mouse Models for Human Diabetic Nephropathy
Matthew Breyer, Vanderbilt University	2004	U01 DK061018	Generating Mouse Mutants with Diabetic Nephropathy
Jan Breslow, Rockefeller University	2001	U01 HL070524	Animal Models of Diabetic Vascular Disease
David Clemmons, University of North Carolina, Chapel Hill	2001	R01 HL069364	Atherosclerosis in Insulin-Resistant, Hyperlipidemic PTS
Thomas Coffman, Duke University	2001	U01 HL070523	Duke-UNC-Stanford AMDC Unit
Willa Hsueh, University of California, Los Angeles	2001	U01 HL070526	Novel Models of Cardiovascular Complications of Diabetes
Donald McClain, University of Utah	2001	U01 HL070525	Animal Models of Diabetic Cardiovascular Complications
<b>Collaborative Studies on Angiogenesis and Diabetic Complications (RFA DK04-022)</b>			
Mathew Breyer, Vanderbilt University	2005	R01 DK074116	Role of Cyclooxygenase Stimulated Neovascularization in
Michael Brownlee, Albert Einstein College of Medicine	2005	R01 DK074153	Progenitor Cell Dysfunction and Impaired Vasculogenesis
Robert Cohen, University of Cincinnati	2005	R01 DK074361	Endothelial Progenitor Cell Biology in Type 1 Diabetes
Timothy Crombleholme, Cincinnati Children's Hospital	2005	R01 DK074055	Endothelial Progenitor Cell Biology in Type 1 Diabetes
Geoffrey Gurtner, New York University School of Medicine	2005	R01 DK074095	Progenitor Cell Dysfunction and Impaired Vasculogenesis
Peter Kaiser, Cleveland Clinic Foundation	2005	R01 EY017528	Vascular Remodeling and Effects of Angiogenic Inhibition in Diabetic Retinopathy
Patricia Parson-Wingerter, NASA Glenn Research Center	2005	R01 EY017529	Vascular Remodeling and Effects of Angiogenic Inhibition in Diabetic Retinopathy
Ambra Pozzi, Vanderbilt University	2005	R01 DK074359	Role of Cyclooxygenase Stimulated Neovascularization in Diabetic Retinopathy
<b>Progression of Cardiovascular Disease in Type 1 Diabetes (RFA HL04-013)</b>			
Zixi Cheng, University of Louisville	2004	R01 HL079636	Cardiac Neuropathy in Type 1 Diabetic and Aging Mice
Barry Goldstein, Thomas Jefferson University	2004	R01 DK071360	Adiponectin Improves Vascular Function In High Glucose
Catherine Hedrick, University of Virginia	2004	R01 HL079621	Sphingolipids and Cardiovascular Disease in Type I Diabetes
George King, Joslin Diabetes Center	2004	R01 DK071359	PKC Activation and Cardiovascular Disease in Diabetes
William Mayhan, University of Nebraska Medical Center	2004	R01 HL079587	Cerebrovascular Disease in Type 1 Diabetes
Trevor Orchard, University of Pittsburgh	2004	R01 DK071487	Progression of Cardiovascular Disease in T1D: CADRE/EDC
Marian Rewers, University of Colorado Health Sciences Center	2004	R01 HL079611	Determinants of Accelerated CVD in Type 1 Diabetes
Ming-Hui Zou, University of Oklahoma	2004	R01 HL079584	Reactive Nitrogen Species and Accelerated Atherosclerosis

Table A2: continued

	Year	Project No.	Project Title
<b>Type 1 Diabetes—Rapid Access to Intervention Development (Projects Relevant to Complications)</b>			
Bo Hedlund, Biomedical Frontiers, Inc.	2005	N01 CO12400/ N02 CM27010	Starch-Deferoxamine (S-DFO) for Diabetic Neuropathy
<b>Feasibility Projects To Test Strategies for Preventing or Slowing the Progression of Diabetic Nephropathy (RFA DK02-025)</b>			
Timothy Meyer, Stanford University	2002	R01 DK063011	Maximizing the Benefit of Ras Blockade in Diabetic Nephropathy
Kumar Sharma, Thomas Jefferson University	2002	R01 DK063017	Pirfenidone: Novel Anti-Scarring Therapy for Diabetic Nephropathy
Robert Toto, University of Texas SW Medical Center	2002	R01 DK063010	Improving Outcomes in Diabetic Nephropathy
<b>Surrogate Endpoints for Diabetic Microvascular Complications (RFA DK02-016)</b>			
Paul Beisswenger, Dartmouth College	2002	R01 DK062995	Enzymatic Controls of Nonenzymatic Glycation
Andrew Boulton, Victoria University of Manchester	2002	R01 NS046259	Non-Invasive Surrogate Markers for Diabetic Neuropathy
Robert Cohen, University of Cincinnati	2002	R01 DK063088	The Glycosylation Gap and Diabetic Complications
Jose Halperin, Harvard University Medical School	2002	R01 DK062994	Complement in the Vascular Complications of Diabetes
George King, Joslin Diabetes Center	2002	R21 DK063000	Monocyte VEGF and PKC, Markers for Diabetic Complications
Oliver Lenz, University of Miami	2002	R21 DK063083	Clonal Selection in Diabetic Nephropathy
Mara Lorenzi, Schepens Eye Research Institute	2002	R01 EY014812	Retinal Blood Flow and Microthrombi in Type 1 Diabetes
Lois Smith, Children's Hospital (Boston)	2002	R21 EY014811	Surrogate Markers for Early Stage Diabetic Retinopathy
Kathryn Thrailkill, Arkansas Children's Hospital	2002	R01 DK062999	Matrix Metalloproteinases and Diabetic Nephropathy
Lance Waller, Emory University	2002	R21 NS046258	Assessing Spatial Patterns of Epidermal Nerve Fibers
<b>Imaging Early Markers of Diabetic Microvascular Complications in Peripheral Tissues (RFA DK02-001)</b>			
Abass Alavi, University of Pennsylvania	2002	R01 DK063579	FDG-PET Imaging in Complicated Diabetic Foot
Randall Barbour, SUNY Downstate Medical Center	2002	R21 DK063692	Functional Imaging of the Vascular Bed
Pierre Carlier, Laboratoire RMN-CEA-AFM	2002	R21 DK063496	NMR of Muscle Perfusion and Oxygenation in Diabetes
George King, Joslin Diabetes Center	2002	R21 DK063511	Retinal Imaging Tests for Microvascular Functions
Jonathan Lindner, University of Virginia, Charlottesville	2002	R01 DK063508	Contrast Ultrasound and Diabetic Microvascular Disease
Ronald Meyer, Michigan State University	2002	R21 DK063497	Functional MRI of Diabetic Peripheral Vascular Disease
<b>Oral Microbiology/Immunology of Type 1 Diabetes (RFA DE01-001)</b>			
Ashraf Fouad, University of Connecticut School of Med/Dnt	2001	R21 DE014476	Endodontic Infections in Type 1 Diabetic Hosts
Evanthia Lalla, Columbia University	2001	R21 DE014490	Periodontal Microbiota, Serum Antibody Response, and IDDM
Paul Moore, University of Pittsburgh	2001	R21 DE014472	Microbiology/Immunology of Periodontal Disease in Type 1 Diabetes
Maria Ryan, State University of New York, Stony Brook	2001	R21 DE014491	Host Modulation/Periodontal Therapy Effects on Diabetes
Thomas Van Dyke, Boston University	2001	R21 DE014478	Periodontal Inflammation in Type 1 Diabetes
<b>Functional Genomics Approaches to Diabetic Complications – IHWG SNPs: Supplements</b>			
Maynard Olson, University of Washington	2001	P50 HG002351	Center for the Study of Natural Genetic Variation
Richard Spielman, University of Pennsylvania	2001	R01 HG002386	Genome-Wide Analysis of Genetic Variation and Expression



Table A2: continued

	Year	Project No.	Project Title
<b>Neurobiology of Diabetic Complications (RFA NS00-002)</b>			
Joseph C. Arezzo, Yeshiva University	2000	R01 NS041194	Electrophysiologic Measures in Diabetic Neuropathy
Thomas K. Baumann, Oregon Health Sciences University	2000	R21 NS041157	Dorsal Root Ganglion as Source of Neuropathic Pain
Joseph Beverly, University of Illinois	2000	R01 DK059755	Glucose Mediation of Noradrenergic Activity in VMH
Scott T. Brady, University of Texas SW Medical Center	2000	R01 NS041170	Regulation of Fast Axonal Transport Diabetic Neuropathy
Rick Dobrowsky, University of Kansas Lawrence	2000	R21 DK059749	Role of Caveolin in Schwann Cell Signal Transduction
Charlene Hafer-Macko, University of Maryland Baltimore	2000	R01 DK059758	Endothelial Dysfunction in Human Diabetic Neuropathy
Lynn Heasley, University of Colorado Health Sciences Center	2000	R01 DK059756	MAP Kinases as Mediators of Diabetic Neuropathy
William R. Kennedy, University of Minnesota	2000	R01 NS041163	A Thermal Probe Method for Staging Diabetic Neuropathy
Kathy J. LePard, Northwestern University	2000	R21 NS039768	Synaptic Transmission in Diabetic Enteric Nervous System
Jill Lincoln, University of London	2000	R01 DK058010	Oxidative Stress: Roles in Diabetic Autonomic Neuropathy
Charles V. Mobbs, Mount Sinai School of Medicine	2000	R01 NS041183	Autonomic Diabetic Neuropathy in Mice
Hui-Lin Pan, Pennsylvania State University	2000	R21 NS041178	Spinal Plasticity in Diabetic Neuropathic Pain
Marise B. Parent, Georgia State University Research Foundation	2000	R01 NS041173	Neurochemical and Behavioral Effects of Hyperglycemia
David C. Randall, University of Kentucky Research Foundation	2000	R01 NS039774	Sympathetic Function in Diabetes
Judith A. Richter, Indiana University	2000	R21 NS041162	Hyperglycemia-Induced Neuronal Sensitization
Nancy Tkacs, University of Pennsylvania	2000	R21 DK059754	Counterregulatory Failure and the Arcuate Nucleus
Vickery Trinkaus-Randall, Boston University	2000	R21 DK059753	Role of Growth Factors on Epidermal and Neuronal Injury
Jeffrey Twiss, University of California, Los Angeles	2000	R21 DK059752	Neurotrophic Factor Responsiveness in Diabetic Neuropathy
<b>Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications (RFA DK99-013)</b>			
Maria Alexander-Bridges, Massachusetts General Hospital	1999	R21 DK057200	DAF16 Homologues and Mediating Complications of Diabetes
Deborah Ellis, Wayne State University	1999	R21 DK057212	Therapy in IDDM Adolescents in Poor Metabolic Control
Patrizia Marchese, Scripps Research Institute	1999	R21 HL065146	Mechanisms of Thrombus Formation in Type 1 Diabetes
N. Nahman, Ohio State University	1999	R21 DK057223	Alpha-Sense of Therapy of Diabetic Glomerulosclerosis
Csaba Szabo, Inotek Corporation	1999	R21 HL065145	Poly Ribose Synthetase and Endothelial Dysfunction
Benjamin Szwergold, Dartmouth College	1999	R21 DK057146	Nonenzymatic Glycation: Enzymatic Mechanism for Control
Helen Vlassara, Mount Sinai School of Medicine	1999	R21 DK057126	Gene Transfer and Diabetic Complications
Ian Zagon, Pennsylvania State University Hershey Medical Center	1999	R21 EY013086	Regulation of Corneal Wound Healing in Type 1 Diabetes
<b>Neurological Complications of Diabetes (RFA NS99-005)</b>			
Nigel Calcutt, University of California, San Diego	1999	R01 NS038855	Prosaposin and Prosaptides in Diabetic Neuropathy
Nicole Gibran, University of Washington	1999	R01 DK058007	Diabetic Neuropathy: Implications for Wound Repair
Rolf Gruetter, University of Minnesota	1999	R21 DK058004	<i>In Vivo</i> Studies of Brain Glycogen in Hypoglycemia
Jean Jew, University of Iowa	1999	R01 NS039771	Diabetic Autonomic Neuropathy and Mitral Valve Dysfunction
Phillip Low, Mayo Clinic Rochester	1999	R01 NS039722	Diabetic Autonomic Neuropathy
Anthony McCall, Oregon Health Sciences University	1999	R01 DK058006	Glucocorticoids, Hypoglycemia, and Brain Glucose Transport
Jose Ochoa, Emanuel Hospital and Health Center	1999	R01 NS039761	New Approaches to C Nociceptors in Diabetic Neuropathy
Kaushik Patel, University of Nebraska Medical Center	1999	R01 NS039751	Altered Nitric Oxide Mechanisms in PVN During Diabetes
Timothy Raabe, St. Mary's University	1999	R21 NS039748	Role of Neuregulin on Axon/Glia Interactions in Diabetes
Mark Yorek, University of Iowa	1999	R01 DK058005	Vascular Disease in Diabetic Neuropathy

Table A2: continued

	Year	Project No.	Project Title
<b>Pathogenesis and Therapy of Complications of Diabetes (RFA DK98-009)</b>			
Evan Abel, Beth Israel Deaconess Medical Center	1998	R21 HL062886	The Role of GLUT4 in the Pathogenesis of Diabetic Cardiomyopathy
Lloyd Aiello, Joslin Diabetes Center	1998	R01 EY012603	Systemic VEGF and Diabetic Retinopathy: Clinical Trials
Mark Alliegro, Louisiana State University	1998	R01 EY012602	Control of VEGF-Stimulated Endothelial Proliferation
Karin Bornfeldt, University of Washington	1998	R01 HL062887	Hyperglycemia, Protein Kinases, and Smooth Muscle Growth
Marshall Corson, University of Washington	1998	R21 HL062885	Endothelial-Fibronectin Interactions in Diabetes
Arup Das, University of New Mexico, Albuquerque	1998	R01 EY012604	Extracellular Proteinases in Retinal Neovascularization
Eva Feldman, University of Michigan, Ann Arbor	1998	R01 NS038849	Glucotoxicity Mediates Apoptosis in Diabetic Neuropathy
Martin Friedlander, Scripps Research Institute	1998	R01 EY012599	Cell-Based Ocular Delivery of Anti-Angiogenics for PDR
Kenneth Gabbay, Baylor College of Medicine	1998	R01 DK055137	Species Susceptibility to Diabetic Complications
Gary Gibbons, Brigham and Women's Hospital	1998	R01 HL062884	Diabetic Macrovascular Disease: Role of Apoptosis
Jonathan Glass, Emory University	1998	R01 NS038848	Calpains in the Pathogenesis of Diabetic Neuropathy
Maria Grant, University of Florida	1998	R01 EY012601	Nitric Oxide in the Pathogenesis of Diabetic Retinopathy
Jose Halperin, Harvard University	1998	R01 DK052855	The Role of Complement in the Complications of Diabetes
William Haynes, University of Iowa	1998	R21 NS038846	Sympathetic Neurovascular Function in Diabetes Mellitus
Cinda Helke, Henry M. Jackson Foundation	1998	R01 NS038845	Neurotrophins and Visceral Afferent Neurons in Diabetes
Michael Humphreys-Beher, University of Florida	1998	R01 DE013290	Factor Effects on Oral Complications of Diabetes
Claudia Kappen, Mayo Foundation	1998	R01 HD037804	Molecular Mechanisms in Diabetic Embryopathy
Francis Kappler, Fox Chase Cancer Center	1998	R21 DK055079	Isolation of a Novel Enzymatic Activity
Alexander Ljubimov, Cedars-Sinai Medical Center	1998	R01 EY012605	Growth-Factor Induced Tenascin-C in Diabetic Retinopathy
Jian-Xing Ma, Medical University of South Carolina	1998	R01 EY012600	Retinal Capillaries in Diabetic Retinopathy
Ramesh Nayak, Tufts University	1998	R21 EY012607	Immunogenetic Mechanisms in Diabetic Retinopathy
Ted Reid, Texas Tech University	1998	R21 NS038847	Role of Substance P in Diabetes-Impaired Wound Healing
David Sane, Wake Forest University	1998	R21 HL062891	Role of Vitronectin in the Vascular Complications of Diabetes
Richard Schaeffer, University of Arizona	1998	R01 DK055151	VEGF-Induced Modulation of Endothelial Structure and Function
Gina Schatteman, University of Iowa	1998	R01 DK055965	Adult Angioblasts in Vascular Maintenance and Repair
Richard Spielman, University of Pennsylvania	1998	R01 DK055227	Genetic Studies of Diabetic Nephropathy
James Beach/James Tiedeman, University of Virginia	1998	R01 EY012606	Role of Vascular Autoregulation in Diabetic Retinopathy
Philip Tsao, Stanford University	1998	R01 HL062889	Signaling Mechanisms in Glucose-Induced MCP-1 Expression
Gordon Williams, Brigham and Women's Hospital	1998	R01 HL062888	Mechanisms Underlying Cardiovascular Risks in Diabetes
Douglas Wright, University of Kansas Medical Center	1998	R21 NS038844	GDNF and Nociceptive Primary Sensory Neurons in Diabetes
<b>Development of Clinical Markers for Kidney Disease: Supplements</b>			
Erwin Bottinger, Yeshiva University	2001	U24 DK058768	Albert Einstein Biotechnology Center
Alfred George, Vanderbilt University	2001	U24 DK058749	Vanderbilt NIDDK Biotechnology Center
Steven Gullans, Brigham and Women's Hospital	2001	U24 DK058849	DNA Microarray Biotechnology Center
Raymond Harris, Vanderbilt University	2001	P50 DK039261	Biology of Progressive Destruction
Arthur Matas, University of Minnesota	2001	P01 DK013083	Organ Transplantation in Animals and Man
Richard Quigg, University of Chicago	2001	U24 DK058820	Massively Parallel Gene Expression Analysis
John Sedor, Case Western Reserve University	2001	P50 DK054178	CWRU O'Brien Renal Research Center
<b>Development of Surrogate Markers for Clinical Trials: Supplement</b>			
Christopher Bradfield, University of Wisconsin	2001	R01 ES005703	Characterization of the AH Receptor Signaling Pathway

Table A2: continued

	Year	Project No.	Project Title
<b>One-Year Supplements for Ongoing Projects</b>			
Robert Eckel, University of Colorado Health Sciences Center	1998	R01 DK042266	Nutrition, Lipoprotein Lipase, and Body Weight Regulation
Martin Friedlander, Scripps Research Institute	1998	R01 EY011254	Integrins and Ocular Angiogenesis
Anthony Iacopino, Texas A & M Baylor College of Dentistry	1998	R29 DE011553	Impaired Wound Signaling in Diabetic Periodontitis
Timothy Kern, Case Western Reserve University	1998	R01 EY000300	Diabetic Retinopathy
George King, Joslin Diabetes Center	1998	R01 EY005110	Cell Biology Approach to Diabetic Retinopathy
Trevor Orchard, University of Pittsburgh	1998	R01 DK034818	Epidemiology of Diabetic Complications
Ann Schmidt, Columbia University	1998	R01 DE011561	Glycation, Receptors, Cytokines in Periodontal Disease
William Tamborlane, Yale University	1998	R01 HD030671	Effects of Puberty on Metabolism and Body Composition
Russell Tracy, University of Vermont and St. Agric College	1998	R01 HL058329	Epidemiology of Impaired Coagulant Balance in Diabetes
<b>GOAL VI: ATTRACT NEW TALENT AND APPLY NEW TECHNOLOGIES TO RESEARCH ON TYPE 1 DIABETES</b>			
<b>Training Programs in Diabetes Research for Pediatric Endocrinologists (RFA DK02-024)</b>			
Silva Arslanian, Children's Hospital of Pittsburgh	2003	T32 DK063686	Research and Academic Training in Pediatric Diabetes
		K12 DK063704	Academic Career Development in Pediatric Diabetes (K12)
Morey Haymond, Baylor College of Medicine	2002	T32 DK063873	Baylor Pediatric Diabetes Research Training Program
		K12 DK063691	Baylor Mentored Diabetes Investigator Award
Georgeanna Klingensmith, University of Colorado Health Sciences Center	2002	T32 DK063687	Training Program in Diabetes Research
		K12 DK063722	Diabetes Research for Pediatric Endocrinologists
Lori Laffel/Joseph Majzoub, Joslin Diabetes Center	2002	T32 DK063702	Training Grant in Diabetes for Pediatric Endocrinologists
		K12 DK063696	Career Development in Diabetes for Pediatric Endocrinologists
Charles Stanley, Children's Hospital (Philadelphia)	2002	T32 DK063688	Ped Endocrine Fellowship Training in Diabetes Research
		K12 DK063682	Ped Endocrine Career Development in Diabetes Research
William Tamborlane, Yale University	2002	T32 DK063703	Training in Pediatric Endocrinology/Diabetes Research
		K12 DK063709	Pediatric Endocrine/Diabetes Physician Scientists
Neil White, Washington University, St. Louis	2003	T32 DK063706	Fellowship Training in Pediatric Diabetes at WUMS
		K12 DK063683	Career Development in Pediatric Diabetes at WUMS
<b>Innovative Partnerships in Type 1 Diabetes (RFA DK02-023)</b>			
Pamela Carmines, University of Nebraska Medical Center	2002	R21 DK063416	Renal Cortical Oxidative and Nitrosative Stress in IDDM
Alexander Chervonsky, The Jackson Laboratory	2002	R21 DK063452	Role of Innate Immunity in Type 1 Diabetes
Craig Crews, Yale University	2002	R21 DK063404	Pancreatic Stem Cell Induction by Small Molecules
Maria Grant, University of Florida	2002	R21 EY014818	CXCR4/SDF-1 Axis in Proliferation of Diabetic Retinopathy
Wayne Hancock, Children's Hospital (Philadelphia)	2002	R21 DK063591	Modulation of Chemokine-Dependent Islet Injury
William Langridge, Loma Linda University	2002	R21 DK063576	Vaccinia Virus Vaccine for Type 1 Diabetes
Sigurd Lenzen, Hannover Medical School	2002	R21 AI055464	Pathophysiological and Genetic Characterization of IDDM Rats
Diane Mathis, Joslin Diabetes Center	2002	R21 DK063660	Diabetes Susceptibility Genes Through Zebrafish Genetics
Jaime Modiano, AMC Cancer Research Center	2002	R21 DK063410	Role of Negative Regulation in Development of Diabetes
Marcus Peter, University of Chicago	2002	R21 AI055465	Fas Internalization and Beta Cells
Alvin Powers, Vanderbilt University	2002	R21 DK063439	Molecular Determinants of Vascularization in Islets
Marian Rewers, University of Colorado Health Sciences Center	2002	R21 AI055466	Viral Triggers of Type 1 Diabetes
Alexander Rudensky, University of Washington	2002	R21 AI055463	Role of Cathepsins S, L, and B in Type 1 Diabetes
Doris Stoffers, University of Pennsylvania	2002	R21 DK063467	cAMP Signaling in the Pancreatic Beta Cell
Michael Uhler, University of Michigan, Ann Arbor	2002	R21 DK063340	Postgenomic Approaches to Diabetic Complications
Elena Zhukova, University of California, Los Angeles	2002	R21 DK063607	Models of Insulin Production in Enteroendocrine Cells

Table A2: continued

	Year	Project No.	Project Title
<b>Innovative Partnerships in Type 1 Diabetes (RFA DK03-015)</b>			
Stelios Andreadis, State University of New York at Buffalo	2004	R01 DK068699	Regulated Insulin Delivery from Tissue Engineered Skin for Treatment of Type 1 Diabetes
David Antonetti, Pennsylvania State University	2004	R01 EY016413	Drug Discovery for Diabetic Retinopathy
Anil Bhushan, University of Southern California	2004	R01 DK068763	Cell Cycle Control of Beta-Cell Mass
Jeffery Chalmers, Ohio State University	2004	R01 DK068757	Magnetic Separation of Liberated Islets During Isolation
Gay Crooks, Children's Hospital, Los Angeles	2004	R01 DK068719	Cell Cycle Control of B-Cell Mass
Nika Danial/Stanley Korsmeyer, Dana Farber Cancer Institute	2004	R01 DK068781	Dissecting the Death Pathway in the Islet beta cell
Teresa DiIorenzo, Albert Einstein College of Medicine	2004	R01 AI064422	Prevention of Diabetes with Lipid Immunomodulators
Francis Doyle, University of California, Santa Barbara	2004	R01 DK068706	A Run-to-Run Algorithm for Glucose Regulation
John Gore, Vanderbilt University	2004	R01 DK068751	Pancreatic Islet Imaging and Blood Flow
Kevan Herold, Columbia University	2004	R01 DK068678	Islet Growth in NOD Mice Tolerant to Autoimmune Diabetes
Lois Jovanovic, Sansum Medical Research Institute	2004	R01 DK068663	A Run-to-Run Algorithm for Glucose Regulation
Keith Kirkwood, University of Michigan	2004	R01 DK068673	Regulated Insulin Delivery from Tissue Engineered Skin for Treatment of Type 1 Diabetes
Rohit Kulkarni, Joslin Diabetes Center	2004	R01 DK068721	Dissecting the Death Pathway in Islet Beta Cells
Suzanne Laychock, State University of New York at Buffalo	2004	R01 DK068700	Regulated Insulin Delivery from Tissue Engineered Skin for Type 1 Diabetes
Fred Levine, University of California, San Diego	2004	R01 DK068754	Small Molecular Regulation of Beta-Cell Differentiation
Mark Mercola, Burnham Institute	2004	R01 DK068715	Small Molecule Regulators of Beta-Cell Differentiation
Virginia Papaioannou, Columbia University	2004	R01 DK068661	Islet Growth in NOD Mice Tolerant to Autoimmune Diabetes
Klearchos Papas, University of Minnesota	2004	R01 DK068717	Magnetic Separation of Liberated Islets During Isolation
Steven Porcelli, Albert Einstein College of Medicine	2004	R01 AI064424	Prevention of Diabetes with Lipid Immunomodulators
Alvin Powers, Vanderbilt University	2004	R01 DK068764	Pancreatic Islet Imaging and Blood Flow
Charles Smith, Pennsylvania State University	2004	R01 EY016448	Drug Discovery for Diabetic Retinopathy
Richard Young, Whitehead Institute for Biomedical Research	2004	R01 DK068655	Transcriptional Regulatory Networks in Pancreatic Islets
<b>Bench to Bedside Research on Type 1 Diabetes (RFA DK02-022)</b>			
Christophe Benoist, Joslin Diabetes Center	2002	R21 AI055467	High Sensitivity Detection of Autoimmune T Cells in Type 1 DM
David Bleich, Beckman Research Institute	2002	R21 DK063351	Prevention of Type 1 Diabetes with MMP Inhibitors
Michael Clare-Salzler, University of Florida	2002	R21 DK063422/ R33 DK063422	Dendritic Cells and the Prevention of Type 1 Diabetes
C. Fathman, Stanford University	2002	R21 AI055468/ R33 A1055468	Adoptive Cellular Gene Therapy in Type 1 Diabetes
Peter Gottlieb, University of Colorado Health Sciences Center	2002	R21 DK063518	Human TCR/HLA Transgenic Mice To Prevent Type 1 Diabetes
Zhiguang Guo, University of Minnesota	2002	R21 AI055469	A Strategy to Cure Type 1 Diabetes
Kevin Lemley, Stanford University	2002	R21 DK063456	Urinary Podocyte Excretion Using FACS Methodology
Jerry Nadler, University of Virginia, Charlottesville	2002	R21 DK063521	New Anti-Inflammatory Agents To Prevent Damage to Islets
Gerald Nepom, Virginia Mason Research Center	2002	R21 DK063423	Treatment of Type 1 Diabetes with hGAD65 Altered Peptide Ligand
David Sachs, Massachusetts General Hospital	2002	R21 DK063503	Islet-Kidney Transplants for Treatment of Diabetic ESRD
Massimo Trucco, Children's Hospital (Pittsburgh)	2002	R21 DK063499/ R33 DK063499	Gene-Engineered Dendritic Cell Therapy for Diabetics

Table A2: continued

	Year	Project No.	Project Title
<b>Bench to Bedside Research on Type 1 Diabetes (RFA DK03-001)</b>			
Sofia Casares, Mount Sinai School of Medicine	2003	R21 DK066421	HLA Chimeric-Based Interventions in Type 1 Diabetes
Alessio Fasano, University of Maryland	2003	R21 DK066630	Gut Permeability in the Pathogenesis of Type 1 Diabetes
Ronald Gill, University of Colorado Health Sciences Center	2003	R21 AI060349	Correcting Dysregulated Peripheral Tolerance in NOD Mice
Raimund Hirschberg, University of California, Los Angeles	2003	R21 DK063360	Prevention of Diabetic Nephropathy by BMP7
Jian-Xing Ma, University of Oklahoma Health Sciences Center	2003	R21 EY015650/ R33 EY015650	A New Therapy for Diabetic Macular Edema
Alvin Powers, Vanderbilt University	2003	R21 DK066636/ R33 DK066636	GLP-1 to Enhance Islet Transplantation
Bellur Prabhakar, University of Illinois at Chicago	2003	R21 AI060386	Induction of Tolerance to Islet Cell Transplants
Nora Sarvetnik, Scripps Research Institute	2003	R21 DK066511	Engraftment of Pancreatic Progenitors
Andrew Shapiro, University of Alberta	2003	R21 DK066512	ICOS-B7h in Islet Transplant Rejection and Autoimmunity
Andrew Stewart, University of Pittsburgh	2003	R33 DK066127	Islet Allograft Gene Therapy for Primate Diabetes
<b>Bench to Bedside Research on Type 1 Diabetes (RFA DK03-019)</b>			
Sridevi Devaraj, University of California, Davis	2004	R21 DK069801	Cellular Pathways of Inflammation in Type 1 Diabetes
Francis Doyle, University of California, Santa Barbara	2004	R21 DK069833	Model-Based Advanced Control of Insulin in T1DM
Kevan Herold, Columbia University	2004	R21 DK069872	Combination of Anti-CD3 and Ag-Specific Immunotherapy
Daniel Kaufman, University of California, Los Angeles	2004	R21 DK069839	Noninvasive PET Imaging of Islet Grafts
David Kurnit, University of Michigan	2004	R21 DK069877	Detection and Treatment of Nephropathy in DM Type 1
Timothy Lyons, University of Oklahoma Health Sciences Center	2004	R21 HL080921	Apolipoproteins and the Complications of Type 1 Diabetes
Ali Naji, University of Pennsylvania	2004	R33 AI065356	B Cell Immunomodulation in Islet Transplantation
David Sachs, Massachusetts General Hospital	2004	R33 DK069827	Islet-Kidney Transplants for Treatment of Diabetic ESRD
Jin-Xiong She, Medical College of Georgia	2004	R21 DK069878	Development of Microarray-Based Biomarkers for Type 1 Diabetes
Rusung Tan, BC's Children's Hospital	2004	R21 AI065179	Detecting Beta Cell Specific T Cells in Type 1 Diabetes
Ian Zagon, Pennsylvania State University	2004	R21 EY016666	Naltrexone as a Novel Treatment for Diabetic Keratopathy
<b>SBIR and STTR RFA in Type 1 Diabetes and Its Complications (RFA DK03-020)</b>			
William Beschoner, Ximerex, Inc.	2004	R44 DK057986	Islet Transplantation with Chimeric Donor Pigs
John Centanni, Stratatech Corporation	2004	R44 DK069924	Antimicrobial, Angiogenic Skin Substitutes for Diabetic Ulcers
Jenny Freeman, HyperMed, Inc.	2004	R41 DK069871	Hyperspectral Imaging To Predict and Assess Foot Ulcers
Joseph Lucisano, Glysens, Inc.	2004	R44 EB005174	Robust Signal Processing for Tissue Glucose Sensor
Uwe Staerz, Isogenis, Inc.	2004	R43 DK069618	Protecting Pancreatic Islet Grafts from Rejection
Rebecca Tirabassi, Biomedical Research Models, Inc.	2004	R43 DK069733	Neurogenic Compounds for Treating Diabetic Complications
John Wilson, Wilson Wolf Manufacturing Corp.	2004	R43 DK069865	Islet Culture, Shipping, and Infusion Device
Todd Zion, Smartcells, Inc.	2004	R43 DK069870	Glucose-Responsive Self-Regulated Insulin Delivery
<b>SBIR: Measurement Tools For Altered Autonomic Function In Spinal Cord Injury And Diabetes (RFA HD04-018)</b>			
Firouz Daneshgari, Neurotron, Inc.	2005	R41 DK074987	Assessment of Altered Function in Diabetic Bladder

Table A2: continued

	Year	Project No.	Project Title
<b>Proteomics and Metabolomics in Type 1 Diabetes and Its Complications (RFA DK03-024)</b>			
M. Amin Arnaout/Darryl Palmer-Toy, Massachusetts General Hospital	2004	R21 DK070212	Metabolomic Analysis of Type 1 Diabetic Nephropathy
Helene Bour-Jordan, University of California, San Francisco	2004	R21 NS052132	Autoimmune Basis of Diabetic Neuropathy
Mark Chance, Albert Einstein College of Medicine	2004	R21 DK070229	Proteomic Approaches to Type I Diabetes Progression
Paul Harris, Columbia University	2004	R21 DK070192	Soluble Protein Markers of T1D Progression
Kathryn Haskins, University of Colorado Health Sciences Center	2004	R21 AI065355	Proteomics Analysis of T Cell Autoantigens in T1D2
Michael Mauer, University of Minnesota	2004	R21 DK070210	Proteomics in Type 1 Diabetes and Its Complications
Sreekumaran Nair, Mayo Clinic	2004	R21 DK070179	Plasma Protein Synthesis and Abundance in T1 Diabetes
Mark Nicolls, University of Colorado	2004	R21 DK070203	Viability Assay for Human Islet Transplantation
Jin-Xiong She, Medical College of Georgia	2004	R21 HD050196	Proteomic Changes/Progression of Human Type 1 Diabetes
Richard Smith, Battelle Pacific Northwest National Laboratory	2004	R21 DK070146	Proteomics and Metabolomics Studies of Type 1 Diabetes
Forest White, Massachusetts Institute of Technology	2004	R21 AI065354	Proteomics of Central Tolerance in NOD vs B6 Mice
<b>Phased Innovation Partnerships - Supplements to Centers</b>			
Yaakov Barak, University of Massachusetts Medical School	2001	P30 DK032520	PPAR Gamma KO and Insulin Resistance
Giacomo Basadonna, Yale University	2001	P30 DK045735	Glucose Responsive Transgene
James Callis, University of Washington	2001	P30 DK017047	Islet Purification
Shaoping Deng, University of Pennsylvania	2001	P30 DK019525	Gene Therapy with PDX
Denise Faustman, Massachusetts General Hospital	2001	P30 DK057521	TNF Apoptosis
Eva Feldman, University of Michigan, Ann Arbor	2001	P60 DK020572	Postgenomic Approaches to Complications
Yang-Xin Fu, University of Chicago	2001	P60 DK020595	Lymphotoxin
Mark Geraci, University of Colorado Health Sciences Center	2001	P30 DK057516	RNA Profile of Islet Development
Wouter Hoff, University of Chicago	2001	P60 DK020595	Glucose Sensing Fusion Proteins
Shin-Ichiro Imai, University of Washington	2001	P30 DK017047	Sir2a in Beta Cell Differentiation
Klaus Kaestner, University of Pennsylvania	2001	P30 DK019525	Islet Stem Cells
Myra Lipes, Joslin Diabetes Center	2001	P30 DK036836	Optimize Gene Expression in Surrogate Beta Cells
Diane Mathis, Joslin Diabetes Center	2001	P30 DK036836	Imaging Inflammation
Ruslan Medzhitov, Yale University	2001	P30 DK045735	Innate Immunity in Type 1 Diabetes
Mark Nicolls, University of Colorado Health Sciences Center	2001	P30 DK057516	Proteomics and Transplantation
William Osborne, University of Washington	2001	P30 DK017047	Glucose Regulated Insulin Delivery
Sunhee Park, University of Massachusetts Medical School	2001	P30 DK032530	ART2 Ligands
Alvin Powers, Vanderbilt University	2001	P60 DK020593	<i>In Vivo</i> Assessment of Transplanted Islets
Alexander Rudensky, University of Washington	2001	P30 DK017047	Cathespins
Jaromir Ruzicka, University of Washington	2001	P30 DK017047	GAD Assay
Harry Shamoon, Yeshiva University	2001	P60 DK020541	Liver Glycogen Metabolism/Hypoglycemia
Li Wen, Yale University	2001	P30 DK045735	Dendritic Cell Therapy
Burton Wice, University of Washington	2001	P30 DK017047	Gut Stem Cells
John Wiley, University of Michigan, Ann Arbor	2001	P60 DK020572	Neuropathy
Kelvin Yamada, University of Washington	2001	P30 DK017047	Hypoglycemia

## DESCRIPTIONS OF RESEARCH EFFORTS SUPPORTED BY THE *SPECIAL FUNDING PROGRAM*

In addition to supporting numerous consortia focused on type 1 diabetes and its complications, presented in the main section of this document, the *Special Funds* were deployed to numerous other initiatives. These initiatives have promoted a broad spectrum of research projects in areas identified as of particular opportunity or challenge to complement the efforts of the consortia. This Appendix includes descriptions of those initiatives, as well as brief descriptions of the consortia that are more fully discussed in the main sections of this Report. The scientific output of these research efforts can be found in the “Assessment” chapter and in the Goal chapters.

For each initiative description in this Appendix, the noted year in which grants were awarded marks the start of the research projects, the majority of which have extended or will extend for multiple years.

### **Goal I—Identify the Genetic and Environmental Causes of Type 1 Diabetes**

#### **Type 1 Diabetes Genetics Consortium (T1DGC)**

T1DGC is organizing international efforts to identify genes that determine an individual’s risk of developing type 1 diabetes. This Consortium is recruiting 2,800 families who have two or more siblings with type 1 diabetes in order to identify genes that increase susceptibility. Finding these genes will not only increase understanding of the underlying molecular mechanisms of disease development, but also aid in the discovery of novel prevention strategies and identification of patients who could benefit from these approaches.

#### **International Histocompatibility Working Group (IHWG)**

The IHWG works to identify single nucleotide polymorphisms (SNPs) in type 1 diabetes candidate genes. Type 1 diabetes is a polygenic disease caused by differences in multiple genes. Identifying genes and polymorphisms associated with type 1 diabetes will enable accurate prediction, diagnosis, and,

ultimately, treatment of this disease. One approach for finding disease-associated genes is to screen affected and unaffected individuals for DNA sequence differences (genetic polymorphisms) in candidate genes.

#### **The Environmental Determinants of Diabetes in the Young (TEDDY)**

##### **RFA-DK-02-029**

The goal of TEDDY is to identify environmental causes of type 1 diabetes in genetically susceptible individuals. This long-term study is enrolling at-risk newborns and then following them until they are 15 years of age. The study is crucial to helping researchers understand the environmental triggers that play a role in type 1 diabetes disease onset and development.

#### **Search for Diabetes in Youth (SEARCH)**

##### **PA 00097, RFA-DP-05-069**

SEARCH is defining the prevalence and incidence of diabetes in children and youth less than 20 years of age in six geographically dispersed populations that encompass the ethnic diversity of the United States. This study will help increase understanding of how type 1 diabetes strikes and unfolds.

#### **Type 1 Diabetes Mouse Repository**

This research resource, located at The Jackson Laboratory in Maine, was established to collect, preserve, and disseminate approximately 150 mouse strains that are important to research in type 1 diabetes. The repository is enhancing access and ensuring the continued availability of these mouse models to the entire research community.

#### **Bioinformatics Integration Support Contract**

##### **RFP-NIH-NIAID-DAIT-02-16**

Advanced technologies are profoundly altering the study of immunology and infectious diseases; offering new approaches to understanding immune activation and regulation;

uncovering the genetic causes of disease susceptibility; and developing new diagnostic, treatment, and intervention strategies. These technologies are also generating large amounts of data to be captured, analyzed, and stored. This project provides advanced support in the production, analysis, archiving, and exchange of scientific data for a diverse community of immunology researchers and access to best practices in the management of scientific information for researchers engaged in allergy, immunology, and transplantation research. Contracts were awarded in FY 2002.

#### **Mammalian Gene Collection (MGC)**

The MGC is a large, trans-NIH program to compile a complete set of full-length (open reading frame) sequences and cDNA clones of expressed genes for human and mouse. The MGC supports the production of cDNA libraries, clones, and sequences. All resources generated by the MGC are publicly accessible to the biomedical research community (<http://mgc.nci.nih.gov>).

#### **Sequencing the NOD Mouse for Immune System Genes for Type 1 Diabetes**

This is a project to generate a finished sequence of the mouse genome, dovetailing with a number of targeted sequencing programs. Sequencing the regions of the NOD mouse genome relevant to type 1 diabetes is crucial to better understanding the role that genetic susceptibility plays in the pathogenesis of type 1 diabetes. The sequencing of these regions will facilitate identification and characterization of potential immunogenic proteins responsible for initiation and progression of autoimmune destruction of islets and potential targets in therapy.

#### **Biotechnology Resource Centers**

##### **RFA-DK-00-002**

This initiative established core expertise in microarray performance and analysis at research centers around the United States. Regularly appropriated funds were provided for nine

centers in FY 2000 to support a wide range of research within the NIDDK mission. An additional center with relevance to type 1 diabetes was awarded using *Special Funds*.

#### **Functional Genomics of the Developing Endocrine Pancreas**

##### **RFA-DK-99-007**

This initiative sought to identify all genes expressed in the developing endocrine pancreas and to generate both microarray and bioinformatics tools, which could be used to study development, function, and disease progression in type 1 diabetes. A supplemental objective was added in FY 2001 to screen cDNA libraries for clones that might be useful as markers for beta cell precursors. The NIDDK and JDRF awarded two resource-related grants in FY 1999 to establish an Endocrine Pancreas Consortium. One project provided the Consortium with expertise in diabetes and high throughput sequencing capacity through the Washington University Genome Sequencing Center. The other project brought expertise in mouse genetics and bioinformatics through the University of Pennsylvania Center for Bioinformatics. A third investigator offered expertise in pancreatic development through subcontracts to both sites. One of the projects (University of Pennsylvania) was converted to a cooperative agreement and incorporated into the Beta Cell Biology Consortium (BCBC).

#### **Public Health Pilot Programs in Newborn Screening**

The CDC fostered, initiated, and supported pilot programs between type 1 diabetes research centers and state public health newborn screening laboratories. The CDC National Diabetes Laboratory used the *Special Funds* for several projects to enhance screening and identification of newborns at risk for type 1 diabetes. The CDC provided additional support from regularly appropriated funds. The Diabetes Evaluation in Washington State (DEWIT) study, with support from the National Diabetes Laboratory, established a cohort of children for pathogenesis studies by testing newborn blood



spots from about 32,000 children at higher genetic risk for type 1 diabetes. In addition, the CDC established proficiency testing programs in the Newborn Screening Quality Assurance Program for type 1 diabetes genetic markers and autoantibody testing on dried blood spots.

### **Proficiency Testing for Laboratory Assays To Measure Markers of Innate and Acquired Risk for Type 1 Diabetes in Dried Blood Spots**

Various analytical approaches are used to test for genetic and serologic markers that identify higher-risk individuals in long-term, multicenter studies of type 1 diabetes. Genetic tests conducted on newborns usually make use of dried blood spots as the sample matrix. Dried blood spots also allow home collection of samples from children enrolled in these studies for surveillance for the appearance of autoantibodies. The CDC Newborn Screening Quality Assurance Program conducts a proficiency testing program in newborn screening laboratories around the world, ensuring the validity of laboratory data over time and among centers.

## **Goal II—Prevent or Reverse Type 1 Diabetes**

### **Type 1 Diabetes TrialNet**

**RFA-DK-01-004**

TrialNet is an international network of investigators, clinical centers, and core support facilities. It supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new-onset patients and to prevent the disease in at-risk patients. TrialNet has launched several studies that are recruiting patients and is currently evaluating several other therapeutic agents to test. This type of collaborative network infrastructure is critical for facilitating clinical trials in type 1 diabetes, as well as for making real improvements in patients' health by identifying new therapeutic agents.

### **Immune Tolerance Network (ITN)**

Immune tolerance is the process by which the immune system accepts a protein or other molecule as “self” and does not attempt to destroy cells or tissues containing that protein. Tolerance induction can block the autoimmune process underlying type 1 diabetes or enable the body to accept transplanted islets without the need to globally suppress the immune system. Research conducted through the ITN is evaluating new treatments to induce tolerance in type 1 diabetes, as well as other disease areas. The ITN is currently conducting and developing several clinical trials related to type 1 diabetes and islet transplantation. Research on tolerance is critical both for developing therapies to slow or reverse type 1 diabetes, as well as for improved approaches to islet transplantation.

### **Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers)**

**RFA-AI-05-026**

The mission of the Prevention Centers is to engage in scientific discovery that significantly advances knowledge about the prevention and regulation of autoimmune disease, including type 1 diabetes. Pre-clinical research conducted by the Prevention Centers is key to the development of strategies for modulating the immune system so that they can be tested in human clinical trials.

### **Standardization Programs**

Standardized assessment of key measures for type 1 diabetes research is extremely important to ensure consistency across laboratories and clinical trial networks, so that data can be compared and combined. Efforts are ongoing to improve and standardize the measurement of autoantibodies (used to identify initiation of autoimmunity), C-peptide (a measure of beta cell mass and function), and HbA1c (a measure of long-term blood glucose control).

### **Trial To Reduce IDDM in the Genetically At Risk (TRIGR)**

This multicenter international study is comparing the development of type 1 diabetes in genetically susceptible infants who are weaned onto a hydrolysate of cow's milk formula, in which many of the cow proteins have been broken down, versus standard cow's milk formula. TRIGR could have a major impact on disease prevention if differences are observed between the two types of formulas.

### **Gene Therapy Approaches for Diabetes and Its Complications**

#### **RFA-DK-01-006**

Scientists have been developing gene transfer techniques for introducing genes into the body's cells to correct a defect or alter the properties of those cells. Many approaches to blocking the development of type 1 diabetes and treating diabetic complications may be amenable to gene transfer technology. This program facilitated preliminary studies, which began in 2001, on the appropriate use and feasibility of this new technology.

### **Innovative Grants on Immune Tolerance**

#### **RFA-AI-00-006, RFA-AI-03-010, and RFA-AI-05-023**

Autoimmune diseases and transplant rejection may one day be treated by the induction of immune tolerance. These initiatives were designed to support innovative, high-impact research on the mechanisms and applications of antigen-specific immune tolerance to promote the development of tolerogenic protocols applicable to immune-mediated diseases, including type 1 diabetes, and transplant rejection. Grants for the first two of these initiatives were awarded in 2001 and 2004; grants in response to the third initiative will be funded in 2006.

### **Pilot Studies for New Therapies for Type 1 Diabetes and Its Complications**

#### **RFA-DK-99-013**

Insulin therapy, though life-sustaining for individuals with type 1 diabetes, is not a cure and does not prevent the devastating complications that affect nearly every organ system. In FY 1999-2000, grants were awarded to explore new therapies for type 1 diabetes and its complications, including studies relevant to: preventing or reversing type 1 diabetes (Goal II), cell replacement therapy (Goal III), prevention of hypoglycemia (Goal IV), and prevention or treatment of diabetic complications (Goal V).

### **Immunopathogenesis of Type 1 Diabetes**

#### **RFA-DK-98-010**

Grants supporting studies related to the development of improved methods for risk prediction, prevention, and therapy for type 1 diabetes were awarded in FY 1998.

### **Biomarkers of Autoimmunity in Type 1 Diabetes**

#### **RFA-DK-06-002**

Patients and those at risk for type 1 diabetes would benefit greatly from intensified research toward improving the prediction and early detection of autoimmune destruction of pancreatic beta cells, and developing biomarkers for ongoing autoimmune disease which could be used to monitor responses in clinical trials. This initiative is intended to facilitate progress in this area by soliciting new applications focused on the detection of the human autoimmune response in type 1 diabetes. Such approaches would have the potential to lead to the development of a test useful in a clinical setting. Grants will be awarded in Fall 2006.

### **Data and Biosample Repository**

#### **RFP-DK-02-004**

In FY 2003, the NIDDK established a central repository for data and biologic samples, such as blood, DNA, and cell lines, collected in the course of large, multisite clinical studies.

The repository will expand the usefulness of these studies by increasing access to trial-related biosamples and data. When appropriate, researchers seeking to reanalyze samples or data will be able to obtain these materials quickly and efficiently.

The repository was established to: (1) gather, store, and distribute samples from completed clinical studies; (2) gather, store, distribute, and facilitate analyses of finished datasets of completed studies; (3) process, analyze, and store samples that are being gathered in ongoing and new studies; and (4) provide support services for genetics studies, including cell line immortalization and DNA extraction. This resource is benefiting multiple type 1 diabetes research consortia and networks, as well as other type 1 diabetes researchers who may further analyze the stored data and samples.

### **Goal III—Develop Cell Replacement Therapy**

#### **Beta Cell Biology Consortium (BCBC)**

##### **RFA-DK-01-014, RFA-DK-04-017, and RFA-DK-04-018**

The BCBC is an international Consortium of investigators pursuing key challenges of enormous relevance to development of therapies for type 1 diabetes. The mission of the BCBC is to facilitate interdisciplinary approaches that will advance understanding of pancreatic islet cell development and function. The long-term scientific goal is to develop a cell-based therapy to restore normal insulin production and action to diabetic patients. Working toward this goal, the BCBC has created and distributed important reagents that will serve the scientific community at large. Research pursued through the BCBC can ultimately help to overcome a major barrier to islet transplantation—the shortage of islets.

#### **Clinical Islet Transplantation Consortium (CIT)**

##### **RFA-DK-04-004 and RFA-DK-04-005**

The purpose of this Consortium is to develop and implement a program of single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. Research pursued through this Consortium aims to make improvements in the field of islet transplantation and to share the data and results with the broad scientific community.

#### **Pilot and Feasibility Program in Human Islet Biology**

##### **RFA-DK-03-021**

Much of the understanding of the basic biology of beta cells and islets had previously been generated from studies of mouse and rat cell lines and, to a lesser extent, from monkey islets. This program was thus designed to stimulate research focusing on the biology of human beta cells and human pancreatic islets. Such research augments knowledge of human islets, and findings can be compared with those from rodent models. Grants were awarded in 2004 and 2005. The information gained from these studies of human beta cells and islets should help in the development of new reagents for *in vivo* imaging studies of the human islet, assays for use in predicting human islet transplant success, and cellular therapies for potential use in the treatment of type 1 diabetes.

#### **Comprehensive Programs in Beta Cell Biology**

##### **RFA-DK-02-014**

Increased understanding of beta cell biology may help researchers improve the viability of islets used for transplantation, lead to the development of new treatments for diabetes (e.g., beta cell replacement), and prevent beta cell destruction through the development of novel therapeutics. This program bolstered investigator-initiated collaborative research aimed at understanding the signaling pathways in the adult pancreatic beta cell, and studying the integration of these signaling

networks among the different cell types of the pancreatic islet. The grants in response to this initiative were awarded, in 2002, to teams of investigators with complementary expertise that came together to tackle important research problems of the beta cell.

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

**RFA-AI-01-006 and RFA-AI-06-018**

This multi-institution Study Group was established to evaluate the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of kidney and islet transplantation. The Group also supports research on immune tolerance. Pre-clinical research conducted by this Group will help scientists move promising therapeutic agents from the laboratory into human clinical trials.

### **Islet Cell Resource Centers (ICRs)**

**RFA-RR-01-002 and RFA-RR-05-003**

The ICRs serve as regional centers that provide clinical-grade human islets to investigators engaged in islet transplantation protocols throughout the country; optimize the procedures used to obtain such islets; and distribute human pancreatic islets to investigators for use in laboratory-based research studies. This resource provides high-quality islets for use in human islet transplantation research and allows researchers to use human islets in basic research studies.

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

The mission of the CITR is to expedite progress and promote safety in islet transplantation through the collection, analysis, and communication of comprehensive, current data on all islet transplants performed in North America. 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

will help to define the overall risks and benefits of islet transplantation as a treatment option for type 1 diabetes patients.

### **Immunobiology of Xenotransplantation Cooperative Research Program**

**RFA-AI-04-042**

This multi-institution Program is developing and evaluating pre-clinical porcine to non-human primate models of xenotransplantation (solid organ, tissue, or cell transplantation between species). The Program supports pre-clinical research to address immunological and physiological issues critical to the engraftment, survival, and function of xenografts. The long-term goal is to develop novel and efficacious strategies for broad clinical application of xenotransplantation.

### **Gene Transfer Approaches To Enhance Islet Transplantation**

**RFA-DK-02-020**

Many scientific and medical issues remain before transplantation can become a routine treatment for type 1 diabetes. A major barrier to widespread use of this technology is the limited supply of transplantable islets. Gene transfer approaches to engineer new beta cells or to enhance islet viability could improve the efficiency and availability of islet transplantation. This initiative promoted innovative projects, funded in 2002, on the application of gene transfer technology to islet transplantation.

### **Imaging Pancreatic Beta Cell Mass, Function, Engraftment or Inflammation**

**RFA-DK-02-002**

In type 1 diabetes, insulin-producing beta cells are destroyed in an autoimmune process that involves infiltration and subsequent inflammation of the pancreatic islets by immune system T cells. Noninvasive methods to image beta cell mass, function, and inflammation and the engraftment of transplanted islets would enhance the ability to monitor disease

progression and response to therapy in individuals who have or are at risk of developing type 1 diabetes. Grants were awarded in 2002 for research toward developing new techniques or reagents for imaging beta cells *in vivo*. (See also the description of RFA-DK-06-003 in this Appendix.)

### **New Strategies for the Treatment of Type 1 Diabetes Mellitus**

#### **RFA-DK-00-001**

This initiative supported research on potential clinical strategies for the prevention, treatment, or cure of type 1 diabetes in human patients. In FY 2000, grants were awarded for clinical trials to improve islet transplantation or to maintain residual beta cell function in new-onset patients.

### **Cellular and Molecular Approaches to Achieving Euglycemia**

#### **RFA-DK-98-007**

This program encouraged the development of therapies to achieve normal glucose levels in patients with type 1 diabetes. Grants were awarded in FY 1998 on a range of relevant topics, including islet and beta cell transplantation, engineering of regulated insulin secretion in non-beta cell surrogates, hematopoietic stem cell therapy for the induction of tolerance, and development of technologies to preserve beta cell function and stimulate beta cell regeneration. Particular emphasis was placed on the development of clinically applicable technologies.

### **Islet Encapsulation Research**

The development of pancreatic islet transplantation holds great promise as a treatment for type 1 diabetes. However, to prevent rejection of donated islets, patients must rely on long-term immunosuppression, which presents the risk of multiple adverse effects. An alternative to immunosuppression is to coat or “encapsulate” the islets with a material that would prevent the islets from being recognized as foreign by

the patient’s immune system, yet allow necessary nutrients to reach the islets. Four pilot and feasibility awards were made with the *Special Funds* in FY 2002.

### **Toward Imaging the Pancreatic Beta Cell in People**

#### **RFA-DK-06-003**

The ability to image or otherwise directly monitor beta cells in people would greatly enhance understanding of the causes and progression of diabetes and the life cycle of the islet. Furthermore, it would also improve the ability of clinicians to study the beta cell in human health and disease, as well as to monitor therapy, particularly islet transplantation. This initiative, for which grants will be awarded late in 2006, was designed to provide resources to further research on imaging the pancreatic beta cell, beta cell function, or inflammation *in vivo*, using approaches that would be clinically applicable. It builds on research from previous efforts, including RFA-DK-02-002 (described previously).

### **Beta Cell Regeneration for Diabetes Therapy**

#### **RFA-DK-05-007**

Regenerative medicine is providing new therapeutic approaches for restoring organ functions lost due to disease or other causes. To enhance tissue and organ regeneration, progenitor cells must be mobilized and provided with an appropriate niche to advance their development. In order to harness the power of regenerative medicine for diabetes therapy, it is important to define further the basic tissue biology and regenerative capacity of the human pancreas, as well as cellular and molecular mechanisms regulating cell turnover, tissue remodeling and regeneration. This initiative aims to support studies that will characterize the regenerative potential of human beta cells or islets *in vivo*, define cellular and molecular factors regulating pancreatic regeneration in normal and diabetic adults, and identify ways to enhance recovery of endogenous beta cell function in diabetic patients.

## **Goal IV—Prevent or Reduce Hypoglycemia in Type 1 Diabetes**

### **Diabetes Research in Children Network (DirecNet)**

#### **RFA-HD-01-009**

The focus of DirecNet is to investigate the use of technological advances in the management of type 1 diabetes in children and to develop a better understanding of hypoglycemia. The Network's goals include assessing the accuracy, efficacy, and effectiveness of continuous glucose monitoring in children with type 1 diabetes, and determining the extent to which exercise contributes to the risk of hypoglycemia. Until cell replacement therapy is a viable treatment option for children with type 1 diabetes, research on glucose sensing and insulin delivery is crucial to improving quality of life and decreasing the number of hypoglycemic episodes.

### **Hypoglycemia in Patients with Type 1 Diabetes**

#### **RFA-DK-03-017**

Large clinical trials have demonstrated the efficacy of intensified glucose control in the prevention of the long-term vascular complications of diabetes. However, episodes of severe hypoglycemia may complicate intensified treatment and are often a major obstacle to the achievement of euglycemia in many patients. This program supports basic and clinical studies to enhance understanding of how the brain and other critical tissues sense and respond to hypoglycemia; to delineate the effects of hypoglycemia on brain function; and to develop improved methodologies to prevent hypoglycemia based on an understanding of physiological glucose sensing and counterregulation. Grants were awarded in 2004.

### **Effects of Hypoglycemia on Neuronal and Glial Cell Function**

#### **RFA-NS-02-008**

Recent therapeutic strategies aimed at closely controlling elevated glucose levels in diabetic individuals put them at risk

for experiencing multiple episodes of hypoglycemia. Acute episodes of hypoglycemia can result in alteration of brain function, confusion, abnormal behavior, seizures, or coma. Likewise, recurrent hypoglycemia can potentially harm the cells of the central nervous system or impose long-lasting damage on the brain. This initiative focused on elucidating the effects of acute and recurrent episodes of hypoglycemia on glial and neuronal cells of the developing and mature central nervous system. Funded in 2002, these research projects should enhance understanding of the effects of hypoglycemia on brain function and could lead to new targets for therapy for this serious complication.

### **Sensor Development and Validation**

#### **RFA-EB-02-002**

Management of type 1 diabetes has been improved by the availability of continuous, noninvasive glucose monitoring systems and insulin pumps. Nonetheless, this advanced technology does not fully replicate the body's natural ability to link insulin secretion directly and continuously to blood glucose levels. The broad scope of this solicitation encompassed research to further advance the field of novel glucose sensing methods and "closed-loop" insulin delivery systems; grants were awarded in 2002.

### **Understanding Hypoglycemia Unawareness in Patients with Diabetes**

#### **RFA-DK-01-031**

Many individuals with diabetes experience a progressive decay in the counter-regulatory response to hypoglycemia over time. Falling blood glucose levels fail to trigger epinephrine secretion, and therefore no neurogenic symptoms occur to warn the patient of a problem. Such "hypoglycemia unawareness" can cause prolonged exposure to hypoglycemia and result in potential brain injury, seizure, or loss of consciousness. The development of hypoglycemia unawareness makes the implementation of intensified blood glucose control more

difficult and puts patients at risk for severe hypoglycemia-related complications. This initiative fostered basic and clinical research on molecular mechanisms underlying hypoglycemia unawareness and novel approaches to prevent or reverse this condition in diabetic patients, with research grants awarded in 2002.

### **Glucose Sensors in the Treatment of Diabetes**

RFA-DK-98-008

Accurate, noninvasive glucose sensors hold great promise for improving glucose control and quality of life for individuals with type 1 diabetes. This initiative, funded in FY 1998, supported research on the development of novel glucose sensors or the creation of a closed-loop system for regulating blood glucose, incorporating advances in chemistry, engineering, cell biology, biochemistry, and endocrinology.

### **Developing New Tools for Detecting and Monitoring Low Blood Glucose for People with Diabetes**

PA 99151 (CDC)

Hypoglycemia is the most common problem limiting diabetes management. This program focused on the development of innovative and minimally invasive technology to alert people with diabetes of an impending hypoglycemic episode, to minimize the morbidity and mortality associated with hypoglycemia, and to aid glycemic control, thus reducing the risk for complications of diabetes. In response to the program announcement, “Innovative Technology Development Grant for the Detection and Monitoring of Diabetic Hypoglycemia by Non- or Minimally-Invasive Techniques,” the CDC funded three research grants in 1999.

### **Standardization Program To Improve the Measurement of Blood Glucose by Portable Monitoring Systems**

People with diabetes and their health care providers rely on the results reported by portable blood glucose monitoring

systems to make treatment decisions. Improper treatment can result if performance is not comparable among the many different systems that are available. This project was launched by the CDC to evaluate the variability among blood glucose monitoring systems and to develop a standardization program to normalize results among these systems.

### **Goal V—Prevent or Reduce the Complications of Type 1 Diabetes**

#### **Epidemiology of Diabetes Interventions and Complications (EDIC)**

The aim of EDIC is to study the clinical course and risk factors associated with the long-term complications of type 1 diabetes, using the cohort of the Diabetes Control and Complications Trial (DCCT). The DCCT/EDIC research group has observed dramatic long-term benefits of intensive glucose control in preventing and delaying complications of the eyes, kidneys, nerves, and heart. These results have had a major impact on the clinical care of diabetes patients.

#### **Family Investigation of Nephropathy and Diabetes (FIND)**

The FIND Consortium is carrying out studies to elucidate the genetic susceptibility to kidney disease in patients with diabetes, as well as genetic susceptibility to retinopathy in diabetic patients. A family-based study recruited more than 2,500 affected and discordant pairs of siblings. A separate case control study is completing recruitment of more than 3,000 individuals. These studies will help researchers understand the genetic underpinnings of the kidney and eye complications of diabetes, which can, in turn, inform prevention and treatment strategies.

### **Genetics of Kidneys in Diabetes Study (GoKinD)**

GoKinD was established to study the genetics of kidney disease in type 1 diabetes patients. The study group has collected and is distributing DNA and other biological samples from more than 1,700 adults with type 1 diabetes in the United States and Canada. Scientists will use these samples to identify genes that are important in the development of, or resistance to, diabetic kidney disease.

### **Diabetic Retinopathy Clinical Research Network (DRCR.net)**

#### **RFA-EY-01-001**

Type 1 diabetes causes damage to the eyes and may lead to blindness. The DRCR.net conducts multicenter clinical research studies to test promising therapeutic agents for the treatment of two forms of diabetic eye disease—diabetic retinopathy and diabetic macular edema—and associated conditions. Because blindness is such a severe and debilitating disease complication, research pursued through DRCR.net could dramatically improve patients' quality of life.

### **Animal Models of Diabetic Complications Consortium (AMDCC)**

#### **RFA-DK-01-009, RFA-HL-01-010, and RFA-DK-05-011**

The AMDCC is an interdisciplinary Consortium designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment. The Consortium has already developed a number of promising models for complications involving the heart, kidneys, and nervous system. Development of animal models is essential for pre-clinical drug development.

### **Collaborative Studies on Angiogenesis and Diabetic Complications**

#### **RFA-DK-04-022**

This program supports studies to bolster understanding of the effects of type 1 diabetes on the development of new blood vessels from preexisting vessels (angiogenesis). Funded in 2005, these studies are exploring the mechanisms of abnormal angiogenesis seen in diabetes complications, such as diabetic kidney and eye disease and defects in wound healing. This research should open new avenues for treatment of diabetic complications.

### **Progression of Cardiovascular Disease in**

#### **Type 1 Diabetes**

#### **RFA-HL-04-013**

The causes of the increased incidence and earlier onset of cardiovascular disease in patients with type 1 diabetes are not fully understood. It is not yet clear whether known risk factors for cardiovascular disease are also important in type 1 diabetes patients, or whether other factors are responsible for or contribute to the enhanced cardiovascular complications in these patients. Understanding the mechanisms involved will facilitate the development of improved prevention and treatment approaches tailored to individuals with type 1 diabetes. The objective of this program is to support basic and clinical studies to enhance understanding of the mechanisms involved in the early development and fast progression of cardiovascular disease in type 1 diabetes. Grants were awarded in 2004.

### **Feasibility Projects To Test Strategies for Preventing or Slowing the Progression of Diabetic Nephropathy**

#### **RFA-DK-02-025**

Type 1 diabetes increases risk for kidney failure. Because many type 1 diabetes patients develop progressive kidney disease despite adequate management of risk factors, new strategies to prevent disease and slow its progression are needed. This initiative supported clinical research on new therapies to



prevent or treat diabetic kidney disease that might potentially be taken to large interventional trials. Support from this program will help ensure that sufficient preliminary data will be available to plan such trials. Grants were awarded in 2002.

### **Surrogate Endpoints for Diabetic Microvascular Complications**

#### **RFA-DK-02-016**

Prevention and treatment of long-term micro- and macrovascular complications remain critical problems in the management of type 1 diabetes. Early identification of patients at risk for the development of diabetic complications and early intervention are essential. By the time disease symptoms are recognized, irreversible organ damage may have already occurred. This program supports research on the development of surrogate endpoints, which are biological markers that can be used to gauge a person's health without having to wait for full-blown disease to develop. Ideally, these biomarkers will predict patients who are at high risk for developing complications and who may benefit from aggressive intervention, aid in early diagnosis of complications, or correlate with disease progression. Such endpoints could be used as diagnostic tools for the individual patient, or as outcome measures for clinical trials of new therapeutic agents. Grants were awarded in 2002.

### **Imaging Early Markers of Diabetic Microvascular Complications in Peripheral Tissue**

#### **RFA-DK-02-001**

Impaired perfusion—the ability of oxygen to reach tissues—may be an early event in the development of microvascular complications of diabetes. This program, funded in 2002, supports research on the development of new, clinically useful imaging tools for the study of microvascular disease in the diabetic population. Tools to measure perfusion and tissue oxygenation at the level of the microvasculature, or to identify inflammation associated with diabetic complications, will help define the mechanisms leading to microvascular complica-

tions of diabetes in peripheral tissues. Moreover, this research may result in the development of new techniques to detect the early stages of these complications, identify patients likely to benefit from therapeutic interventions, and monitor disease progression and response to therapy.

### **Oral Microbiology/Immunology of Type 1 Diabetes**

#### **RFA-DE-01-001**

Diabetes is a significant factor for severe and extensive periodontal (gum) disease. Recent studies indicate that diabetes alters the immune system and connective tissue, making the patient more susceptible to oral tissue destruction and inflammation. Research projects funded through this initiative, beginning in 2001, involved exploratory research to broaden the understanding of the microbiology and immunology of oral complications associated with type 1 diabetes.

### **Neurobiology of Diabetic Complications**

#### **RFA-NS-00-002**

Chronically high blood glucose levels result in significant nerve damage in more than half of all diabetic individuals. Diabetic peripheral neuropathy—affecting the hands, arms, feet, and legs—is associated with vascular disease and impaired wound healing, and often results in chronic skin ulcers and limb amputation. The nervous system also controls the body's counter-regulatory response to hypoglycemia. This program was designed to support research on the mechanisms by which diabetes results in painful, disabling peripheral neuropathy, autonomic neuropathy, impaired counter-regulation and hypoglycemia unawareness, and other neurological complications. Because of two initiatives supported by the *Special Funds*, RFA-NS99-005, funded in FY 1999 (see below) and RFA-NS00-002, funded in FY 2000, the number of funded research projects in diabetic neuropathy became far greater than it would have been otherwise.

## **Neurological Complications of Diabetes**

### **RFA-NS-99-005**

Neurological complications are significant problems for diabetic individuals. In many patients, symptoms such as pain, numbness, weakness, or even paralysis are serious enough to interfere with daily activities. Other symptoms of diabetic neuropathy may include heart rate abnormalities, high blood pressure, dizziness, digestive disturbances, and impotence. Autonomic neuropathy can cause sudden cardiac death in persons with diabetes. Prevention and treatment are often ineffective, so new approaches are needed. This program was designed to encourage research on the mechanisms by which diabetes results in painful and disabling neuropathies and other neurological complications, and on the development of interventions to prevent, limit, or reverse these conditions. Grants were funded in FY 1999.

## **Pathogenesis and Therapy of Complications of Diabetes**

### **RFA-DK-98-009**

Central medical issues for patients with type 1 diabetes are prevention and treatment of chronic complications, including blindness, end-stage renal disease, non-traumatic lower leg amputations, and macrovascular complications. With grants awarded in FY 1998, this program encouraged research on the mechanisms by which hyperglycemia causes vascular complications and the application of this information to the development of interventions to prevent or treat diabetic complications.

## **Administrative Supplements for a Drug Screening Program for Diabetic Complications**

### **NOT-DK-05-017**

An important, but elusive, goal for diabetes care has been therapeutics that would prevent or reverse the cellular injury induced by hyperglycemia. Research on hyperglycemic

cellular injury has increased knowledge of the pathologic pathways, but translation of this knowledge to clinically useful drugs has been largely unsuccessful. In a new approach to this problem, this program is fostering a collaborative effort to screen a collection of about 1,000 FDA-approved compounds over approximately 6 months in individual laboratories, using assays relevant to diabetic complications. The purposes of this program are to encourage laboratory scientists to participate in translational research; highlight the best assays for diabetic complications; uncover new metabolic or signaling pathways involved in the cellular injury of diabetes; discover new potential drugs for diabetic complications; and piggy-back on the knowledge base of these FDA-approved compounds to hasten clinical trials. Funding was awarded in early 2006.

## **Goal VI—Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes**

### **Training Programs in Diabetes Research for Pediatric Endocrinologists**

#### **RFA-DK-02-024**

This program provides support of research training and career development in pediatric diabetes at institutions that have environments, mentors, and programs that will make them particularly effective in enhancing the number of independent investigators contributing to research in pediatric diabetes. The awards, through the T32 (institutional research training) and K12 (clinical scientist career development program) grant mechanisms of the NIH, are intended to provide an opportunity for continuous training from the clinical fellowship years to emergence as a fully trained independent investigator. These integrated programs are designed to prepare pediatricians, selected by the institution, for careers in pediatric endocrinology research related to diabetes.

### **Innovative Partnerships in Type 1 Diabetes and Its Complications**

**RFA-DK-02-023 and RFA-DK-03-015**

This innovative partnership program promotes collaboration among diabetes researchers and those in areas other than diabetes who have expertise or technology that could advance diabetes research projects. The goal is to encourage diabetes researchers to act as “talent scouts” to identify other researchers who could contribute to research breakthroughs in diabetes.

### **Bench to Bedside Research on Type 1 Diabetes and Its Complications**

**RFA-DK-02-022, RFA-DK-03-001, and RFA-DK-03-019**

An innovative bench to bedside program in type 1 diabetes supports collaboration between basic research scientists, whose findings have potential direct applicability to the development of new treatments or diagnostic tests, and clinical scientists, who can help translate these basic discoveries into pre-clinical studies or clinical trials.

### **Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID)**

The T1D-RAID program provides resources for manufacture and pre-clinical development of drugs, natural products, and biologics that will be tested in type 1 diabetes clinical trials. The goal of T1D-RAID is to facilitate the translation of promising therapeutic agents from bench to bedside in order to more rapidly impact patients’ health.

### **Small Business Innovation Research and Small Business Technology Transfer To Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes (T1D) and Its Complications (SBIR [R43/R44])**

**RFA-DK-05-016 and RFA-DK-05-015**

These parallel initiatives are intended to support innovative research on type 1 diabetes and its complications in the

biotechnology industry. Examples of research areas that would be encompassed by these initiatives include development of novel or improved therapeutics for prevention or treatment, and development of new methods to monitor the initiation, progression, and therapy of type 1 diabetes and its complications. Grants will be awarded in Fall 2006.

### **Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) RFA in Type 1 Diabetes and Its Complications**

**RFA-DK-03-020**

This initiative was designed to encourage the small business community to apply cutting edge technology to research on developing treatment or prevention approaches for type 1 diabetes and its complications. Grants were awarded in 2004.

### **Measurement Tools for Altered Autonomic Function in Spinal Cord Injury and Diabetes: SBIR/STTR**

**RFA-HD-04-018**

This initiative solicited small business grant applications to conduct research on measurement tools or devices for altered autonomic functions in persons with spinal cord injury or diabetes mellitus. A grant was awarded in 2005.

### **Proteomics and Metabolomics in Type 1 Diabetes and Its Complications**

**RFA-DK-03-024**

Proteomic approaches have been successfully used for studying complex biological problems and for the identification of disease markers. However, these technologies had previously been applied to study type 1 diabetes and its complications only in a limited way. This program was designed to support research using proteomics and metabolomics technologies to study type 1 diabetes and its complications, particularly as collaborative efforts between investigators with expertise in these technologies and those with expertise in type 1 diabetes. Grants were awarded in 2004.

# **APPENDIX 2: TYPE 1 DIABETES CONSORTIA COORDINATION**

This Appendix describes the numerous collaborative efforts among the type 1 diabetes consortia and networks that have occurred or are ongoing. It also describes the steps that the NIH and CDC have taken to enhance coordination and collaboration among research programs with related and distinct interests.

## TYPE 1 DIABETES CONSORTIA COORDINATING COMMITTEE

**A**t an ad hoc planning and evaluation meeting convened in January 2005, on the Special Statutory Funding Program for Type 1 Diabetes Research (see Appendix 3), an expert panel strongly recommended that the NIH and CDC extend and capitalize on existing research efforts by maximizing connections among research groups with both related and distinct interests. The panel recommended that strong existing coordination across consortia be further enhanced to synergize research efforts. These interactions should not be limited to consortia with overlapping interests. Collaboration between researchers with distinct interests could facilitate the pursuit of novel research directions. In addition, increased coordination can prevent duplicative work by promoting the sharing of resources and methodology, as well as by facilitating cross-disciplinary research approaches.

In 2003, the NIDDK established a Type 1 Diabetes Consortia Coordinating Committee, which consists of representatives from multiple research consortia, and networks to enhance ongoing collaboration and coordination among the research consortia and networks supported by the *Special Funding Program*. The charge of this Committee has been to coordinate issues of recruitment and enrollment; standardize assays, phenotyping, and consents; promote the use of clinical populations for development and validation of assays for immune and metabolic monitoring; and coordinate bioinformatics issues and ancillary studies.

This Committee met multiple times via teleconference and once in person to discuss issues of coordination and collaboration. The Committee also spearheaded the development of a website to aid type 1 diabetes patient recruitment efforts ([www.T1Diabetes.nih.gov/patient](http://www.T1Diabetes.nih.gov/patient)), as well as a website to facilitate resource sharing across consortia ([www.T1Diabetes.nih.gov/investigator](http://www.T1Diabetes.nih.gov/investigator)).

## EXAMPLES OF MEETINGS TO FACILITATE COLLABORATION AND COORDINATION AMONG TYPE 1 DIABETES CONSORTIA

### **Type 1 Diabetes Consortia Coordinating Committee Meeting**

May 15, 2005, Boston, MA

The expert panel at the January 2005, meeting on the *Special Funding Program* recommended a face-to-face meeting of the Type 1 Diabetes Consortia Coordinating Committee to explore novel avenues for collaboration. In response to this recommendation, the NIDDK convened a meeting of the Committee in association with the annual meeting of the Federation of Clinical Immunology Societies (FOCIS) in Boston. Over 20 representatives from consortia and networks supported by the *Special Funding Program* attended the meeting and discussed ongoing research efforts and areas for enhanced collaboration.

One of the recommendations emanating from this meeting was for the NIDDK to expand its website on the *Special Funding Program* so that it could be used as a resource for sharing across consortia. The Committee recommended that the following types of information and resources be posted on the website for public dissemination: organization charts showing committees and committee charges; consortia policies (e.g., publications and presentations, ancillary studies, quality control, intellectual property); opportunities available through consortia for new investigators; case report forms; standardized vocabularies; research resources (e.g., antibodies, animal models, cell lines, microarrays). In addition, because many of the consortia have data, biosamples, and protocols that are available to share with the broader research community, the Committee strongly recommended that this material also be posted on the NIDDK's website.

In response to this recommendation, the NIDDK launched an expanded public website dedicated to research supported by the *Special Funding Program* in February 2006 ([www.T1Diabetes.nih.gov](http://www.T1Diabetes.nih.gov)). The website includes information for both

researchers and patients/family members. Patients can search for clinical research studies that are enrolling participants; read brief descriptions of the studies to help them determine if they are eligible; and find out who to call if they are interested in enrolling ([www.T1Diabetes.nih.gov/patient](http://www.T1Diabetes.nih.gov/patient)). Investigators can access current funding opportunities; descriptions of ongoing research consortia and networks; information on research resources (such as those described above); and descriptions of upcoming and past meetings relevant to type 1 diabetes research ([www.T1Diabetes.nih.gov/investigator](http://www.T1Diabetes.nih.gov/investigator)). The public website permits investigators in the broad scientific community to access resources, data, and materials generated by the research consortia, thereby maximizing the investment in these research efforts.

### **Coordination of Type 1 Diabetes Studies Involving Newborns**

May 15, 2005, Boston, MA

Prior to the larger type 1 diabetes Committee meeting (described above), representatives from consortia studying newborns (TEDDY, TRIGR, and TrialNet) met to discuss opportunities for enhancing coordination and collaboration. The participants discussed how to obtain the most useful information when looking at these studies as a group. Common data variables across the studies and future analytic strategies were also discussed.

### **Genetics of Diabetes and Its Complications: Consortia Meeting**

July 20, 2005, Bethesda, MD

Meeting Summary: [www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf](http://www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf)

The expert panel at the January 2005 meeting on the *Special Funding Program* strongly encouraged enhanced coordination among the four major genetics consortia supported by

the *Special Program*: Family Investigation of Nephropathy and Diabetes (FIND), Genetics of Kidneys in Diabetes Study (GoKinD), Epidemiology of Diabetes Interventions and Complications Study (EDIC), and Type 1 Diabetes Genetics Consortium (T1DGC). In response to this recommendation, the NIDDK convened a meeting with representatives from all four genetics consortia. At the meeting, recommendations

were developed for facilitating interactions among the studies and for future analytic strategies. The importance of interactions between consortia was emphasized to enhance the value of the individual studies that aim to develop new strategies for prevention and treatment to alleviate the suffering from type 1 diabetes.

**Table A3: “At a Glance” Matrix of Type 1 Diabetes Consortia Coordination Activities**

■ Red-shaded squares indicate collaboration between the consortia

	AMDCC	Prevention Centers	BCBC	CIT	CITR	EDIC	FIND	GoKinD	ITN	Immunobiology of Xenotransplantation	ICRs	Mouse Repositories	NHPCSG	SEARCH	Standardization Programs	TEDDY	TRIGR	T1DGC	T1D-RAID	TrialNet
Animal Models of Diabetic Complications Consortium (AMDCC)	■					■	■	■												
Cooperative Study Group for Autoimmune Disease Prevention		■								■										
Beta Cell Biology Consortium (BCBC)			■							■	■									
Clinical Islet Transplantation Consortium (CIT)				■	■				■	■		■				■		■	■	■
Collaborative Islet Transplant Registry (CITR)					■				■	■										
Epidemiology of Diabetes Interventions and Complications (EDIC)	■					■	■	■							■				■	
Family Investigation of Nephropathy and Diabetes (FIND)	■					■	■	■											■	
Genetics of Kidneys and Diabetes Study (GoKinD)	■						■	■											■	
Immune Tolerance Network (ITN)				■	■			■	■				■			■	■		■	■
Immunobiology of Xenotransplantation Cooperative Research Program									■	■		■	■							
Islet Cell Resource Centers (ICRs)		■	■	■	■			■	■	■	■			■			■		■	■
Mouse Repositories			■								■	■								
NHP Transplantation Tolerance Cooperative Study Group (NHPCSG)				■					■	■		■	■				■		■	■
SEARCH for Diabetes in Youth										■			■	■	■	■		■	■	■
Standardization Programs (C-peptide, HbA1c, DASP)						■								■	■	■				■
The Environmental Determinants of Diabetes in the Young (TEDDY)				■					■					■	■	■	■		■	■
Trial to Reduce IDDM in the Genetically At Risk (TRIGR)									■					■	■	■	■		■	■
Type 1 Diabetes Genetics Consortium (T1DGC)				■		■	■	■						■	■	■		■	■	■
Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID)				■					■	■		■						■	■	■
Type 1 Diabetes TrialNet (TrialNet)				■					■					■	■	■	■	■	■	■

## HIGHLIGHTS OF TYPE 1 DIABETES CONSORTIA COLLABORATION AND COORDINATION

The following section highlights the ongoing collaborations and coordination efforts among type 1 diabetes research consortia and networks supported by the *Special Funding Program* (please see Appendix 7 for a list of program abbreviations and websites). Because this section is organized by consortium, collaborative efforts appear more than once. For example, collaborations between TEDDY and TRIGR are listed under each consortium. A matrix (Table A3) provides a concise analysis of these collaborations.

### Animal Models of Diabetic Complications Consortium (AMDCC)

**FIND, GoKinD, and EDIC:** The AMDCC semi-annual meeting on March 22-24, 2005, included presentations by representatives from FIND, GoKinD, and EDIC to initiate collaborations such that data originating from the genetics consortia will direct the creation of new animal models by the AMDCC, which will, in turn, validate the findings of the genetics consortia.

**Mouse Metabolic Phenotyping Centers (MMPCs):** The AMDCC and the MMPCs have formed a new partnership. The mission of the MMPCs is to conduct detailed metabolic phenotyping of genetically-altered mice. Thus, it is a logical extension of both consortia to have all mice generated by the AMDCC shipped to MMPC facilities. This close partnership will not only allow a number of organizational efficiencies, but more importantly, will make certain that all animals generated by the AMDCC are fully phenotyped across each relevant metabolic and diabetic complication.

### Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers)

**ICRs:** Investigators participating in the Prevention Centers receive islets for basic research through the ICR basic science human islet distribution program.

### Beta Cell Biology Consortium (BCBC)

#### ICRs:

- ▶ BCBC website announces availability of human islets for basic research through the ICRs ([www.betacell.org/news/index.php?view=41](http://www.betacell.org/news/index.php?view=41)).
- ▶ BCBC investigators use human islets obtained through the ICR basic science human islet distribution program.
- ▶ Data collected from BCBC investigators using ICR samples are repositied with the informatics coordination center of the ICRs.
- ▶ PancChips made available for potential ICR quality assessments.
- ▶ Provision of islets for BCBC investigators pursuing studies under RFA-DK03-021 (Pilot and Feasibility Program in Human Islet Biology).

#### Mouse Repositories:

- ▶ Mouse strains developed by BCBC investigators are available through NCCR-funded repositories (T1DR and the Mutant Mouse Regional Resource Centers [MMRRC]), which provides greater access to these resources by the scientific community.
- ▶ BCBC mouse database design based on International Mouse Strain Resource (IMSR) model used by The Jackson Laboratory's repositories, including T1DR and MMRRC.
- ▶ BCBC mouse database designed to directly interface with IMSR, T1DR, and MMRRC.

### Clinical Islet Transplantation Consortium (CIT)

**CITR:** CITR is planning to list all active islet transplantation protocols on their website. CIT plans to use this information as part of their informed consent process for enrollees.



**CITR and ICRs:**

- ▶ On-site data review of transplantation centers is performed by the CITR and is provided to the ICRs. These data include determination of islet quality and collection of transplant outcome information.
- ▶ CIT investigators who use ICR resources must agree to place their clinical study data in the CITR.
- ▶ Data sharing agreements have been developed between CIT, CITR, 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.

**ICRs:** Clinical grade islets are provided for islet transplantation trials. CIT investigators receive islets for basic research through the ICR basic science human islet distribution program.

**ITN:** 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.

**NHPCSG:** Cross-representation of investigators between NHPCSG and CIT led to collaborative design of pre-clinical studies and pre-clinical testing of therapeutics in non-human primates.

**NHPCSG and ITN:** CIT, ITN, and NHPCSG are interested in utilizing similar reagents for use as immune modulators for the treatment of type 1 diabetes or for islet transplantation.

**TEDDY, T1DGC, and TrialNet:** Collaborative media effort between TEDDY, T1DGC, TrialNet, and CIT. Media needs of all of these groups are being jointly handled by a single media contract to optimize coordination of type 1 diabetes clinical trials.

**T1D-RAID:** Provision of novel reagents for testing to reduce islet autoimmune destruction after transplantation.

**Collaborative Islet Transplant Registry (CITR)****ICRs:**

- ▶ Monthly conference calls are held between CITR and the ICRs to discuss status of initiatives and any logistical concern between the two projects.
- ▶ Investigators who use ICRs must agree to place their clinical study data in CITR.

**ICRs and CIT:**

- ▶ On-site data review of transplantation centers is performed by CITR and is provided to the ICRs. These data include determination of islet quality and collection of transplant outcome information.
- ▶ Data sharing agreements have been developed between CIT, CITR, 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.

**ITN:** Results of pertinent trials are archived.

## Epidemiology of Diabetes Interventions and Complications (EDIC)

**AMDCC:** The AMDCC semi-annual meeting on March 22-24, 2005, included presentations by representatives from FIND, GoKinD, and EDIC to initiate collaborations such that data originating from the genetics consortia will direct the creation of new animal models by the AMDCC, which will, in turn, validate the findings of the genetics consortia.

### FIND and GoKinD:

- ▶ A series of ongoing database coordination meetings between EDIC, FIND, and GoKinD is seeking to standardize patient consent forms and permit investigators to search data across databases.
- ▶ The NIDDK is coordinating an integrated database of the parameters in the genetics studies of kidney disease in diabetes, which will include EDIC, GoKinD, and FIND.

**FIND, GoKinD, and T1DGC:** In July 2005, consortia supported by the *Special Funding Program* that study genetics (GoKinD, FIND, EDIC) participated in a meeting with T1DGC. In response to recommendations from this meeting, new initiatives are being developed to coordinate future efforts among the studies. A summary of the meeting can be accessed on the NIDDK's website ([www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf](http://www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf)).

**Standardization Programs:** The National Glycohemoglobin Standardization Program certifies clinical laboratories to use the standard set by DCCT/EDIC for measurements of HbA1c.

## Family Investigation of Nephropathy and Diabetes (FIND)

**AMDCC:** The AMDCC semi-annual meeting on March 22-24, 2005, included presentations by representatives from FIND, GoKinD, and EDIC to initiate collaborations such that data

originating from the genetics consortia will direct the creation of new animal models by the AMDCC, which will, in turn, validate the findings of the genetics consortia.

### GoKinD, EDIC, and T1DGC:

- ▶ In July 2005, consortia supported by the *Special Funding Program* that study genetics (GoKinD, FIND, EDIC) participated in a meeting with T1DGC. In response to recommendations from this meeting, new initiatives are being developed to coordinate future efforts among the studies. A summary of the meeting can be accessed on the NIDDK's website ([www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf](http://www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf)).
- ▶ FIND Steering Committee meetings from the past 4 years have frequently included presentations by GoKinD and EDIC study representatives.
- ▶ The NIDDK is coordinating an integrated database of the parameters in the genetic studies of kidney disease in diabetes, which will include EDIC, GoKinD, and FIND.
- ▶ A series of ongoing database coordination meetings between EDIC, FIND, and GoKinD is seeking to standardize patient consent forms and permit investigators to search data across databases.

**GoKinD:** Key personnel from FIND serve in official advisory capacities for GoKinD.

## Genetics of Kidneys in Diabetes Study (GoKinD)

**AMDCC:** The AMDCC semi-annual meeting on March 22-24, 2005, included presentations by representatives from FIND, GoKinD, and EDIC to initiate collaborations such that data originating from the genetics consortia will direct the creation of new animal models by the AMDCC, which will, in turn, validate the findings of the genetics consortia.

**FIND:** There has been a coordination conference call with FIND representatives.

**FIND and EDIC:** A series of ongoing database coordination meetings between EDIC, FIND, and GoKinD is seeking to standardize patient consent forms and permit investigators to search data across databases.

**FIND, EDIC, and T1DGC:**

- ▶ In July 2005, consortia supported by the *Special Funding Program* that study genetics (GoKinD, FIND, EDIC) participated in a meeting with T1DGC. In response to recommendations from this meeting, new initiatives are being developed to coordinate future efforts among the studies. A summary of the meeting can be accessed on the NIDDK's website ([www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf](http://www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf)).
- ▶ The NIDDK is coordinating an integrated database of the parameters in the genetic studies of kidney disease in diabetes, which will include EDIC, GoKinD, and FIND.

**ICRs:** GoKinD investigators receive islets for basic research through the ICR basic science human islet distribution program.

**Immune Tolerance Network (ITN)**

**CIT:** 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.

**CITR:** Results of trials archived with CITR.

**ICRs:** Islet sources for multicentered clinical study sites utilizing the Edmonton Protocol. ITN investigators receive islets for basic research through the ICR basic science human islet distribution program.

**NHPCSG:**

- ▶ Cross-representation of investigators between the NHPCSG and ITN.
- ▶ ITN priorities for pre-clinical testing of new therapeutics considered in evaluating Opportunities Pool applications. Several of the high priority strategies are currently funded as pilot projects.
- ▶ NIAID program staff attend ITN transplantation mechanistic assay meetings to represent NHPCSG interests.

**NHPCSG and CIT:** CIT, ITN, and NHPCSG are interested in utilizing similar reagents for use as immune modulators for the treatment of type 1 diabetes or for islet transplantation.

**TEDDY:** TEDDY had several discussions with ITN and has adopted the ITN standard for messenger RNA (mRNA) extraction.

**T1D-RAID:** Provision and pre-clinical testing of novel reagents.

**TrialNet:**

- ▶ ITN collaborates with TrialNet on the development and implementation of protocols in type 1 diabetes, where both parties agree it is beneficial. The studies in which TrialNet and ITN collaborate include: (1) Natural History Study; (2) Mycophenolate Mofetil – Daclizumab (MMF/DZB); (3) T Cell Validation Study; and (4) The Effects of Rituximab on the Progression of Type 1 Diabetes in New Onset Patients.
- ▶ The ITN supplies collection kits and training to laboratories for isolating peripheral blood mononuclear cells (PBMCs).
- ▶ ITN provides RNA isolation on batched specimens.
- ▶ ITN coordinates the transfer of frozen PBMCs, RNA, and plasma specimens to the NIDDK Repository from laboratories for studies, as applicable.

- ▶ ITN coordinates the collection of blood and the transfer of samples from the clinical sites to the Flow Core Laboratory for analysis.
- ▶ Research staff from ITN and TrialNet collaborate on joint studies, communicating daily and convening 1 hour weekly to discuss critical site/study/technical issues. They also use this time to update each other regarding each Center's status in ongoing studies.
- ▶ ITN and the TrialNet Coordinating Center participate in monthly meetings where key study members discuss the status and any pending problems or issues with ongoing studies.
- ▶ ITN and TrialNet use a common Data and Safety Monitoring Board.
- ▶ Protocols potentially of interest to both TrialNet and ITN are considered by both Networks with the goal of joint sponsorship.
- ▶ TrialNet and ITN did a joint mailing (with the help of JDRF, New England chapter) to introduce/advertise the TrialNet Natural History Study and the ITN Insulin Study.

**TRIGR:** There is coordination of T cell assays being done by TRIGR and ITN.

## Immunobiology of Xenotransplantation Cooperative Research Program

### NHPCSG:

- ▶ Cross representation between programs, both at the Principal Investigator (PI) and Program Director levels.
- ▶ Plans are in place for sharing of reagents, techniques, and protocols that may be relevant to the two programs.

## Islet Cell Resource Centers (ICRs)

**Multiple Consortia:** Investigators from the following consortia supported by the *Special Funding Program* receive islets for basic research through the ICR basic science human islet distribution program: Cooperative Study Group for Autoimmune Disease Prevention, BCBC, CIT, GoKinD, ITN, and SEARCH.

### BCBC:

- ▶ BCBC website announces availability of human islets for research from ICRs ([www.betacell.org/news/index.php?view=41](http://www.betacell.org/news/index.php?view=41)).
- ▶ Data collected from BCBC investigators using ICR samples are repositied with the informatics coordination center of the ICRs.
- ▶ PancChips made available for potential ICR quality assessments.
- ▶ Provision of islets for BCBC investigators pursuing studies under RFA-DK03-021 (Pilot and Feasibility Program in Human Islet Biology).

**CIT:** Clinical grade islets are provided for CIT transplantation trials.

**CITR:** Investigators who use ICR resources must agree to place their clinical study data in the CITR.

### CIT and CITR:

- ▶ On-site data review of transplantation centers is performed by the CITR and is provided to the ICRs. These data include determination of islet quality and collection of transplant outcome information.
- ▶ Data sharing agreements have been developed between CIT, CITR, 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.

**ITN:** Islet source for multicenter clinical studies utilizing the Edmonton Protocol.

**T1D-RAID:** Provision of novel reagents as media additives to improve function and survival of islets in culture.

### **Mouse Repositories: Type 1 Diabetes Mouse Repository (T1DR) and Mutant Mouse Regional Resource Centers (MMRRC)**

#### **BCBC:**

- ▶ Mouse strains developed by BCBC investigators are available through NCRR-funded repositories (T1DR and MMRRC), which provides greater access to these resources by the scientific community.
- ▶ BCBC mouse database design based on IMSR model used by the Jackson Laboratory's repositories, including T1DR and MMRRC.
- ▶ BCBC mouse database designed to directly interface with IMSR, T1DR, and MMRRC.

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

**CIT:** Cross-representation of investigators between NHPCSG and CIT led to collaborative design of pre-clinical studies and pre-clinical testing of therapeutics in non-human primates.

#### **Immunobiology of Xenotransplantation Cooperative Research Program:**

- ▶ Cross representation between programs, 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.

#### **ITN:**

- ▶ Cross-representation of investigators between the ITN and NHPCSG.
- ▶ ITN priorities for pre-clinical testing of new therapeutics considered in evaluating Opportunities Pool applications. Several of the ITN high priority strategies are currently funded as pilot projects.
- ▶ NIAID program staff attend ITN transplantation mechanistic assay meetings to represent NHPCSG interests.

**ITN and CIT:** CIT, ITN and NHPCSG are interested in utilizing similar reagents for use as immune modulators for the treatment of type 1 diabetes or for islet transplantation.

**T1D-RAID:** Provision of novel reagents and potential for pre-clinical testing.

### **Search for Diabetes in Youth (SEARCH)**

**ICRs:** SEARCH investigators receive islets for basic research studies through the ICR basic science human islet distribution program.

**T1DGC:** Four SEARCH sites (Cincinnati, Southern California, Seattle, and South Carolina) are participating as recruitment centers for the T1DGC North American Network. Investigators and staff from the SEARCH sites have attended T1DGC training sessions (December 2003) and the annual T1DGC North American Network meeting (January 2005).

#### **TEDDY:**

- ▶ Investigators at the Denver SEARCH site are directly collaborating with TEDDY, or are PIs of TEDDY.
- ▶ The PIs of the South Carolina SEARCH site is an EAB member of the TEDDY study.

**TrialNet:**

- ▶ A TrialNet researcher has provided a coordinating function by leading development of the TrialNet protocol to compare C-peptide stimulation tests and assess variability of test results, participating on the C-peptide measurement standardization working group, and working with SEARCH investigators to analyze SEARCH C-peptide data.
- ▶ In Colorado and in South Carolina, SEARCH is collaborating with TrialNet by helping them recruit eligible cases. They are informing SEARCH participants about TrialNet and referring them to the TrialNet coordinator.
- ▶ A SEARCH investigator is establishing an affiliate site with the TrialNet University of Florida Center. SEARCH will serve as one of the recruitment sources for this affiliate site.

**TrialNet and T1DGC:** The PI for the T1DGC North American Network provided coordination between TrialNet, SEARCH, and T1DGC through her involvement in all three studies. Procedures across the three studies were standardized to the extent possible.

**TRIGR:**

- ▶ The Kaiser Permanente Southern California SEARCH site is participating in the TRIGR study. Institutional Review Board (IRB)-approved passive recruitment site: identify physicians and other health care providers (e.g., pediatric endocrinologists, endocrinologists, perinatologists, obstetricians) who would work with families eligible for the study, provide education/information about the study to these providers, put study recruitment brochures and flyers in their waiting rooms, answer questions from potential participants who then self-refer to TRIGR's UCLA study site.

- ▶ The Denver SEARCH site is distributing brochures about TRIGR.

## Standardization Programs

### Diabetes Autoantibody Standardization Program (DASP)

**SEARCH:** The SEARCH central laboratory at the University of Washington, Seattle, is participating in DASP.

**TEDDY, T1DGC, and TrialNet:** DASP interacts with the TEDDY, T1DGC, and TrialNet autoantibody labs, by providing laboratory materials and proficiency testing to facilitate their autoantibody measurements.

**Type 1 Diabetes Proteomics Investigators:** DASP is working with NIDDK-supported investigators studying proteomics and type 1 diabetes, and collaborating with Pacific Northwest Laboratories, to find new biomarkers to improve diagnosis of and prediction of risk for this disease. This collaborative project will use blood samples collected by DASP from newly-diagnosed type 1 diabetes patients and healthy people. The samples will be analyzed with proteomic and metabolomic technologies; that is, large-scale profiling and characterization of the component proteins and small molecules, respectively. Differences identified between samples from patients and healthy individuals can be further investigated for potential predictive or diagnostic value.

### C-peptide Standardization

**C-peptide Standardization Committee:** Performed studies at the Diabetes Diagnostic Laboratory, University of Missouri, for the C-peptide Standardization Committee to evaluate C-peptide stability.

**TrialNet:**

- ▶ The Diabetes Diagnostic Laboratory, University of Missouri, conducted an international round-robin comparison of C-peptide assays, which included two labs from TrialNet. The results from the comparison study illustrated the need to identify and minimize the major sources of variation in C-peptide measurements in multicenter, multi-laboratory clinical studies.
- ▶ A TrialNet investigator participates on the C-peptide measurement standardization working group.

**HbA1c Standardization**

**EDIC and TrialNet:** EDIC, TrialNet, and other clinical studies supported by the *Special Funding Program* use laboratories certified through the program.

**The Environmental Determinants of Diabetes in the Young (TEDDY)**

**ITN:** TEDDY had several discussions with ITN and has adopted the ITN standard for mRNA extraction.

**NIDDK Central Repositories:** TEDDY is repositing biological samples and data into the Repository and will make the material available to the broad scientific community. The NIDDK has developed an initiative to support investigator-initiated ancillary studies to ongoing studies, including TEDDY (PAR-06-216, Ancillary Studies to Major Ongoing NIDDK and NHLBI Clinical Research Studies).

**SEARCH:**

- ▶ Investigators at the Denver SEARCH site are directly collaborating with TEDDY or are PIs of TEDDY.
- ▶ The PI of the South Carolina SEARCH site is an External Advisory Board member of the TEDDY study.

**Standardization Programs:** DASP interacts with the TEDDY autoantibody lab by providing laboratory materials and proficiency testing to facilitate laboratory measurements.

**TrialNet:**

- ▶ The central human leukocyte antigen (HLA) laboratory for TEDDY is the same laboratory that provides the HLA strips to the central HLA laboratory for TrialNet. Both laboratories perform HLA typing using the same methodology. This coordination will permit direct comparison between results obtained in both studies.
- ▶ TEDDY has shared HLA screening procedures, data forms, and parts of the Manual of Operation concerning follow-up of high-risk children with TrialNet investigators during the development of the Nutritional Intervention To Prevent (NIP) Type 1 Diabetes Study. Investigators in the two studies have avoided direct competition for eligible participants through concerted action to define exclusive study geographic areas.

**TrialNet and T1DGC:**

- ▶ TEDDY, TrialNet, and T1DGC share the same laboratories for measurement of autoantibodies (IA-2 and GAD65). This fact permitted coordination of efforts to bring the laboratories together in a common protocol and quality control effort. This coordination will permit direct comparison between TEDDY, T1DGC, and TrialNet data.
- ▶ The central HLA laboratory for TEDDY and the North American network HLA laboratory for T1DGC are the same. The rest of the networks in T1DGC are performing HLA in an identical manner. TrialNet gets the HLA strips from the same laboratory as TEDDY and T1DGC. This will permit direct comparison between results obtained in TEDDY, T1DGC, and TrialNet.

**TrialNet, T1DGC, and CIT:** Collaborative media effort between TEDDY, T1DGC, TrialNet, and CIT. Media needs of all of these groups are being jointly handled by a single media contract to optimize coordination of type 1 diabetes clinical trials.

**TRIGR:**

- ▶ TEDDY and TRIGR share the same Data Coordinating Center, which has resulted in implementation of similar standards in data collection, entry, and management quality control and analyses for both studies.
- ▶ TEDDY and TRIGR have implemented similar standards in data collection and entry, thus permitting direct comparison between results obtained in each study.
- ▶ The same investigator is the Director of the HLA screening laboratory for the Germany and Finland sites in TEDDY and for all European sites in TRIGR. This will permit the direct comparison between HLA results in the studies.

**TRIGR and TrialNet:** TEDDY participated in a coordination meeting in May 2005, with investigators from TRIGR and TrialNet's NIP Diabetes Study to discuss how to obtain the most useful information when looking at these studies as a group. Common data variables across the studies and future analytic strategies were discussed.

### **Trial To Reduce IDDM in the Genetically at Risk (TRIGR)**

**ITN:** There is coordination of T cell assays being done by TRIGR and ITN.

**SEARCH:**

- ▶ The Kaiser Permanente Southern California SEARCH site is participating in the TRIGR study. IRB-approved passive recruitment site: identify physicians and other health care providers (e.g., pediatric endocrinologists,

endocrinologists, perinatologists, obstetricians) that would work with families eligible for the study, provide education/information about the study to these providers, put study recruitment brochures and flyers in their waiting rooms, answer questions from potential participants who then self-refer to TRIGR's UCLA study site.

- ▶ The Denver SEARCH site is distributing brochures about TRIGR.

**TEDDY:**

- ▶ TEDDY and TRIGR share the same Data Coordinating Center, which has resulted in implementation of similar standards in data collection, entry, and management quality control and analyses for both studies.
- ▶ TEDDY and TRIGR have implemented similar standards in data collection and entry, thus permitting direct comparison between results obtained in each study.
- ▶ The same investigator is the Director of the HLA screening laboratory for the Germany and Finland sites in TEDDY and for all European sites in TRIGR. This will permit the direct comparison between results for HLA.

**TEDDY and TrialNet:** TRIGR participated in a coordination meeting in May 2005, with investigators from TEDDY and TrialNet to discuss how to obtain the most useful information when looking at these studies as a group. Common data variables across the studies and future analytic strategies were discussed.

### **Type 1 Diabetes Genetics Consortium (T1DGC)**

**GoKinD, EDIC, and FIND:** In July 2005, consortia supported by the *Special Funding Program* that study genetics (GoKinD, FIND, EDIC) participated in a meeting with T1DGC. In response to recommendations from this meeting, new initiatives are being developed to coordinate future efforts among the studies. A summary of the meeting can be accessed on the



NIDDK's website ([www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf](http://www.niddk.nih.gov/fund/other/genetics-diabetes/Workshopexecsummary.pdf)).

**NIDDK Central Repositories:** T1DGC is repositing samples and data in all three Repositories (Biosamples, Genetics, and Data).

**SEARCH:** Four SEARCH sites are participating as recruitment centers for the T1DGC North American Network. Investigators and staff from the SEARCH sites have attended T1DGC training sessions (December 2003) and the annual T1DGC North American Network meeting (January 2005).

**Standardization Programs:** DASP interacts with the T1DGC autoantibody lab by providing laboratory materials and proficiency testing to facilitate laboratory measurements.

**TrialNet:**

- ▶ All 14 TrialNet centers participate as recruitment centers for the T1DGC North American Network. Investigators and staff from the TrialNet sites have attended T1DGC training sessions (December 2003) and the annual T1DGC North American Network meeting (January 2005).
- ▶ The Deputy Director and Project Manager at the T1DGC Coordinating Center participated in conference calls to assist the TrialNet Coordinating Center staff in establishing their international sites. A comprehensive list of issues and topics related to implementing international data collection formed the basis of these calls. As requested by the TrialNet Coordinating Center, the T1DGC Coordinating Center provided a study form related to destruction of samples and provided the ethnicity categories adopted for use in the T1DGC.

**TrialNet and SEARCH:** The PI for the T1DGC North American Network provided coordination between TrialNet,

SEARCH, and T1DGC through her involvement in all three studies. Procedures across the three studies were standardized to the extent possible.

**TrialNet and TEDDY:** T1DGC, TrialNet, and TEDDY share the same laboratories for measurement of autoantibodies (IA-2 and GAD65). This fact permitted coordination of efforts to bring the laboratories together in a common protocol and quality control effort. This coordination will permit direct comparison between results obtained in each study.

**TrialNet, TEDDY, and CIT:** Collaborative media effort between TEDDY, T1DGC, TrialNet, and CIT. Media needs of all of these groups are being jointly handled by a single media contract to optimize coordination of type 1 diabetes clinical trials.

**Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID)**

**CIT:** T1D-RAID is supporting the manufacture of lisofylline, which will be tested in the CIT to determine if it can reduce islet autoimmune destruction after transplantation.

**ICRs:** Provision of novel reagents as media additives to improve function and prolong survival of islets in culture.

**ITN and TrialNet:** T1D-RAID is assisting in the manufacture of hOKT3-Gamma-1 (Ala-Ala) monoclonal antibody, which will be tested in a clinical trial conducted by ITN to determine if it can halt further destruction of beta cells in new-onset type 1 diabetes patients. The agent is also to be used in a possible TrialNet study.

**NHPCSG:** Provision of novel reagents and potential for pre-clinical testing.

## Type 1 Diabetes TrialNet (TrialNet)

**ICRs:** TrialNet investigators receive islets for basic research through the ICR basic science human islet distribution program.

### ITN:

- ▶ ITN collaborates with TrialNet on the development and implementation of protocols in type 1 diabetes when both parties agree it is beneficial. The studies in which TrialNet and ITN collaborate include: (1) Natural History Study; (2) Mycophenolate Mofetil – Daclizumab (MMF/DZB); (3) T Cell Validation Study; and (4) The Effects of Rituximab on the Progression of Type 1 Diabetes in New Onset Patients.
- ▶ The ITN supplies collection kits and training to laboratories for isolating PBMCs.
- ▶ ITN provides RNA isolation on batched specimens.
- ▶ Coordinates the transfer of frozen PBMCs, RNA, and plasma specimens to the NIDDK Repository from laboratories for studies, as applicable.
- ▶ Coordinates the collection of blood and the transfer of samples from the clinical sites to the Flow Core Laboratory for analysis.
- ▶ Research staff from ITN and TrialNet collaborate on joint studies, communicating daily and convening 1 hour weekly to discuss critical site/study/technical issues. They also use this time to update each other regarding each Center's status in ongoing studies.
- ▶ ITN and the TrialNet Coordinating Center participate in monthly meetings where key study members discuss the status and any pending problems or issues with ongoing studies.
- ▶ ITN and TrialNet use a common Data and Safety Monitoring Board.
- ▶ Protocols potentially of interest to both TrialNet and ITN are considered by both Networks with the goal of joint sponsorship.

- ▶ TrialNet and ITN did a joint mailing (with the help of JDRE, New England chapter) to introduce/advertise the TrialNet Natural History Study and the ITN Insulin Study.

### SEARCH:

- ▶ A TrialNet investigator has provided a coordinating function by leading development of the TrialNet protocol to compare C-peptide stimulation tests and assess variability of test results, participating on the C-peptide measurement standardization working group, and working with SEARCH investigators to analyze SEARCH C-peptide data.
- ▶ In Denver, SEARCH is collaborating with TrialNet by helping them recruit eligible cases. They are informing SEARCH participants about TrialNet and referring them to the TrialNet coordinator.
- ▶ A SEARCH investigator is establishing an affiliate site with the TrialNet University of Florida Center. SEARCH will serve as a recruitment source for this affiliate site.

### Standardization Programs:

- ▶ A TrialNet investigator participates on the C-peptide measurement standardization working group.
- ▶ The Diabetes Diagnostic Laboratory, University of Missouri, conducted an international round-robin comparison of C-peptide assays which included two TrialNet laboratories. The results from the comparison study illustrated the need to identify and minimize the major sources of variation in C-peptide measurements in multi-center, multi-laboratory clinical studies.
- ▶ TrialNet uses laboratories certified through the HbA1c standardization program.

### T1DGC:

- ▶ TrialNet collects/provides samples for T1DGC.
- ▶ All 14 TrialNet centers are participating as recruitment

centers for the T1DGC North American Network. Investigators and staff from the TrialNet sites have attended T1DGC training sessions (December 2003) and the annual T1DGC North American Network meeting (January 2005).

- ▶ The PI for the T1DGC North American Network provided coordination between TrialNet and T1DGC through her involvement in both studies. Procedures across both studies were standardized to the extent possible.
- ▶ The Deputy Director and Project Manager at the T1DGC Coordinating Center participated in conference calls to assist the TrialNet Coordinating Center staff in establishing their international sites. A comprehensive list of issues and topics related to implementing international data collection formed the basis of these calls. As requested by the TrialNet Coordinating Center, the T1DGC Coordinating Center provided a study form related to destruction of samples and provided the ethnicity categories adopted for use in the T1DGC.
- ▶ The North American Network HLA laboratory for T1DGC provides the HLA strips to the central HLA laboratory for TrialNet. Both laboratories perform HLA using the same methodology. This will permit direct comparison between results obtained in both studies.
- ▶ T1DGC and TrialNet share the same North American laboratory for measurement of autoantibodies. This coordination will permit direct comparison between results obtained in each study.

#### **TEDDY:**

- ▶ TEDDY and TrialNet share the same laboratories for measurement of autoantibodies (IA-2 and GAD65). This will permit direct comparison between results obtained in each study.

- ▶ The central HLA laboratory for TEDDY is the same laboratory that provides the HLA strips to the central HLA laboratory for TrialNet. Both laboratories perform HLA typing using the same methodology. This will permit direct comparison between results obtained in both studies.
- ▶ TEDDY has shared HLA-screening procedures, data forms, and parts of the Manual of Operation concerning follow-up of high-risk children, with TrialNet investigators during the development of the NIP Diabetes Study. Investigators in the two studies have avoided direct competition for eligible participants through concerted action to define exclusive study geographic areas.

#### **TEDDY and TRIGR:**

- ▶ TrialNet participated in a coordination meeting in May 2005, with investigators from TEDDY and TRIGR to discuss how to obtain the most useful information when looking at these studies as a group. Common data variables across the studies and future analytic strategies were discussed.
- ▶ The mechanistic samples obtained from each of the consortia can be used to make up a larger common database.
- ▶ The sites are not competing for patient recruitment (coordination of recruiting effort).

**TEDDY, T1DGC, and CIT:** Collaborative media effort between TEDDY, T1DGC, TrialNet, and CIT. Media needs of all of these groups are being jointly handled by a single media contract to optimize coordination of type 1 diabetes clinical trials.

# APPENDIX 3: SUPPLEMENTAL MATERIAL ON THE PLANNING AND IMPLEMENTATION OF THE SPECIAL FUNDING PROGRAM

This Appendix provides information on the diabetes research plans and reports, planning and evaluation meetings, and interagency coordinating committee meetings that have informed program planning and implementation of the *Special Funding Program*. As described in this Appendix, the NIH and CDC have solicited broad and extensive input from the external scientific community, patients, members of professional and lay advocacy organizations, and other Federal agencies, to inform program planning and resource allocation.

## DIABETES RESEARCH PLANS AND REPORTS

### **1998 Administrative Plan for the Special Type 1 Diabetes Research Funding Program**

In January 1998, the Director, NIH, submitted to HHS an administrative plan for the use of funds provided by the Balanced Budget Act of 1997 (P.L. 105-33) for type 1 diabetes research. The overall objective of the plan, formulated through meetings with both NIH and HHS components and the external diabetes research community, was to promote innovative, clinically relevant, and multidisciplinary research on type 1 diabetes. Particularly crucial to this initial plan were recommendations emanating from a 1997 trans-NIH symposium, “Diabetes Mellitus: Challenges and Opportunities,” which was sponsored by the Director, NIH, along with nine institute directors. In addition, the chairmen of four working groups from this conference (i.e., Type 1 Diabetes—Etiology and Pathogenesis, Therapy, Microvascular Complications, and Macrovascular Complications) were involved in formulating this initial research plan for the *Special Funding Program*.

The *Special Funding Program* was expected to bring the best research talent, the most promising research ideas, and the most technologically advanced research tools to bear on combating type 1 diabetes, with particular attention to clinical and therapeutic issues. In addition, a budget strategy was developed to stratify the deployment of funds, so that a commitment base would not be established in FY 1998 that would preclude funding of emerging scientific opportunities in the later years of the program. Within the overarching scientific and budgetary goals of the program, a plan was developed to support the immediate pursuit of highly promising, innovative science through trans-NIH research solicitations; the establishment of a CDC National Diabetes Laboratory; the development of approaches to exploit other areas of high scientific priority through small, 1-3 year funding strategies; the encouragement of technology development and application to exploit scientific opportunities through 1-year funding

commitments; and the further pursuit of initiatives supported in the early years that proved most successful.

### **1999 Diabetes Research Working Group Strategic Plan**

The Congress established the Diabetes Research Working Group (DRWG) as an independent panel of scientific experts from academia, industry, voluntary organizations, and the NIH, through Senate and House report language accompanying the Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 1998. The DRWG was charged with the development of a comprehensive plan for NIH-funded diabetes research efforts. This plan covered all aspects of diabetes research, including both type 1 and type 2 diabetes.

The DRWG identified five “Extraordinary Research Opportunities”—Genetics, Autoimmunity and the Beta Cell; Cell Signaling and Cell Regulation; Obesity; and Clinical Research and Clinical Trials of Critical Importance. In addition, “Special Needs for Special Problems,” which included diabetic complications, optimizing glucose control, and others, and “Resource and Infrastructural Needs” were addressed. The full DRWG report, “Conquering Diabetes: a Strategic Plan for the 21st Century,” can be accessed on the NIDDK’s website ([www.niddk.nih.gov/federal/dwg/fr.pdf](http://www.niddk.nih.gov/federal/dwg/fr.pdf)). Since its completion in 1999, the plan has greatly enhanced the framing of diabetes initiatives at the NIH, including the *Special Statutory Funding Program for Type 1 Diabetes Research*. An update on new opportunities, scientific advances, and research progress made since issuance of the DRWG report was prepared in 2002 ([www.niddk.nih.gov/federal/dwg/2002/dwg02.htm](http://www.niddk.nih.gov/federal/dwg/2002/dwg02.htm)).

## **2000 Interim Evaluation Report on the Special Type 1 Diabetes Research Funds**

In response to the Balanced Budget Act of 1997 that originally established the *Special Statutory Funding Program for Type 1 Diabetes Research*, an interim evaluation report was submitted to the Congress in 2000. Although it was premature at that time to assess scientific accomplishments of the *Special Funding Program*, the report evaluated the planning and implementation process that guided the use of the *Special Funds*. The full report is posted on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) website ([www.niddk.nih.gov/federal/initiative.htm](http://www.niddk.nih.gov/federal/initiative.htm)).

## **2000 Ad Hoc External Advisory Panel Summary Report**

A panel of scientific advisors met with representatives of the NIH, the CDC, the ADA, and the JDRF to consider 22 proposals, totaling \$57.65 million, submitted by the Institutes and Centers of the NIH and CDC for funding, with \$19.5 million to become available in FY 2001 under the provisions of the Balanced Budget Act of 1997.

Dr. Allen Spiegel, Director of NIDDK, asked the scientific advisors to determine which of these 22 proposals offer the best opportunity to develop knowledge that will lead to improved methods to prevent, treat, or cure type 1 diabetes. They were also encouraged to suggest other initiatives that could make important contributions toward advancing research on type 1 diabetes and its complications. Dr. Spiegel noted that Institutes and Centers had been encouraged to propose trans-NIH initiatives involving multiple components of the NIH and initiatives to which they were also willing to commit Institute funds.

Eleven of the 22 proposals were recommended with the highest enthusiasm; a twelfth highly recommended project emerged from the discussion. To achieve a total recommended budget of \$20 million in FY 2001, many proposals were

reduced in scope and allocated less than the funds requested. The proposals selected and the amount of Balanced Budget Act funding in FY 2001 for each follow.

### **Comprehensive Atlas of Beta Cell Biology (\$3.0M)**

As initially proposed, this project included seven components. The committee recommended supporting five components as part of this project: online database to disseminate information arising from this project to the scientific community; development of a human beta cell line which maintains physiologic responsiveness to glucose and other factors involved in regulation of insulin secretion and cell growth and development; functional genomics and proteomics of the beta cell; development of monoclonal antibodies to cell surface components of the beta cell for use in stem cell identification; and functional imaging of the beta cell to detect changes in cell number, cell mass, function, and metabolism. The two additional components initially proposed as part of this initiative were recommended for inclusion as components of other proposals: diagnostic tools for beta cell transplantation was included in the human islet resource centers, and identification of single nucleotide polymorphisms (SNPs) for type 1 diabetes candidate genes was included in the Immune Response Diversity Project. It was recognized that the \$3.0 million allocated from Balanced Budget Act Funds would not be sufficient to pursue all the components of this initiative found to have outstanding merit, and the NIDDK promised to provide substantial additional Institute funds for this project.

### **Human Islet Transplantation (\$2.5M)**

As initially proposed, this project would fund regional resource centers to supply human islet cells to researchers for use in trials of human islet transplantation. The committee recommended incorporating into these resource centers the development of methods to assess the quality, purity, and viability of harvested islets *in vivo* and the determination of optimal methods of islet preparation, using tools developed

from the functional genomics component of the Comprehensive Atlas of Beta Cell Biology Project. The committee also recommended that these resource centers screen donors for evidence of autoimmunity and provide organs not suitable for use in islet transplantation to researchers for studies of pathogenesis of type 1 diabetes. Two million dollars in Balanced Budget Act funds were recommended for these components, with additional funding for the islet resource centers in FY 2001 to be provided from the NCCR. An additional \$0.5 million was recommended to support an islet/beta cell transplant registry to collect and analyze data, both pre- and post-transplantation, from all institutions performing islet and beta cell transplants in North America.

#### **Consortium for Development of Improved Animal Models (\$4.0M)**

This project focused on development of animal models of diabetes-associated micro- and macrovascular complications. The emphasis was on the mouse, but larger animals, such as swine and other species, were proposed as well. The committee strongly supported the research proposed and recommended that, in addition to micro- and macrovascular complications, models useful for study of wound healing in diabetes be developed.

#### **Immune Response Diversity Project (\$1.0M)**

This project integrates the genomics of host immunity with advanced bioinformatics to aid discoveries in immune mediated diseases. While this proposal was felt to be highly meritorious, concern was raised about the support of aspects of the proposal that appeared to lack a focus on type 1 diabetes with funds targeted for type 1 diabetes. Reduced funding was recommended to support components of the proposal specifically focused on type 1 diabetes, particularly identification of SNPs in type 1 diabetes candidate genes.

#### **Preventive Vaccines for Autoimmune Diabetes (\$3.0M)**

This project was recommended without modification and with the highest priority. Additional regularly appropriated funds will be provided for this initiative.

#### **Studies of New Therapies That Prevent or Reduce the Microvascular Complications of Diabetes (\$1.0M)**

Several promising new drugs are under development to prevent retinopathy and other microvascular complications. Some surrogate outcomes have recently been developed which can be used for short-term pilot studies to prevent retinopathy. This initiative would support small pilot studies of promising agents to aid in the transition from the bench to clinical investigation. Additional support for these pilot trials would come from NIH and industry funds.

#### **Gene Therapy Approaches for Type 1 Diabetes and Its Complications (\$1.0M)**

The committee recommended that this project focus particularly on methods of targeting gene transfer to the beta cell *in vivo*, and on developing gene therapy approaches to prevention and treatment of complications, such as delivery of growth factors. Additional regularly appropriated funds will be required for this initiative.

#### **Functional Genomics Approaches to Diabetes Complications (\$1.0M)**

As proposed, this initiative included two components focused on hypoglycemia and microvascular complications. The committee strongly endorsed application of gene profiling techniques to studies of glucose sensing and noted that common mechanisms are involved in beta cell and brain glucose sensing. However, it was felt that this component of the initiative should be deferred until FY 2002 so that it can be developed in the context of recommendations from a planned workshop on hypoglycemia and the brain. One million dollars

was recommended in FY 2001 to fund application of gene profiling technologies to peripheral vascular tissue to aid in understanding of microvascular complications.

**Population-Based Registry for Diabetes in Children (\$1.0M) and Pilot Programs for Population-Based Screening of Risk Factors for Type 1 Diabetes in Children Using State and Territorial Public Health Laboratories (\$0.5M)**

It was noted that there are a number of practical problems in developing population-based registries for diabetes in children in the U.S. Despite the uncertainty of success, the committee recommended that \$1.0 million be allocated to support one or two pilot projects. Such registries are of critical importance in documenting the true incidence of type 1 and type 2 diabetes in children and in assessing changes over time in incidence and age of development of diabetes. It was felt that pilot programs for screening for risk of type 1 diabetes in the general population are feasible because assays are now available for use on dried blood spots, and the initiation of pilot studies was highly recommended.

**Studies To Identify Genetic Associations in Patients with Microvascular Complications of Diabetes (\$0.5M)**

The committee noted that the NIDDK and the JDRF have recently initiated efforts to identify genes for diabetic nephropathy and recommended support for the initiation of studies to identify genes predisposing and contributing to the development of retinopathy. Additional regularly appropriated funds will be provided for this initiative.

**Assessment of Oral Microflora and Immune Responses in Type 1 Diabetic Patients (\$0.5M)**

The committee recommended support of this initiative, which was developed based on recommendations from a recent

workshop on oral complications of diabetes. Additional regularly appropriated funds will be provided for this initiative.

**Evaluation of Use of Minimally-Invasive Glucose Sensors in Children (\$1.0M)**

Committee members proposed this initiative after considering a proposal to study the metabolic and developmental consequences of intensive insulin therapy in children. The committee felt that proposal was not feasible due to the very long follow-up which would be required and the likely changes in methods of glycemic control which would occur in the interim. Instead the committee recommended that new technologies should be evaluated in children. It was recommended that the use of recently developed minimally-invasive glucose sensors should be studied in children to assess their efficacy in achieving improved metabolic control and reducing the risk of hypoglycemia.

**2001 Administrative Plan for the Special Type 1 Diabetes Research Funding Program**

In February 2001, the Acting Director, NIH, submitted to HHS an administrative research plan for the expanded *Special Funding Program* provided by the FY 2001 Consolidated Appropriations Act (P.L. 106-554). This plan, developed through consultation with NIH and other HHS components and the diabetes research community, clearly articulated the six broad research goals that frame the *Special Program*.

Through this careful priority-setting process, the NIH developed a scientifically-meritorious research plan that was within the budgetary targets and that complemented research initiatives launched with the P.L. 105-33 funds. Importantly, budget flexibility was maintained to support modifications during the later years of the program as science developed, and to address unanticipated needs or sudden shifts in focus that would optimize the use of the *Special Funds* for the benefit of type 1 diabetes research. Advice garnered from the April 2000 *ad hoc*



Advisory Meeting was invaluable in prioritizing the allocation of the increased funds provided for FY 2001-2003.

## **2002 Executive Summary of the *Ad Hoc* Advisory Meeting Report**

An external advisory panel of scientific and lay experts with respect to type 1 diabetes research convened at the NIH on May 16, 2002, to discuss the *Special Statutory Funding Program for Type 1 Diabetes Research*. The advisors were charged with evaluating the research efforts supported by the *Special Funds*, identifying scientific gaps and opportunities for future research, and advising the NIH and the CDC on the use of remaining funds for FY 2002 and FY 2003. This meeting constitutes a major source of input for a mandated report to the Congress evaluating the *Special Funding Program*.

The panel expressed great enthusiasm for research coordination mechanisms—consortia, clinical trial networks, repositories, databases, and registries—that have been established, in whole or in part, with the *Special Funds* and urged the development of additional programs of this nature. The importance of continuity of support for these valuable research resources and infrastructure was strongly emphasized. Several strategies for facilitating the maximal use of these resources were proposed. Significant ideas included the addition of ancillary studies to large clinical trials, an increase in coordination among the various research groups, and expansion of the core missions of some research consortia to encompass emerging issues of high scientific priority. In addition, the advisors were pleased with the support of innovative, high-impact research through funding of pilot and feasibility grants to individual investigators. They appreciated the success of solicitations issued with these funds in attracting new investigators and established investigators who were new to diabetes research. The initiatives undertaken were felt to maintain an appropriate balance between large-scale research programs and

investigator-initiated research. Moreover, these Requests for Applications (RFAs) have been issued periodically throughout the duration of the *Special Funding Program* to ensure that they attracted the best, most cutting-edge science. The advisory panel emphasized that it was not yet possible to fully assess the outcome of the *Special Funding Program* in that many projects were recently or newly initiated, not all of the FY 2002 funds had been deployed, and funding plans for FY 2003 have not yet been finalized.

### **Research Coordination and Connections**

The advisory panel made several recommendations for extending and capitalizing on existing research coordination efforts, maximizing connections among research groups with related interests, and developing new resources to enhance cross-disciplinary research in complex scientific fields.

The panel identified the following elements as important to coordination:

- ▶ Bioinformatics initiatives to integrate data from multiple consortia and trial networks;
- ▶ A multi-Institutional Review Board (IRB) to review multi-site clinical research;
- ▶ Common informed consent documents;
- ▶ Improved assay standardization;
- ▶ Ancillary studies and other mechanisms to ensure that maximal value is obtained from research data and samples from clinical research study participants;
- ▶ Partnerships between industry and academia to spur drug development and testing, including fast track mechanisms to facilitate clinical trials;
- ▶ Mechanisms to bring discoveries with therapeutic applications that originate in academic laboratories through pre-clinical development—the NCI's Rapid Access to Intervention Development (RAID) program was discussed as a possible model.

The panel identified additional opportunities for coordination of efforts in several research areas:

- ▶ Enhancement of research on diabetic complications by:
  - Creating a central knowledge base to coordinate information on NIH-wide initiatives related to diabetic complications;
  - Improving dissemination of information about existing animal models;
  - Facilitating animal model research projects that address multiple complications and evaluate multiple tissues in the same animal(s); and
  - Stimulating the development of new animal models for complications research.
- ▶ Systematic evaluation of approaches to islet transplantation including:
  - Pancreas harvesting;
  - Islet isolation, evaluation, and preservation;
  - Site and method of islet transplantation; and
  - Immunosuppression, tolerance, and other aspects of immunomodulation.
- ▶ Expansion of the islet cell resource centers' mission to include the procurement of pancreata for basic research on insulinitis;
- ▶ Application of insights from angiogenesis research to the study of islet graft vascularization;
- ▶ Investigating hypoglycemia unawareness in new islet transplant recipients;
- ▶ Recruitment of neuroscientists and brain-imaging specialists to study similarities in the glucose-sensing mechanisms of the pancreatic beta cells, the brain, and other glucose-sensitive tissues;
- ▶ Establishment of type 1 diabetes as a reportable illness throughout the U.S.; and
- ▶ The use of type 1 diabetes as a model for understanding immunology and autoimmunity.

### Major Research Opportunities

Based on recent research progress in type 1 diabetes as well as in broader areas relevant to diabetes research, the advisors recognized several critical areas of opportunity. Pursuing initiatives in these areas would expand on recent scientific advances to enhance progress on the understanding, treatment, or prevention of type 1 diabetes:

- ▶ Understanding the autoimmune basis of type 1 diabetes:
  - The role of HLA molecules in the development of autoimmunity;
  - Central tolerance and reprogramming of T cells;
  - The effect of parental type 1 diabetes on possible immune tolerization of offspring during pregnancy;
  - Beta cell antigen identity;
  - Developing assays for pathogenic T cells;
  - Applying new methodologies, such as proteomics approaches, to studying insulinitis and identifying circulating beta cell markers;
  - Designing beta cell imaging technology for use in assessing progression of autoimmune destruction of beta cells; and
  - Identifying genes conferring susceptibility to or protection from development of type 1 diabetes.
- ▶ Pursuing stem cells or stimulators of stem cells as a source of beta cells that could overcome the short supply of islets available for transplantation by current protocols;
- ▶ Improving islet transplantation procedures and documenting their risks and benefits, including issues of cost-effectiveness, quality of life, and the development of complications;
- ▶ Understanding the mechanisms of hypoglycemia unawareness and nocturnal hypoglycemia; and
- ▶ Uncovering the role of inflammation in vascular complications of diabetes, particularly functional interactions between monocytes and endothelial cells.

## Conclusions

Recent progress in type 1 diabetes research has allowed great strides in our understanding of this disease, but much work remains to be done. Studies to identify how genetic propensities and environmental triggers initiate the disease process in humans are now critical. Continued research on animal and cell models will be needed to understand mechanisms and develop novel preventive agents for type 1 diabetes and its devastating complications. Ongoing investment in clinical trials and research will help scientists translate research advances into real improvements in patients' health. The research initiatives and resource development undertaken with the *Special Funding Program* to date have sparked exciting new opportunities for future, cutting-edge research on understanding, preventing, and treating type 1 diabetes.

The full report can be accessed at: [www.niddk.nih.gov/federal/planning/type1summary.pdf](http://www.niddk.nih.gov/federal/planning/type1summary.pdf)

## 2003 Report on Progress and Opportunities

The *Special Funding Program* has mandated reporting requirements to the Congress. The first mandated interim report was transmitted to the Congress in 2000 (described above). The NIDDK prepared a second report to meet a January 2003 statutory reporting requirement to the Congress. That reporting requirement was changed to January 2007, as a result of the President's signature into law of P.L. 107-360. Therefore, in April 2003, the NIDDK published the second report it prepared to meet the statutory requirement as an interim report on progress and opportunities. The interim report provided an important assessment of the *Special Program* by external scientific experts, grant recipients, and NIDDK staff who analyzed the associated scientific literature and other relevant data on the *Program*. Moreover, the report contains a highly useful summary of research opportunities identified by external experts in the field. These opportunities served as a scientific guidepost in developing this program in later years. The full

report can be accessed at: [www.niddk.nih.gov/federal/planning/type1\\_specialfund/](http://www.niddk.nih.gov/federal/planning/type1_specialfund/)

## 2005 Executive Summary of the *Ad Hoc Planning and Evaluation Meeting Report*

An external panel of 16 scientific and lay experts with expertise relevant to type 1 diabetes and its complications convened in Bethesda, MD, January 18-19, 2005, to discuss the *Special Statutory Funding Program for Type 1 Diabetes Research*. The goals of the 2-day meeting were to perform a mid-course assessment of current efforts supported by the *Program*, to identify new and emerging opportunities, and to solicit recommendations for future type 1 diabetes research. The meeting focused largely on the program's research consortia and networks. The meeting constitutes a major source of input for a congressionally-mandated program evaluation report, which is due to the Congress by January, 2007.

## Type 1 Diabetes Research Goals

The meeting was framed around six major research goals that offer exceptional promise for the treatment and prevention of type 1 diabetes:

- ▶ Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes
- ▶ Goal II: Prevent or Reverse Type 1 Diabetes
- ▶ Goal III: Develop Cell Replacement Therapy
- ▶ Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes
- ▶ Goal V: Prevent or Reduce the Complications of Type 1 Diabetes
- ▶ Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

## Cross-Cutting Recommendations

The panel was charged with reviewing specific ongoing projects supported by the program and making recommendations for future research opportunities. Throughout the meeting,

many common themes emerged, which cut across research efforts supported by the program.

The panel identified several cross-cutting opportunities to enhance and synergize type 1 diabetes research efforts:

**Extend and capitalize on existing research efforts by maximizing connections among research groups with both related and distinct interests:** The panel recommended that strong existing coordination across consortia be further enhanced in order to synergize research efforts. These interactions should not be limited to consortia with overlapping interests. Collaboration between researchers with distinct interests can facilitate the pursuit of novel research directions. Increased coordination can prevent duplicative work by promoting the sharing of resources and methodology, as well as by facilitating cross-disciplinary research approaches.

**Develop new modes of interaction to foster diabetes research:** The panel encouraged interactions between biologists and chemists to identify small molecules that could be used as therapeutics for disease. The panel strongly endorsed the use of novel mechanisms such as innovative partnership awards to foster collaboration and interaction between diabetes researchers and researchers outside of the diabetes field, such as neuroscientists and bioengineers. These types of partnerships can accelerate research progress by fostering the application of novel technologies and expertise to the type 1 diabetes research field.

**Enhance opportunities for data sharing and integrated analysis:** The panel recommended that bioinformatics approaches to data creation and maintenance be coordinated and integrated across the multiple research consortia in order to enhance communication and data sharing/analysis.

**Foster translational research to enhance the timely transfer of important advances in the laboratory to a clinical research setting:** The panel endorsed ongoing efforts and encouraged continued support of the *Special Funding Program* regarding translational research such as the T1D-RAID program. The panel stressed the importance of promoting interaction between basic and clinical scientists in order to facilitate translational research. Additionally, the NIH commitment to research clinicians, particularly at the junior faculty level, was seen as critical for attracting and retaining research talent.

**Capitalize on research investments with patient follow-up:** The panel recognized the opportunity to maximize data collection in longitudinal trials, particularly those involving children and newly diagnosed cases of type 1 diabetes, by maintaining contact with the patients and their families to track their medical progression.

**Promote partnerships with industry to advance research:** The panel encouraged interactions between type 1 diabetes clinical trials consortia and industry to promote testing of potential therapeutic agents. The panel favored utilizing the SBIR program to produce reagents that would facilitate basic science and the translation of laboratory discoveries to the clinic.

**Maintain strong oversight mechanisms for ongoing efforts:** The panel strongly endorsed the contributions of External Advisory Boards (EABs) that have been created to guide and monitor the progress of consortia and resources supported with the *Special Funding Program*. The panel encouraged the NIDDK to ensure that all consortia receive regular oversight from such panels.

**Develop strategic plan for future type 1 diabetes research:** To build upon the new and emerging opportunities identified at the meeting, the panel strongly endorsed a broad state-of-the-science review and development of a long-range plan for type 1 diabetes research.

### Major Research Opportunities

The expert panel recognized several critical areas of research opportunity that will accelerate research progress in type 1 diabetes. Pursuing initiatives in these areas would expand on recent scientific advances to enhance progress in the understanding, treatment, and prevention of type 1 diabetes:

- ▶ Identifying novel biomarkers and surrogate endpoints that would enhance therapeutic development and the conduct of type 1 diabetes clinical trials;
- ▶ Understanding the autoimmune basis of type 1 diabetes by enhancing research in the field of human type 1 diabetes and regulatory T cells;
- ▶ Exploring the role of the gastrointestinal mucosal barrier in the pathogenesis and prevention of type 1 diabetes;
- ▶ Creating a renewable source of human beta cells by developing approaches to expanding functional islets and to creating conditions to differentiate embryonic and adult stem cells to islet/beta cells;
- ▶ Defining normal glucose profiles in children;
- ▶ Improving animal models to study type 1 diabetes and its complications;
- ▶ Alleviating type 1 diabetes and its complications by understanding regenerative pathways;
- ▶ Promoting collaborative research by supporting multidisciplinary “self-assembled” research consortia to tackle current barriers that limit progress in type 1 diabetes research;
- ▶ Providing support to investigators to pursue high-risk, high-payoff projects without requiring extensive preliminary data; and

- ▶ Supporting focused “innovative partnership” programs that facilitate collaborative interactions and attract new research talent.

### Conclusions

The *Special Funding Program* has supported research that has greatly increased our understanding of type 1 diabetes. Because many of the programs are newly established, the future potential for directly impacting patients’ health is extremely high. However, there is still much work to be done. It is critical to coordinate efforts of these consortia and networks in order to provide an integrated understanding of the disease. Continued support of basic research will help to provide insights on the molecular underpinnings of disease development, as well as to identify novel therapeutic targets and agents. Ongoing investment in basic and clinical research will help investigators translate positive results from the laboratory to the clinic to improvements in patients’ health. The projects supported by the program and the future research opportunities endorsed by the panel are critical to the understanding, prevention, and treatment of type 1 diabetes.

The full report can be accessed on the NIDDK’s website ([www.niddk.nih.gov/federal/planning/Jan-18-19-T1D-Final.pdf](http://www.niddk.nih.gov/federal/planning/Jan-18-19-T1D-Final.pdf)).

### 2006 Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan

At a January 2005, *ad hoc* planning and evaluation meeting of external scientific and lay experts with expertise relevant to type 1 diabetes and its complications (described above), one of the recommendations emanating from the meeting was to initiate a much broader review of the entire state-of-the-science with respect to type 1 diabetes, including recent research advances and emerging opportunities. In response

to this recommendation, the NIDDK Director announced in March 2005, that the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC), chaired by the NIDDK, would spearhead a new type 1 diabetes research strategic planning effort. The membership of the DMICC includes all NIH components involved in diabetes research, as well as other relevant federal agencies. Based on the same general content, two versions of the Strategic Plan were developed with broad external input from scientists, patients, and representatives of patient advocacy organizations. One version of the Plan was developed for patients and the public, and the other version of

the Plan was developed for the scientific research community. The purpose of the Strategic Plan is to serve as a scientific guidepost to the NIH and to the investigative and lay communities by identifying compelling research opportunities that will inform the priority-setting process for the type 1 diabetes research field and propel research progress on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. The “Summary and Recommendations” section of the Strategic Plan is found in Appendix 6; both versions of the Plan can be accessed on the NIDDK’s website ([www.T1Diabetes.nih.gov/plan](http://www.T1Diabetes.nih.gov/plan)).

## DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE (DMICC) MEETINGS FOCUSED ON THE SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

This listing provides highlights of DMICC meetings specifically focused on the *Special Funding Program*. For a listing of other recent DMICC meetings on topics relevant to type 1 diabetes and its complications, please see Appendix 4.

### Diabetes Mellitus Interagency Coordinating Committee Overview

The DMICC, chaired by the NIDDK, was authorized by Public Law 93-354 and was established in the fall of 1974. It includes representatives from Federal departments and agencies whose programs are relevant to diabetes mellitus and its complications. The DMICC facilitates cooperation, communication, and collaboration among agencies that conduct or support diabetes-related activities. DMICC meetings and projects currently tend to focus on bringing together in depth information from the varied programs represented by the member organizations; being the catalyst for the initiation of projects; and guiding the progress of projects involving several agencies. The following recent DMICC meetings were used as a venue to discuss research relevant to type 1 diabetes and its complications, and in some cases, to solicit input from members on program planning and evaluation of the *Special Statutory Funding Program for Type 1 Diabetes Research*.

### Type 1 Diabetes Initiatives (January 15, 1999)

This DMICC meeting focused on the process of setting priorities for the use of *Special Statutory Funds*. DMICC members provided updates of type 1 diabetes activities in their Institute, Center, or agency. The NIDDK also provided an update to DMICC on the use of the *Special Funds*, as well as the awards funded under recent initiatives. The summary minutes can be accessed at: [www.niddk.nih.gov/federal/dmicc/minutes\\_19990115.htm](http://www.niddk.nih.gov/federal/dmicc/minutes_19990115.htm).

### Use of *Special Funds* for Type 1 Diabetes Research (April 14, 2003)

This meeting began with a brief legislative history of the *Special Funding Program*, which has grown from the original \$30 million per year in 1998 to \$150 million per year for FY 2004–2008, for a total of \$1.14 billion for FY 1998–2008. The discussion then centered around six major goals for type 1 diabetes research: a description of each goal was provided, followed by discussion regarding recommendations and potential research opportunities. A proposal was discussed outlining a mechanism to seed collaborative research supplements for shared resources. Finally, reports were provided on the consortia and resources, new and re-issued research solicitations, and potential SBIR and STTR program announcement topics. The summary minutes can be accessed at: [www.niddk.nih.gov/federal/dmicc/Final-Edited-DMICC-4-13-03.pdf](http://www.niddk.nih.gov/federal/dmicc/Final-Edited-DMICC-4-13-03.pdf).

### Meeting on the *Special Statutory Funding Program for Type 1 Diabetes Research* (July 28, 2004)

This meeting opened with an update about the *Special Statutory Funding Program for Type 1 Diabetes Research* and a discussion to help plan for an evaluation of the program. Much of the funding had been devoted to: establishing large-scale collaborative, infrastructure-intensive fundamental initiatives that could not be pursued with R01 funds; creating major clinical trials networks; promoting innovative, high-risk, high-impact research that is different from typical R01 research; and promoting translational research to develop new therapies. An update was provided on *Special Program* initiatives started between April 2003 and July 2004. The DMICC used the meeting to plan for the January 2005 *ad hoc* planning and evaluation meeting (described above), discussing the goals and topics of the meeting, as well as the advice to be obtained

by the expert panel. Finally, an introduction was provided to the mandated program evaluation due to Congress by January 1, 2007. The summary minutes can be accessed at: [www.niddk.nih.gov/federal/dmicc/Final-July-28-Summary.pdf](http://www.niddk.nih.gov/federal/dmicc/Final-July-28-Summary.pdf).

### **Update on Current and Planned Initiatives (March 21, 2005)**

A review was provided of the implementation status of recommendations from the January 2005 *ad hoc* planning and evaluation meeting on the *Special Statutory Funding Program for Type 1 Diabetes Research*. One recommendation of the expert

panel was to initiate a broader review of the entire state-of-the-science regarding type 1 diabetes with an emphasis on new and emerging opportunities that could be pursued with the *Special Funds*. To implement this recommendation, the NIDDK launched a new strategic planning effort in type 1 diabetes research (described above) to be spearheaded by the DMICC. The DMICC was apprised of current plans and asked for input into the strategic planning process. It also received updates on diabetes-related activities by its members. The summary minutes can be accessed at: [www.niddk.nih.gov/federal/dmicc/2005/03-21-05-Summary-Final.pdf](http://www.niddk.nih.gov/federal/dmicc/2005/03-21-05-Summary-Final.pdf).



## SOLICITATION OF INNOVATIVE IDEAS FROM THE BROAD EXTERNAL SCIENTIFIC COMMUNITY

Since the inception of the *Special Funding Program*, the NIH has solicited input and recommendations from scientists external to the NIH through forums such as scientific and planning/evaluation panel meetings, as described in this Appendix. To solicit broader input for future research opportunities from the scientific community as a whole, the NIDDK issued a Request for Information (RFI) calling for innovative ideas to advance prevention, treatment, and cure of type 1 diabetes (see “Text of RFI,” below). The RFI—initially suggested at a DMICC meeting on July 28, 2004—was announced to the scientific community in the NIH Guide for Grants and Contracts and in the journal *Science*. The NIDDK’s announcement made clear that ideas submitted would not be treated as confidential or proprietary and that there was no research funding associated with this process. The NIDDK collected ideas for 7 weeks.

The NIDDK received over 80 submissions, which were presented to the expert panel at the January 2005 *ad hoc* planning and evaluation meeting focused on the *Special Funding Program* (described above). The panel members were given the submitted innovative ideas in advance of the meeting and were asked to consider them. During the meeting, time was set aside to discuss and consider the ideas. A synopsis of the discussions is found under each “Goal” chapter in the summary of the January 2005 meeting (accessed at: [www.niddk.nih.gov/federal/planning/Jan-18-19-T1D-Final.pdf](http://www.niddk.nih.gov/federal/planning/Jan-18-19-T1D-Final.pdf)).

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### Text of RFI

Release Date: August 31, 2004

Notice Number: NOT-DK-04-013

Issued by: NIDDK ([www.niddk.nih.gov/](http://www.niddk.nih.gov/))

Purpose: To invite ideas for opportunities that can accelerate research progress and overcome current research barriers to

the prevention, treatment and cure of type 1 diabetes and its complications.

Background: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), leads a Special Statutory Funding Program (\$150 million/year) for Type 1 Diabetes Research, on behalf of the Secretary of the Department of Health and Human Services. The *Special Program* supports research to pursue compelling opportunities in type 1 diabetes research (more information on the program can be found at: [www.T1Diabetes.nih.gov](http://www.T1Diabetes.nih.gov)). The program is framed around six broad, scientific goals: Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes, Goal II: Prevent or Reverse Type 1 Diabetes, Goal III: Develop Cell Replacement Therapy, Goal IV: Prevent or Reduce Hypoglycemia, Goal V: Prevent or Reduce the Complications of Type 1 Diabetes, Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes.

Information Requested: The NIDDK invites submission of innovative ideas and approaches toward accelerating progress and overcoming research barriers to the prevention, treatment and cure of type 1 diabetes and its complications. There is significant flexibility in the use of the special funds; opportunities could be pursued through solicitations for traditional research grants or through mechanisms to support larger collaborative efforts. Suggestions should focus on identifying the opportunity and approaches, technology and expertise useful for its development rather than on a funding instrument or solicitation design. Suggestions that will involve creative scientists and scientific communities not currently working on type 1 diabetes, and with the potential to contribute to prevention, treatment and cure of type 1 diabetes, are particularly encouraged.

Response and Process: Submissions in response to this RFI will be considered by NIH and CDC scientists and by an *ad hoc* evaluation panel to be convened by the NIDDK as part of the process guiding use of the *Special Statutory Funding Program for Type 1 Diabetes Research*.

This Request for Information is for information and planning purposes only and shall not be construed as a solicitation or as an obligation on the part of the NIDDK. The NIDDK does not intend to award a grant or contract on the basis of responses nor otherwise pay for the preparation of any information submitted or the Government's use of such information. Acknowledgment of receipt of responses will not be made, nor

will respondents be notified of the Institute's evaluation of the information received. Responses will not be held in a confidential manner. Responses may be anonymous.

Please describe your suggested opportunity or approach including: (1) how it could potentially have a major, positive impact on one or more of the six goals above, and/or (2) the current research barriers it could help overcome. You may submit more than one idea, but please limit the description of each to one page in length.

For full consideration, submissions are due by Friday, October 22, 2004.

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# **APPENDIX 4: SUPPLEMENTAL MATERIAL ON SCIENTIFIC CONFERENCES, WORKSHOPS, AND MEETINGS RELEVANT TO TYPE 1 DIABETES AND ITS COMPLICATIONS**

This Appendix provides information on scientific conferences, workshops, and meetings with relevance to type 1 diabetes and its complications. The input that the NIH received informed the planning process for use of the *Special Funds*.

## RESEARCH CONFERENCES AND WORKSHOPS

### **1997 Diabetes Mellitus: Challenges and Opportunities**

*(September 4-5, Bethesda, MD, sponsored by the NIH Office of the Director, NIDDK, NCRR, NEI, NHGRI, NHLBI, NIA, NIAID, NICHD, and NINDS)* Diabetes is a multifaceted, complex disease that directly affects many of the body's organ systems. This trans-NIH symposium brought together leading experts in diabetes and related fields to examine the state of the science and identify research gaps and opportunities that could be pursued across the NIH. Working groups convened to develop specific, in-depth recommendations on five topics of critical importance: Type 1 Diabetes—Etiology and Pathophysiology; Type 2 Diabetes—Etiology and Pathophysiology; Therapy; Microvascular Complications; and Macrovascular Complications. Cross-cutting recommendations from these groups included: expand research resources and facilities, such as tissue repositories and research databases; provide diabetes investigators necessary tools; develop new research methods and measures to foster diabetes research; pursue the development of clinical trials of potential therapies for diabetes and its complications; ensure a cadre of talented diabetes researchers by intensifying research training and career development efforts; foster translational research to enhance the timely transfer of important advances in diabetes research to the practice of medicine; develop new modes of interaction among academia, the NIH, and industry to foster diabetes research; and continue the planning process for diabetes research, for example through future workshops and conferences that could help guide program planning efforts and develop standardized research measures and assays.

### **1998 Expert Panel on Immune Tolerance**

*(February, Bethesda, MD, sponsored by NIAID)* Developing methods to achieve immune tolerance has the potential to halt the autoimmune destruction of beta cells in type 1 diabetes and to prevent immune-mediated rejection of transplanted

islets. Leading investigators in basic and clinical immunology convened to discuss plans for accelerating research on immune tolerance. Among the plans endorsed by this panel were recommendations for the creation of interactive, multi-institutional research programs that bring together experts in relevant basic and clinical disciplines to conduct large-scale research that cannot be accommodated within a single institution. Further, the panel advised the inclusion of mechanistic studies in conjunction with clinical trials and the establishment of immunology cooperative study groups to provide a central resource for the development of standardized assays and the identification and validation of surrogate markers of disease.

### **1998 Working Group on Cellular and Molecular Mechanisms of Diabetic Cardiomyopathy**

*(July 16, Bethesda, MD, sponsored by NHLBI)* Diabetes significantly increases an individual's risk of illness and death from cardiovascular disease. A panel of scientific experts reviewed the state of knowledge and research in diabetic cardiomyopathy and made recommendations for future research initiatives. The panel supported multidisciplinary, collaborative research on the cellular and molecular mechanisms of diabetic cardiomyopathy; the development of animal models that better simulate human disease; clinical research to characterize the epidemiology and pathophysiology of diabetic cardiomyopathy; and clinical trials to test novel interventions.

### **1998 Etiology of Type 1 Diabetes**

*(August 31-September 1, Washington, DC, sponsored by NIAID, NIDCR, NIDDK, and the JDRF)* Although there is known to be a genetic component to type 1 diabetes, genetic predisposition does not fully account for development of this disease. This workshop reviewed evidence for viral infections or other environmental factors that may trigger type 1 diabetes. Scientists with expertise in the development of

diabetes recommended that research efforts be launched to identify those at high risk for type 1 diabetes, to understand the environmental factors and natural history of the disease, and to test potential interventional agents. Participants also encouraged the development of training and career advancement mechanisms to recruit new researchers into the field of diabetes research.

### **1999 Imaging the Pancreatic Beta Cell**

*(April 19-20, Washington, DC, sponsored by NIDDK, JDRF)*

Type 1 diabetes is characterized by an inadequate mass of functional pancreatic islets; yet, without the ability to visualize these cells in an animal or human, many questions of the natural history of the disease remain to be answered. This meeting brought together scientific experts in the fields of beta cell biology and imaging technology for discussions on the potential impact of new imaging technologies on understanding and managing diabetes. Participants advocated funding support for exploratory, interdisciplinary research that would jump start new approaches and attract new research talent to the imaging field.

### **1999 Advances in Neurobiology: A Key to Understanding Diabetic Neuropathy**

*(September 14-15, Bethesda, MD, sponsored by NIDDK, NINDS, JDRF)* Despite recent advances in the management of diabetes, neuropathy remains one of the most troubling complications of diabetes and constitutes a major public health problem. A workshop was held to re-examine the pathophysiology of diabetic neuropathy in light of recent advances in neurobiology. The goal of the workshop was to bring together investigators from the diabetes and neuroscience communities to examine new insights into the molecular and cellular biology of the neuron in the setting of diabetes. Researchers discussed new advances, highlighted potential areas of research that could lead to new therapies, and encouraged collaborations between neuroscientists and diabetologists.

### **1999 Gene Therapy Approaches for Diabetes and Its Complications**

*(November 8-9, Rockville, MD, sponsored by NIDDK, NCRR, NHLBI, NIAID, ADA, JDRF)* As technology for introducing new genes into cells has been improving, the disease targets for gene therapy have expanded beyond traditional genetic diseases to chronic diseases such as diabetes. Investigators met to discuss their results utilizing gene therapy approaches to treat diabetes in animal models and human patients. The workshop recommended support for research efforts in four key areas: insulin expression in tissues where the hormone is not normally produced; interference with the autoimmune destruction of beta cells in type 1 diabetes; creation of surrogate beta cell lines for transplantation; and treatment of macrovascular and microvascular complications of diabetes.

### **1999 Workshop on Oral Diseases and Diabetes**

*(December 6-7, Washington, DC, sponsored by NIDCR)* Oral complications, including gum disease, salivary dysfunction, mucosal infections, and neurological problems of taste and smell, are major health problems in diabetic individuals. This workshop served as a forum for evaluation of the state-of-the-science on diabetes and oral health. Recommendations for future research that arose from this meeting included more study of the oral microbiology and immunology of diabetes.

### **2000 Stem Cells and Pancreatic Development**

*(April 10-11, Bethesda, MD, sponsored by NIDDK, ADA, JDRF)* Stem cells, which are capable of self-renewal and differentiation into multiple cell lineages, have therapeutic potential for the treatment of diabetes. Researchers met to discuss issues in isolating and characterizing pancreatic stem cells that have the ability to reconstitute all pancreatic cell types. Among the recommendations that emerged from this workshop were the establishment of research alliances (e.g., consortia) of inves-

tigators from the stem cell biology, developmental biology, and diabetes research fields and the development of incentives to attract and train new clinical investigators in the fields of endocrinology and stem cell biology.

### **2000 Hypoglycemia and the Brain**

*(September 7-8, Washington, DC, sponsored by NIDDK, NINDS, NICHD, the National Aeronautics and Space Administration [NASA], ADA, JDRF)* Episodes of severe hypoglycemia are a major obstacle in the management of diabetes and prevention of long-term complications. Further, hypoglycemia confers a risk of loss of consciousness, coma, and potential brain injury. This workshop was organized to review what is known about the brain's response to metabolic changes, to set research priorities for future efforts, and to stimulate research on the molecular and cellular mechanisms by which hypoglycemia injures and kills neural cells. The participants identified several critical areas of research opportunity, including the need to develop strategies to promote glucose sensing by the brain and to restore the counter-regulatory hormonal responses in type 1 diabetes.

### **2000 Genetics of Diabetic Retinopathy**

*(September 21-22, Bethesda, MD, sponsored by NEI)* Diabetic retinopathy (eye disease) is a common, long-term complication of diabetes. A multidisciplinary group of scientists met to explore whether advances in genetic research could increase the opportunity for understanding the genetic predisposition underlying the development and/or progression of diabetic retinopathy. The group identified several high-priority recommendations for facilitating future research, including ancillary studies to identify the retinopathy phenotype in existing genetics studies; the support of interdisciplinary, collaborative research to evaluate the genetics of diabetes and its complications; the development of new research reagents and tools, such as improved animal models and microarray resources; and the recruitment of geneticists to work in vision research.

### **2000 Genetics of Type 1 Diabetes**

*(November 20, Rockville, MD, sponsored by NIDDK, JDRF)* Prior to this meeting, three genome-wide scans for type 1 diabetes genes had led to the identification of several chromosomal loci that showed evidence of harboring a diabetes susceptibility gene. Experts in the field of type 1 diabetes genetics met to explore the establishment of a collaborative effort on understanding the genetic basis of type 1 diabetes. As a result of this meeting, the Type 1 Diabetes Genetics Consortium was formed to pursue large-scale genetics research beyond the means of a single investigator study.

### **2001 Pancreatic Development, Proliferation, and Stem Cells**

*(October 18-19, Bethesda, MD, sponsored by NIDDK, ADA, JDRF)* Replacement or regeneration of the pancreatic beta cells lost in diabetes hold promise as future therapeutic interventions for the treatment of this disease. Investigators from multiple disciplines doing cutting-edge research in developmental biology of the pancreas, islet cell biology, and stem cell biology met to discuss new insights into this rapidly developing field. Participants expressed support for the generation of essential reagents, assays, and a database of islet cell development and function, for research on the molecular mechanisms of islet cell neogenesis, proliferation, and programmed cell death, and for basic research on mouse and human stem cell biology.

### **2001 Etiology and Epidemiology of Early Autoimmune Type 1 Diabetes in Humans**

*(October 25-26, Alexandria, VA, sponsored by NIDDK)* Large-scale epidemiological studies will be required to fully elucidate the complex interactions of genetics and environment that trigger type 1 diabetes. Researchers met to guide the NIH in the design of meaningful studies for understanding the immunologic mechanisms of diabetes. Meeting participants agreed

on the need for a large-scale, cooperative trial that can screen sufficient numbers of at-risk patients, and for standardized assays and centralized laboratory and storage resources to facilitate data collection.

### **2001 Beta Cell Biology in the 21st Century**

*(November 26-28, Bethesda, MD, sponsored by NIDDK, ADA, JDRF)* Loss or dysfunction of insulin-producing pancreatic beta cells is central to the development of diabetes. This workshop convened beta cell biology researchers to assess the state of the science in beta cell structure, function, and physiology and to discuss ways to advance knowledge of the complex signaling pathways that govern beta cell function. Participants identified key scientific questions that guided future research in this field, including: definition of the factors required for maintenance of differentiated beta cells; identification of signaling cascades and networks within the beta cell and among beta cells and other cells of the pancreatic islets; understanding the minimal requirements for engineering a surrogate beta cell; and the application of genomics, proteomics, and other emerging technologies to the study of the beta cell.

### **2001 Encapsulation and Immunoprotective Strategies of Islet Cells**

*(December 6-7, Washington, DC, sponsored by NIDDK, NCRR, NASA, JDRF)* Encapsulation of transplanted islet cells holds promise as a means of preventing rejection by the body's immune system. Workshop participants met to review the current state of encapsulation technology and to develop a strategy for future research in this area. Two high-priority issues were identified as a result of this meeting: the need for successful animal studies for further evidence and ultimate validation, and standardization of capsule materials and implantation procedures.

### **2002 Epidemiology of Diabetes Interventions and Complications (EDIC) Autonomic Neuropathy Advisory Group Meeting**

*(May 29, Bethesda, MD, sponsored by NIDDK)* Diabetic autonomic neuropathy is a clinically significant outcome of diabetes with serious impact on quality-of-life, morbidity, and probably mortality. Yet, it is very much an uncharted discipline in diabetes research. Experts were convened to discuss the clinical importance of various forms of diabetic autonomic neuropathy, including gastroparesis, diabetic diarrhea/constipation, gall bladder dysfunction, bladder dysfunction, sexual dysfunction, orthostatic hypotension, cardiac sudden death, sweating dysfunction, and hypoglycemia unawareness. The advisory group suggested new studies to measure cardiovascular autonomic neuropathy with consideration given to using Holter monitors to measure RR intervals, perhaps with up to 24-hour blood pressure monitoring. In addition, the group recommended using the saved biologic samples of the DCCT/EDIC participants to measure several suggested markers and predictors of neuropathy.

### **2003 Metabolic Imprinting and the Long-Term Complications of Diabetes Mellitus: Bench to Bedside and Back: 20th Anniversary of the Diabetes Control and Complications Trial (DCCT)/EDIC Study**

*(April 10-11, Bethesda, MD, Sponsored by NIDDK)* The DCCT/EDIC study resoundingly answered its seminal question with regard to diabetes research and is widely recognized as a well-designed and implemented study. The conference goals were: to celebrate and commemorate the accomplishments of the DCCT/EDIC on its 20th anniversary; to explore the possible mechanistic basis for what has been tentatively termed “metabolic memory”; and to generate plans for the



fostering of research in developing new theories for the complications of type 1 diabetes. Although tremendous progress has been made toward improving the lives of people with type 1 diabetes, premature death from complications remains an issue of great concern. With representatives of multiple Institutes and organizations in attendance, the participants exchanged ideas on research efforts to be supported by the *Special Funding Program*.

Based on external input garnered at this meeting, the NIDDK utilized a novel “co-principal investigator” mechanism with its “Innovative Partnerships in Type 1 Diabetes Research” initiative, which is supported by the *Special Funding Program*. The standard policy at the NIH was to award a grant to only one Principal Investigator (PI), while the partner was listed as a co-investigator—an arrangement that did not recognize both partners as being equal and thus posed a barrier to collaboration. The novel solicitation was developed so that both partners were named as co-equal PIs. The co-PI mechanism is now being piloted for broader implementation by the NIH as a whole through the NIH Roadmap.

### **2003 Imaging the Pancreatic Beta Cell**

*(April 21-22, Bethesda, MD, Sponsored by the NIBIB, NIDDK, JDRF)* Recent advances in noninvasive imaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), other nuclear imaging techniques, and optical absorption or fluorescence spectroscopy and imaging, make it likely that a clinical exam to monitor beta cell number, mass, function, or lymphocyte infiltration/inflammatory activity can soon be established. This would allow at-risk individuals to be monitored prior to onset of diabetes. Patients could be monitored over the course of their disease, to follow individual responses to therapy, and to assess success of engraftment following islet transplantation. Researchers

would learn about the natural history of diabetes. The goals for this meeting were to report on ongoing work in the area of beta cell imaging using MRI, PET, ultrasound, or optical technologies; form community among those researchers who are interested in this area; and help NIH identify obstacles and opportunities toward a clinical exam for the measurement of pancreatic beta cell mass, number, function, inflammation, or engraftment.

### **2003 Proteomics and Diabetes**

*(April 24-25, Bethesda, MD, Sponsored by NIDDK)* Proteomic approaches have been successfully used for studying complex biological problems and for the identification of disease markers. Recent developments in proteomics indicate that the technologies available are already sufficiently advanced to approach many biological questions relevant to the NIDDK mandate. This workshop provided a venue to bring together investigators with expertise in proteomics and those interested in applying this technology to problems related to diabetes, endocrinology, and metabolic diseases. Several leaders in the field illustrated the state of the art in proteomics and their possible use to study diabetes.

### **2003 Meeting on Cardiovascular Complications of Type 1 Diabetes: Identifying New Opportunities for Prevention and Treatment**

*(April 27-28, Bethesda, MD, Sponsored by NHLBI, NIDDK)* Cardiovascular disease (CVD) is the major cause of mortality and morbidity in both type 1 and type 2 diabetes patients. Although the microvascular complications of type 1 diabetes have been studied, macrovascular CVD, its treatment, and link to diabetes have been investigated primarily in patients with type 2 diabetes. This meeting was convened to identify research strategies to improve prevention and treatment of CVD in patients with type 1 diabetes. Conference participants were asked to evaluate opportunities for studying the patho-

genesis of CVD and intervention strategies in type 1 diabetes patients. The meeting included sessions devoted to: current understanding of type 1 diabetes and CVD; opportunities to expand understanding of the pathogenesis and clinical course of CVD in type 1 diabetes; and opportunities for intervention studies to reduce cardiovascular complications.

### **2003 Meeting on Islet Transplantation**

*(May 30, Bethesda, MD, Sponsored by NIDDK, NIAID, JDRF)*

This *ad hoc* advisory meeting was convened to solicit recommendations for future research directions in islet transplantation from external experts in the field. The meeting helped to inform the development of the Clinical Islet Transplantation (CIT) Consortium. Recommendations stemming from the meeting included: develop core facilities for non-human primate reagents for wide distribution and use; increase coordination; better define clinical outcomes; and continue studies on gene therapy and xenotransplantation.

### **2003 Diabetic Complications: Progress Through Animal Models**

*(October 20-21, Bethesda, MD, Sponsored by NIDDK, NHLBI, NINDS, NEI, JDRF)* Animal models provide a vital link for translation of clinical research. This meeting addressed recent progress with animal models used to study diabetic complications. The first day was devoted to exploring the state of the art in animal models, focusing on their promise and limitations, and translation from bench to bedside. The second day was devoted to discovery, with sessions dedicated to identifying new pathways, potential targets, biomarker and surrogate identification and validation, and the development of novel therapeutic approaches.

### **2004 From Clinical Trials to Community: The Science of Translating Diabetes and Obesity Research**

*(January 12-13, Bethesda, MD, Sponsored by NIDDK, the NIH Office of Behavioral and Social Science Research [OBSSR], the Centers for Disease Control and Prevention [CDC])* Dramatic advances in diabetes treatment and prevention have occurred over the past decade. Unfortunately, the therapies proven to delay or prevent the complications of type 1 diabetes have not been widely operationalized. Translational research aims to determine what can improve outcomes in diverse, real-world populations and how to achieve these goals in a practical way that positively affects public health. This conference brought together investigators, health care providers, NIH representatives, and payers to discuss barriers to translation, translational research, translational interventions, community-based approaches, and public health efforts. A primary conference objective was to foster ideas to improve treatment for individuals with or at risk for diabetes through implementation of known and newly emerging prevention and treatment strategies. In addition, a “Grant Writing Workshop” was held for investigators interested in submitting translational research proposals.

### **2004 Immunobarriers for Pancreatic Islet Transplantation**

*(March 29-30, Washington, DC, Sponsored by NIDDK, NIBIB, JDRF)* This workshop was convened to review the state-of-the-art in barrier material for tissue immunoisolation with the emphasis on pancreatic islet transplantation and other cell therapies for the treatment of diabetes. Participants were invited from academia and industry and included biomedical engineers, immunobiologists, cell biologists, diabetologists, and transplant surgeons. The meeting was organized to provide a forum for exchange of the most recent data and the latest insights and perspectives on the biomaterial components of what is commonly termed “the bioartificial pancreas.” The meeting served to identify opportunities and barriers

to scientific progress. Chief among these was the need for a clearer understanding of the mechanisms of both rejection and survival of encapsulated tissue, and less emphasis upon show-and-tell survival experiments in relatively compliant rodent models. Interdisciplinary teams with strong capabilities in islet-cell biology, membrane transport, biomaterials, and immunology were identified as necessary to achieve success in this field. Finally, a need was identified for basic biology studies to uncover whether sufficient nutrients are delivered; to detail the complex nature of the host defense; and to define the mechanisms by which materials fail in the transplanted environment.

#### **2004 NIH Trans-Institute Angiogenesis Research Program (TARP) Workshop**

*(May 10-12, Bethesda, MD, Sponsored by NIDDK, NINDS, NHLBI, JDRF, NCI, NEI)* The workshop was held: to assess the state of current knowledge about angiogenesis; to define areas of research need; and to make recommendations to expand on successes and close gaps. The workshop provided a forum to examine the state of the science in angiogenesis research as it relates to a variety of pathologic disease states; determine areas of need and overlap among the various disciplines studying angiogenesis; discuss what research could be conducted and how; and discuss novel models, systems, and core resources applicable to or needed by the community. Based on the recommendations, both NIH and JDRF announced availability of research funding for scientists to investigate angiogenesis as it relates to type 1 diabetes.

#### **2004 Food and Drug Administration (FDA)/NIH Joint Symposium on Diabetes: Targeting Safe and Effective Prevention and Treatment**

*(May 13-14, Bethesda, MD, Sponsored by NIH, NIDDK, FDA)* The purpose of the symposium was to define the current state of the prevention and management of diabetes and to identify

and discuss therapeutic gaps and hurdles to safe and effective prevention and treatment of type 1 and type 2 diabetes. The symposium was intended to provide assistance to FDA, clinical and basic scientists, and the interested pharmaceutical industry in their efforts to reduce the burden of diabetes and improve the health of all people with diabetes. The symposium addressed important disease outcomes that should be targeted in the development of drugs and devices; issues surrounding the use of surrogate or intermediate measures of clinical effect in assessments of novel therapeutic approaches to prevention and treatment; and clinical, scientific, and regulatory issues surrounding development of new medical technologies.

#### **2005 Biostatistical Issues and the Design of Type 1 Diabetes TrialNet (TrialNet) Protocols**

*(March 7, Bethesda, MD, Sponsored by NIDDK)* The meeting was convened to address creative approaches to protocol design. Experts in the areas of biostatistics, endocrinology, and clinical trials were brought together to discuss mechanisms to ensure that multiple clinical trials can be successfully performed concurrently and rigorously within TrialNet.

#### **2005 Genetics of Diabetes and Its Complications: Consortia Meeting**

*(July 20, Bethesda, MD, Sponsored by NIDDK)* This workshop was convened in response to specific recommendations of the expert panel on the *Special Statutory Funding Program for Type 1 Diabetes Research* in their January 2005 meeting. The panel strongly encouraged coordination between the four major genetics consortia supported by the *Special Funding Program*: Family Investigation of Nephropathy and Diabetes (FIND), Genetics of Kidneys in Diabetes Study (GoKinD), EDIC, and the Type 1 Diabetes Genetics Consortium (T1DGC). Recommendations were developed for facilitating interactions among the studies and for future analytic strategies. The importance of interactions between consortia was

emphasized to enhance the value of the individual studies that aim to develop new strategies for prevention and treatment to alleviate the suffering from type 1 diabetes.

### **2005 Obstacles and Opportunities on the Road to an Artificial Pancreas: Closing the Loop**

*(December 19, Bethesda, MD, Sponsored by NIH, NIDDK, JDRF, FDA)* The objective of the workshop was to evaluate the current state of development of the artificial pancreas and to determine the research needs to achieve a functional and safe closed-loop system. Clinical investigators discussed the optimal targets for normal glycemia and their experience with the closed-loop system. Basic research scientists addressed the technological difficulties. Participation from industry and FDA representatives provided a broad view of the current

difficulties associated with reaching the goal of an artificial pancreas.

### **2006 Imaging the Pancreatic Beta Cell**

*(April 24-25, Washington, DC, Sponsored by JDRF, HHS, NIH, NIDDK, NCI, NIBIB, NIAID)* The purpose of this meeting was to explore progress in the field of imaging or otherwise visualizing the pancreatic islet cell mass to assess its functionality in health and disease. The workshop showcased studies aimed at visualizing the pancreatic islet and/or beta cell *in vivo*, so as to elucidate the natural history of islet destruction underlying diabetes pathogenesis and to monitor survival during disease therapy. The goals for this workshop were to share results from promising approaches and those proven unsuccessful in this area; to learn from other applied disciplines; and to foster collaboration among scientists in the diabetes community.

## **DIABETES MELLITUS INTERAGENCY COORDINATING COMMITTEE (DMICC) MEETINGS RELEVANT TO RESEARCH ON TYPE 1 DIABETES AND ITS COMPLICATIONS**

This listing provides highlights of recent DMICC meetings relevant to type 1 diabetes but not specifically focused on the *Special Funding Program*. For a description of DMICC meetings focused on the *Special Funding Program*, please see Appendix 3.

### **Opportunities for Research To Develop New Therapies for Vascular Complications of Diabetes (April 11, 2003)**

This DMICC meeting was appended to the 20th Anniversary Symposium of the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) Study entitled “Metabolic Imprinting and the Long-Term Complications of Diabetes Mellitus: Bench to Bedside and Back” (described in Appendix 3). The DMICC members and guests discussed the funding of future bench-to-bedside research, highlighting the success of DCCT/EDIC. Participants discussed: the major gaps in knowledge of the pathogenesis and therapy of vascular complications; the mechanisms to foster development of animal models; developing novel surrogate markers; identification of new therapeutic targets and agents; advancing research in therapies for complications; and translation of findings from bench to bedside. The meeting provided intriguing areas for future research, as well as identified available resources for carrying ideas to fruition. One of the recommendations emanating from this meeting was for the NIDDK to implement a novel co-PI mechanism for initiatives in which multiple scientists contribute equally to a project. This recognition was thought to be a crucial aspect of team research. In response to this recommendation, the NIDDK employed the co-PI mechanism to an “Innovative Partnerships in Type 1 Diabetes Research” initiative supported by the *Special Funding Program* (Goal VI). The summary minutes can be accessed on the NIDDK’s website ([www.niddk.nih.gov/federal/dmicc/Final-April-11-Summary.pdf](http://www.niddk.nih.gov/federal/dmicc/Final-April-11-Summary.pdf)).

### **Joint Meeting of the Skin Diseases Interagency Coordinating Committee and the Diabetes Mellitus Interagency Coordinating Committee (November 18, 2003)**

This meeting provided an opportunity for the NIDDK and NIAMS to join with representatives of other institutes and agencies to discuss wound healing, a topic of great significance in and of itself, but particularly in relationship to diabetes. The goals of the meeting were to discuss the research efforts being done across agencies, as well as to identify opportunities and gap areas for future research directions. A complete summary of the meeting can be accessed on the NIDDK’s website ([www.niddk.nih.gov/federal/dmicc/FINALNov-ICC-Summary.pdf](http://www.niddk.nih.gov/federal/dmicc/FINALNov-ICC-Summary.pdf)).

### **Meeting on Islet Transplantation (November 23, 2004)**

This meeting was held to discuss, in part, implementation of recent legislation: the Pancreatic Islet Cell Transplantation Act of 2004 (P.L. 108-362). The law included two key provisions: (1) making pancreata procured by an organ procurement organization (OPO) and used for islet cell transplantation count for purposes of certification, and (2) requiring the DMICC to include in its annual report an assessment of Federal activities related to islet transplantation. One purpose of this meeting was to discuss approaches being initiated by DMICC member agencies, either independently or through cooperative arrangements with other agencies, that could be included in the mandated report.

In addition to discussing legislative implementation, an overview of islet transplantation was provided, addressing NIH, FDA, and CMS perspectives. Furthermore, an update on the Health Resources and Services Administration (HRSA)/Organ Procurement and Transplantation Network (OPTN) activities in pancreas and islet transplantation was provided. Several issues were discussed, including: islets as a cellular

therapy versus tissue versus organ; the development of the special organ product (cells or tissue derived from organs) category for transplantation; resolution of issues related to credit for OPOs when pancreata are used for islets (with passage of the Pancreatic Islet Cell Transplantation Act of 2004); an update on the Clinical Islet Transplantation Consortium; an update on the Medicare islet transplantation clinical investigation; and the consensus conference on pancreas allocation for whole-organ and islet transplantation sponsored by the Kidney and Pancreas Transplantation Committee of the OPTN/UNOS on January 23-24, 2005. The meeting was concluded with a discussion of the next step for the Committee, including creating a DMICC subcommittee to address the responsibilities related to promoting islet transplantation under the new legislation. The meeting summary is found at: [www.niddk.nih.gov/federal/dmicc/Meeting\\_112304\\_final.pdf](http://www.niddk.nih.gov/federal/dmicc/Meeting_112304_final.pdf)

### **HbA1c, Diabetes, and Public Health (December 12, 2005)**

Even though scientifically-based evidence supports current guidelines for HbA1c levels in type 1 and type 2 diabetes, national data suggest that a majority of Americans with diabetes are not meeting these guidelines. The goals of this meeting were to pool expertise and identify barriers and solutions to affect changes in the disparity between HbA1c guidelines and practice. Improved glycemic control will benefit individuals by helping them prevent or delay the development of complications and help reduce the public health burden of diabetes. Input from this meeting was used to inform a congressionally-mandated report on steps that the federal government could take to reduce the disparity between HbA1c guidelines and practice. The meeting summary is found at: [www.niddk.nih.gov/federal/dmicc/2005/12-12-05/summary.pdf](http://www.niddk.nih.gov/federal/dmicc/2005/12-12-05/summary.pdf)



# **APPENDIX 5: SUPPLEMENTAL MATERIAL ON THE EVALUATION OF THE SPECIAL FUNDING PROGRAM**

This Appendix provides methodology and detailed information for some of the approaches used to evaluate the *Special Funding Program* initially described in the “Assessment” chapter. An additional major component of this evaluation was based on the professional judgment of scientific and lay experts with expertise relevant to type 1 diabetes and its complications. Information on these expert panel meetings can be found in Appendix 3.



## **SURVEYS OF INVESTIGATORS SUPPORTED BY THE SPECIAL FUNDING PROGRAM**

The NIDDK received approval from the Office of Management and Budget (OMB) to survey extramural scientists who received research grants supported by the *Special Funding Program*. A preliminary survey of all investigators funded by the *Special Program* from FY 1998-2000 was conducted in July 2002. The results of the preliminary survey were used in the preparation of the April 2003 Interim Report on Progress and Opportunities (see Appendix 2 of that report [pp. 154-155] at: [www.niddk.nih.gov/federal/planning/type1\\_specialfund/appendix2.pdf](http://www.niddk.nih.gov/federal/planning/type1_specialfund/appendix2.pdf)).

The NIDDK launched a final survey in February 2006 to expand the respondent pool to investigators funded from 1998 through 2005 and to follow up the responses of investigators that replied to the first survey. In both surveys, potential respondents were informed of the voluntary nature of the survey and the confidentiality of their responses to the extent provided by law. Furthermore, grantees were advised that

information collected through the survey would not impact current or future decisions regarding their research grants. The response period for both surveys was 1 month.

### **Survey Instrument, 2006**

The original instrument was developed and pilot tested with three grantees in January 2002, with OMB approval provided in June 2002. The instrument was updated and approved by OMB in December 2005 (OMB No. 0925-0503). The final survey instrument was administered via a password protected web-based platform. Investigators who took part in the 2002 survey were able to view their previous responses while completing the 2006 survey. Some investigators have multiple grants supported by the *Special Program*; grantees were requested to answer the following questions for each individual grant.

- 
- 1) Was this the first, independent, NIH-supported research grant for which you were the principal investigator?  
Respond with "Yes" only if the specified grant was the first regular research grant (i.e., R01, U19, or other R-coded or U-coded award) that you received from any NIH institute or center for which you were designated as the principal investigator. In determining whether this was your first such grant, do not include support from training grants (i.e., NRSA, T35, or other T-coded award) or career development awards (i.e., K01 or other K-coded award).
  
  - 2) Was this your first grant, from any source, related to type 1 diabetes research?  
Respond with "Yes" only if the specified grant was the first grant that you received in support of research applicable to the understanding, prevention, treatment, or cure of diabetes from any institute or center of NIH or any other source of research funding.
  
  - 3) Have you continued to pursue diabetes research?  
Respond with "Yes" only if, since receiving the specified grant, you have applied for a new grant or if you have applied to renew an existing grant in either type 1 or type 2 diabetes research.

4) Did this grant permit clinically relevant research that you otherwise would not have been able to pursue?

If “Yes,” please discuss this research in your response to question 8.

5) Did this grant permit innovative or high-risk research that you otherwise would not have been able to pursue?

If “Yes,” please discuss this research in your response to question 8.

6 a) Did the research supported by this grant contribute to successful competition for funding in the same line of research?

6 b) If “Yes,” what is the source of that funding (e.g., NIH, American Diabetes Association (ADA), Juvenile Diabetes Research Foundation (JDRF), other)?

6 c) If the source of continued funding was an NIH grant, provide the grant identification number. (e.g., R01 DX123456)

7 a) Did the research supported by this grant require Institutional Review Board (IRB) approval?

7 b) Did the research supported by this grant involve large animals or non-human primates?

8 a) Identify the major accomplishment(s) resulting from the research supported by this grant that impact the understanding, prevention, treatment, or cure of type 1 diabetes or its complications.

Please respond with 3-5 sentences maximum.

8 b) Discuss new opportunities or ideas in the field of type 1 diabetes research that emerged as a result of this research.

Please respond with 3-5 sentences maximum.

8 c) Describe the diagnostic, therapeutic or clinical implications of the research and/or how this research project has contributed to the translation of fundamental new knowledge to clinical studies.

Please respond with 3-5 sentences maximum.

9) If you are working in a research partnership such as a consortium, an “Innovative Partnership” grant, or other collaboration, please describe any specific opportunities, insights, technologies or lines of research that are a direct result of collaboration with other investigators.

Responses should indicate collaborations formed in connection with this grant. Please indicate whether the research team was self-assembled or resulted from grouping determined by the granting agency (e.g., NIH, the Centers for Disease Control and Prevention [CDC], other).

10) Describe the impact of this grant on your career. Please list any awards or honors you have received since working on this grant.

Responses should indicate whether the specified grant affected the recruitment of the principal investigator or retention in the field of type 1 diabetes research in particular.

11) Please supplement this list by adding any publications, including manuscripts in press, that resulted from research supported in whole or in part by this grant. Please do NOT send abstracts or submitted papers that have not yet been accepted for publication.

Publication information should include author(s), year, title, journal, volume, and page numbers.

12) List all patents or patent applications resulting from research supported in whole or in part by this grant.

List only the title of any patents or patent applications that were based in whole or in part on research supported by the specified grant. Indicate whether that patent has been granted or is pending. Please also describe any technology transfer agreements that have resulted from this work.

13 a) Are you aware of the NIDDK website ([www.T1Diabetes.nih.gov](http://www.T1Diabetes.nih.gov)) dedicated to the *Special Funding Program*?

13 b) If you were aware of the website, have you found it useful?

14 a) Describe any new research tools or resources of value to the type 1 diabetes research community that were developed as a result of this grant.

Examples of new research tools or resources include, but are not limited to: animal models, cell lines, instrumentation, diagnostic reagents, or clinical techniques. Responses may be formatted in a “bulleted” list.

14 b) Have you used research resources developed with the *Special Funds*?

Research resources include, but are not limited to: PancChip microarrays created by the Beta Cell Biology Consortium, islet cells produced in the Islet Cell Resource Centers, animal lines from the T1D Mouse Repository, clinical trial datasets, and access to small molecule synthesis (T1D-Rapid Access to Intervention Development). For list of research resources, please see the *Special Funding Program* website resources page ([www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/resources.asp](http://www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/resources.asp)).

14 c) If yes, please indicate which resources were used, whether they were useful, and how you learned about them.  
Please indicate whether you learned about these research resources from the *Special Funding Program* website.

14 d) What additional research resources might be helpful for your research?  
Please indicate resources with general applicability to type 1 diabetes research.

15) What opportunities and/or obstacles related to type 1 diabetes research should be addressed in the future?  
Responses should indicate technical barriers that prevent progress in an area of research.  
THERE IS NO FUNDING ASSOCIATED WITH THIS OR ANY OTHER QUESTION ON THIS SURVEY.

16) Provide any other comments you have regarding the impact or value of this grant or funding source.

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## **Selection Criteria for Grants Included in the Survey**

The survey was targeted at independent investigators who received research project grants from the NIH through the *Special Funding Program*. The following funding mechanisms were excluded from the survey: grants that were part of a research consortium or trial network (progress on these efforts was reported for the consortium as a whole; see main text), or that initially started as investigator-initiated research but were later incorporated into a consortium; standardization programs; clinical investigator training programs; projects whose funding started in 2006 or later; grants to diabetes research centers that supported multiple projects; a grant whose funding was prematurely discontinued; administrative supplements to grants funded by regular NIH appropriations; and contracts.

The *Special Funding Program* supported 496 projects between 1998 and 2005; the survey universe included 358 projects that fit the criteria listed above. However, current contact

information could not be verified for recipients of 22 grants; also, 2 grant recipients were known to be deceased at the time of the survey. Thus, 334 surveys were distributed to grantees.

## **Grantee Survey Response Rate**

Of the 334 projects in the survey universe, the NIDDK received 280 responses (83.5 percent response rate). Of those, 274 were complete (82 percent response rate) and used in all analyses contained in this evaluation report. The six surveys that were only partially completed were used for obtaining publication references only. Certain investigators had multiple grants supported by the *Special Program* and were asked to complete a different survey for each project. The survey covered 284 unique investigators and generated responses from 239 of them (84 percent response rate). The survey was neither biased towards investigators who received funds early in the program nor recipients with more recent grants. As noted in Figure A1, the response rate was evenly distributed among grantees funded by the *Special Funding Program* at different times over the 8 years covered by the survey.

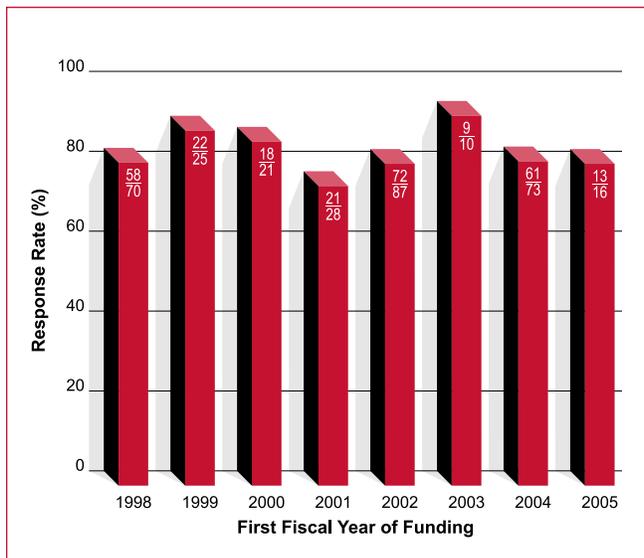


Figure A1: Distribution of survey responses.

The overall response rate of the final survey (82 percent) is a significant improvement over the 54.4 percent response rate from the 2002 survey. This improvement largely reflects the efforts of a contractor, Macro International Inc., which NIDDK retained to administer the survey. Steps taken to improve response rate included: easy-to-use, password-protected, web-

based platform that permitted investigators to save and return to the survey as often as needed; pre-survey contacts to announce the survey and verify address information; assiduous follow-up using a combination of e-mails, letters, and phone calls to request participation in the survey.

### Use of Survey Data

Information collected through the survey of special type 1 diabetes grant recipients has been incorporated throughout this evaluation report. Journal citations (survey question 11) were used to supplement the list of citations collected through database searches (see next section and “Assessment” chapter). Patent information (survey question 12) is described in this Appendix. Representative comments that are generally indicative of the types of comments received regarding the impact of these grants on investigators’ research or careers (survey question 10) and the value of this funding program in general (survey question 16) are quoted verbatim, though without attribution, in the “Evaluation of Investigator-Initiated Research” sections in the Goal chapters. Other questions from the survey were used in various analyses, as cited, in the “Assessment” chapter.

## METHODOLOGY FOR BIBLIOMETRIC ANALYSIS

### Compendium of *Special Funding Program*-Supported Scientific Publications

As one measure of the impact of the *Special Funding Program*, the NIDDK sought to identify the scientific publications that the *Program* made possible in whole or in part. First, the names of *Special Funding Program* grantees were used to search PubMed, the National Library of Medicine's bibliographic database covering medical and pre-clinical sciences. The papers thus identified were searched for indicated grant support and were included in the analysis if they cited one or more *Special Funding Program* grants. However, authors do not always cite their grant support, and in fact some journals do not allow them to do so. Therefore, the resulting compendium was supplemented in the following two ways:

- ▶ Scientific program directors at the NIH responsible for management of the *Special Funding Program* consortia and trial networks were asked to identify any major papers produced by the consortia that had not been identified in the PubMed search.
- ▶ The grantee survey (see preceding section), which covered investigator-initiated grants not associated with the research consortia and trial networks, asked grantees to report all publications that they had produced using those grants.

The resulting collection of publications, which included only papers published between January 1, 1998, and January 1, 2006, was culled to ensure that redundant publications were removed. Publication Pool A was then restricted to those papers associated with grants awarded through initiatives, clinical trials, or consortia made possible through the *Special*

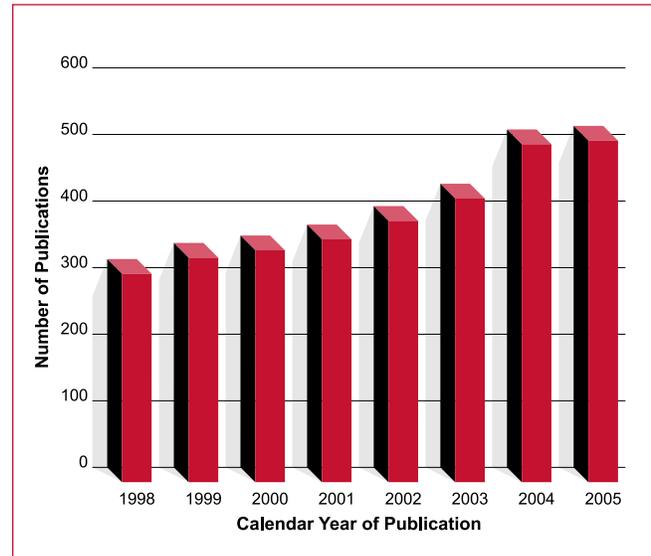


Figure A2: Publications from Pool B (*Special Fund*-augmented grants). Data only include the identified 3,203 papers published before January 1, 2006, that cite Pool B grants and do not also cite other *Special Program* grants.

*Funding Program*. For a complete listing of the publications in each pool, and of the groups of grants included in each pool, please see [www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm](http://www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm).

The publications in Pool B—papers associated with grants and programs that predated the *Special Funding Program* but which were augmented by it—were collected by searches using the relevant grant numbers. Thus, the Pool B library does not include papers funded under these grants if the grant numbers were not cited. The distribution of the publications from Pool B grants is represented in Figure A2. Because it is difficult to assess the relative importance of the supplementary funds compared to the original award, these papers are listed separately and were not analyzed further.

## **Citation Analysis**

Papers in Pool A were then further analyzed in an attempt to evaluate their impact on the scientific community. The Thomson ISI Web of Knowledge database was searched to identify the number of times each paper was cited in other publications prior to January 1, 2006. The number of citations is reported in each bibliographic record (see [www.niddk.](http://www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm)

[nih.gov/fund/diabetesspecialfunds/investigator/data.htm](http://www.niddk.nih.gov/fund/diabetesspecialfunds/investigator/data.htm)).

Because earlier papers have had more time to become known and to influence other researchers than more recent works, and therefore are expected to have more citations, the papers are reported by year. More recent publications will necessarily tend to have fewer citations.

## METHODOLOGY FOR IDENTIFYING FILED U.S. PATENTS

In addition to collecting information on scientific publications and research accomplishments, the NIH examined data on U.S. patent applications and technology transfer agreements as another metric to assess the investigator-initiated research project grants. The following list represents the patents that were self-reported in the survey of grantees as having been derived from research supported by the *Special Funding Program*. The patent numbers were independently verified from records accessed at the U.S. Patent and Trademark Office (USPTO) website. This list only includes projects covered by the grantee survey of investigator-initiated research project grants. It therefore does not include any patents derived from research conducted by the scientific consortia or clinical trial networks, training grants, contracts, or administrative supplements. Furthermore, it is important to again underscore that not all investigators responded to the survey and, even in some cases where grantees did list patents, responses were occasionally missing information, making it impossible to unambiguously identify the patent.

### Patents Issued

- ▶ “Human Pancreatic Cell Lines: Developments and Uses” Levine, F.; Wang, S.; Beattie, G.; Hayek, A. U.S. Pat. #5,723,333 (1998)
- ▶ “Development and Use of Human Pancreatic Cell Lines” Levine, F.; Wang, S.; Beattie, G.; Hayek, A. U.S. Pat. #6,110,743 (2000)
- ▶ “Implantable Sensor and System for Measurement and Control of Blood Constituent Levels” Sun, X.; Joseph, J.; Crothall, K. U.S. Pat. #6,122,536 (2000)
- ▶ “Engineered Proteins for Analyte Sensing” Lakowicz, J.; Tolosa, L.; Eichhorn, L.; Rao, G. U.S. Pat. #6,197,534 (2001)
- ▶ “Polymers From Vinylic Monomers Peroxides and Amines” Lim, D.; Gough, D.; Rourke, A. U.S. Pat. #6,348,429 (2002)
- ▶ “Inducing Insulin Gene Expression in Pancreas Cells Expressing Recombinant PDX-1” Levine, F.; Dufayet, D. U.S. Pat. #6,448,045 (2002)
- ▶ “Implant Coating for Control of Tissue/Implant Interactions” Moussy, F.; Kreutzer, D.; Burgess, D.; Koberstein, J.; Papadimitrakopoulos, F.; Huang, S. U.S. Pat. #6,497,729 (2002)
- ▶ “Polymerized Crystalline Colloidal Arrays” Asher, S. U.S. Pat. #6,544,800 (2003)
- ▶ “Photochemically Controlled Photonic Crystal Diffraction” Asher, S.; Kamenjicki, M.; Lednev, I.; Meier, V. U.S. Pat. #6,589,452 (2003)
- ▶ “Sensor Probe for Determining Hydrogen Peroxide Concentration and Method of Use Thereof” Schmid-Schoenbein, G.; Baker, D.; Gough, D. U.S. Pat. #6,592,746 (2003)
- ▶ “*In Vivo* Biosensor Apparatus and Method of Use” Saylor, G.; Simpson, M.; Applegate, B.; Ripp, S. U.S. Pat. #6,673,596 (2004)
- ▶ “Saccharide Sensing Molecules Having Enhanced Fluorescent Properties” Satcher, Jr., J.; Lane, S.; Darrow, C.; Cary, D.; Tran, J. U.S. Pat. #6,673,625 (2004)
- ▶ “Glucose Sensing Molecules Having Selected Fluorescent Properties” Satcher, Jr., J.; Lane, S.; Darrow, C.; Cary, D.; Tran, J. U.S. Pat. #6,682,938 (2004)
- ▶ “Membrane and Electrode Structure for Implantable Sensor” Gough, D. U.S. Pat. #6,721,587 (2004)
- ▶ “Polymerized Crystalline Colloidal Array Chemical Sensing Materials For Use in High Ionic Strength Solutions” Asher, S.A.; Reese, C. U.S. Pat. #6,753,191 (2004)
- ▶ “Long Wave Fluorophore Sensor Compounds and Other Fluorescent Sensor Compounds in Polymers” Walsh, J.; Heiss, A.; Noronha, G.; Vachon, D.; Lane, S.; Satcher, Jr., J.; Peyser, T.; Van Antwerp, W.; Mastrototaro, J. U.S. Pat. #6,766,183 (2004)



- ▶ “Methods and Substances for Preventing and Treating Autoimmune Disease” Langridge, W.; Arakawa, T. U.S. Pat. #6,777,546 (2004)
  - ▶ “Multivalent MHC Class II - Peptide Chimeras” Brumeanu, T.; Casares, S.; Bona, C. U.S. Pat. #6,811,785 (2004)
  - ▶ “Methods, Products and Treatments for Diabetes” Halperin, J. U.S. Pat. #6,835,545 (2004)
  - ▶ “Induction of Beta Cell Differentiation in Human Cells by Stimulation of the GLP-1 Receptor” Levine, F.; Dufayet, D. U.S. Pat. #6,884,585 (2005)
  - ▶ “Induction of Beta Cell Differentiation in Human Cells” Levine, F.; Gouty, D.; Itkin-Ansari, P. U.S. Pat. #6,911,324 (2005)
  - ▶ “Fluorescent Sensor Compounds for Detecting Saccharides” Wang, B.; Weston, B.; Yang, W. U.S. Pat. #6,916,660 (2005)
  - ▶ “Method of Use of Peptide Antagonists of Zonulin to Prevent or Delay the Onset of Diabetes” Fasano, A.; Watts, T. U.S. Pat. #7,026,294 (2006)
  - ▶ “Methods, Products and Treatments for Diabetes” Halperin, J. U.S. Pat. #7,049,082 (2006)
  - ▶ “Contact Lenses Colored With Crystalline Colloidal Array Technology” Asher, S. U.S. Pat. #7,059,719 (2006)
- In addition to the 25 U.S. patents that were issued, grantees reported 39 additional patents that had been filed with the USPTO, but had not yet been issued. A provisional patent is a 1-year intellectual property protection, often used as a preliminary step before filing a non-provisional patent. In addition, survey respondents reported eight provisional patents that had been allowed by the USPTO. In total, independent investigators responding to the survey reported 72 U.S. patent applications.

## METHODOLOGY FOR RESEARCH PORTFOLIO ANALYSIS

In the “Assessment” chapter, the research portfolio analyses of *Special Funding Program* grants administered by the NIH were based on data retrieval from the NIH database of grants and applications: Information for Management, Planning, Analysis, and Coordination (IMPAC II). The Query/View/Report tool was used to search IMPAC II for archival budget and programmatic data based on the list of the NIH grant numbers for all the projects supported by the *Special Funding Program*. Separate searches were conducted for each fiscal year based on so-called “frozen records”—the finalized budget data for each fiscal year; changes incorporated after the data have been finalized are not captured in the frozen records. In these analyses, awards that spanned multiple fiscal years were only counted once, in the year that they first received *Special Funds*. Projects supported by the *Special Funding Program* that were successfully renewed for additional cycles of funding were counted again in the year that they were competitively awarded.

The analyses focused solely on research project grants (R01, R21, R24, R29, R33, R37), cooperative agreements (U01, U10, U19, U24, U42) and small business grants (R41, R43, R44). Supplements to ongoing grants were not included because it would not be possible to determine if the categorization of the research as “clinical” (an important evaluation question) related to the supplement portion of the grant or only to the primary grant. Institutional (T32) and career (K12) training programs were categorically eliminated from the analysis. Also excluded were all contracts, as well as grants to research programs and centers (P01, P30, P40, P50, P51, P60, M01).

The following methodology was used in the analyses reported in the “Assessment” chapter:

**Clinical Research Portfolio:** For reporting purposes, the NIH applies special codes to research grants and applications in its IMPAC II database. Several special codes are used

to designate human subjects research, ranging from human tissue sample analysis to Phase III clinical trials. In this evaluation report, clinical research was defined as all human subject research (excluding research labeled as human subject research, but that only involved human tissue samples). Sometimes, research grants in the NIH database were not flagged as clinical research in the first year of funding, but this flag was applied to the research in later years. Any research grant that met these criteria at any point in its grant history was considered “clinical research” for the first year it was funded.

**New Investigators:** In this evaluation report, for the purpose of review and funding, applicants were considered to be new investigators if they had not previously served as the principal investigators on any Public Health Service-supported research project other than a small grant (R03), an Academic Research Enhancement Award (R15), an exploratory/developmental grant (R21), or certain research career awards directed principally to physicians, dentists, or veterinarians at the beginning of their research careers (K01, K08, and K12). Current or past recipients of Independent Scientist and other non-mentored career awards (K02, K04) were not considered new investigators. In the IMPAC II NIH database, either the grant applicant or the Scientific Review Administrator can flag an application as “new investigator” based on these criteria. The NIH began tracking new investigators in the IMPAC II database in 1999; however, this tracking was phased in, so the reporting for 1999 is likely underestimated. Only new competing research project grants (R01 and R21) from FY 1999 to 2005 were included in this evaluation report. It is possible that an investigator received his or her first grant from the *Special Funding Program* and subsequently received an additional grant from the *Program*. This investigator would be counted as a new investigator the first time only; however, both grants would be included in the denominator of total grants analyzed. Using IMPAC II, the same search criteria were used to estimate the fraction of new investigators across

all the Institutes and Centers at the NIH: of the 37,490 new competing R01 and R21 grants awarded between FY 1999 and FY 2005, 9,528 applications had been marked as a new investigator (25.4 percent). The self-identification of new investigator status on grant applications underestimates the true number of new investigators. Hence, the NIH Office of Extramural Research (OER) uses the Consolidated Grant Applicant Files to track new investigators. These data were used as an alternate method to calculate the fraction of new investigators funded by the NIH. These data can be accessed at: [http://grants.nih.gov/grants/new\\_investigators/New\\_Invest\\_by\\_Activity.xls](http://grants.nih.gov/grants/new_investigators/New_Invest_by_Activity.xls)

**Continuation of Research Funding:** Only R01 grants were included in this analysis. There were 100 R01 grants funded by the *Special Funding Program* with an original project end

date before September 30, 2005. Using the grant numbers for the 100 R01 grants, the IMPAC II database was searched for competitive renewal applications (application type 2). If an application is not funded after its initial submission, the investigator can amend it up to two times and resubmit it for a subsequent review cycle. Renewal applications with one or more amendments were only counted once. This query retrieved 54 applications for renewal, as of July 2006. The NIH database indicates which applications were awarded, pending, withdrawn, or not recommended for further consideration during the review process. The success rate of *Special Funding Program* grants was compared to the NIH average success rate for continuing R01 grants based on OER data for FY 2000-2005: [http://grants1.nih.gov/grants/award/success/Success\\_ByActivity.cfm](http://grants1.nih.gov/grants/award/success/Success_ByActivity.cfm)

# **APPENDIX 6: ADVANCES AND EMERGING OPPORTUNITIES IN TYPE 1 DIABETES RESEARCH: A STRATEGIC PLAN**

This Appendix provides the “Summary and Recommendations” section of the Type 1 Diabetes Research Strategic Plan, which was published in August 2006. Two versions of the Plan were developed for: (1) patients and the public; and (2) the scientific community. The Strategic Plan was developed to serve as a scientific guidepost to the NIH and to the investigative and lay communities by identifying compelling research opportunities that will inform future type 1 diabetes research efforts and propel research progress on the understanding, prevention, treatment, and cure of type 1 diabetes and its complications. Both versions can be accessed on the NIDDK’s website ([www.T1Diabetes.nih.gov/plan](http://www.T1Diabetes.nih.gov/plan)).

## SUMMARY AND RECOMMENDATIONS

### Overview of Type 1 Diabetes

Type 1 diabetes is a devastating disease in which the body's immune system attacks and destroys insulin-producing beta cells, which are found in clusters in the pancreas called islets. Without this vital hormone, the cells and tissues cannot absorb glucose (sugar), and patients' cells can starve to death, despite high levels of glucose in the bloodstream. Therefore, patients require daily insulin administration for survival. Type 1 diabetes, as patients and parents say, "never takes a day off." Patients or caregivers must constantly monitor glucose levels. If they are too high, patients must take insulin. If too low, they must eat food to boost their glucose levels. The constant burden of this disease greatly affects the quality of life of patients and family members.

Although life-saving, insulin therapy is not a cure. Despite the vigilant efforts of patients to keep their glucose levels as close to normal as possible, chronically high glucose levels (hyperglycemia) damage their organs. This damage, in turn, can result in the development of life-threatening disease complications, such as blindness, kidney failure, nerve damage, lower limb amputation, heart disease, and stroke. These complications can reduce average life span by many years. Given the unremitting demands of diabetes, it is not surprising that it heightens the risks for various psychiatric disorders, such as depression. On the flip side, when patients aggressively manage their glucose levels with insulin therapy to try to prevent these devastating complications, they are at risk for dangerous episodes of low blood glucose (hypoglycemia). Patients may not even be aware that they are experiencing these episodes (hypoglycemia unawareness). If left untreated, hypoglycemia can result in coma and even death. Patients with type 1 diabetes must constantly walk a tightrope to balance the risks of the immediate danger of hypoglycemia and the long-term danger of complications from high blood glucose levels.

Type 1 diabetes differs from type 2 diabetes, which is more commonly diagnosed in adulthood, is strongly associated with overweight and obesity, and disproportionately affects minority populations. However, both forms of the disease share the same complications. Treating diabetes and its complications places an enormous public health burden on the United States.

### Research Objectives

The Strategic Plan identifies key research objectives that will guide future NIH efforts to achieve six overarching Goals of type 1 diabetes research. The objectives outlined in the Plan build upon recent scientific advances and represent scientific opportunities for overcoming current barriers and achieving progress in type 1 diabetes research over the next 10 years.

#### Goal I: Identify the Genetic and Environmental Causes of Type 1 Diabetes

Type 1 diabetes results from an interplay of genetic and environmental factors. Several key genes involved in the disease have been identified, but many more remain unknown. Environmental factors have also been found to play a role, but no single trigger has been conclusively identified. Research on genetic and environmental factors could help predict who will develop type 1 diabetes and could also lead to the identification of novel prevention strategies. Key research objectives in this area are:

##### Genetic Causes

- ▶ Create Resources for the Study of Type 1 Diabetes Genetics
- ▶ Identify Human Genes Causing Type 1 Diabetes
- ▶ Use Knowledge About the Genetic Underpinnings of Type 1 Diabetes To Prevent and Treat the Disease

### **Environmental Causes**

- ▶ Monitor Rates of Type 1 Diabetes
- ▶ Assess Environmental Causes of Type 1 Diabetes

### **Goal II: Prevent or Reverse Type 1 Diabetes**

Preventing type 1 diabetes onset would obviate the need for daily insulin administration and the serious disease complications. Research to explore the defects in the immune system that are associated with autoimmunity could lead to new methods to predict, diagnose, treat, and ultimately prevent the disease. In addition, research is required to halt or reverse beta cell destruction after disease onset, to preserve patients' insulin producing capacity. Key research objectives in this area are:

#### **Risk Assessment**

- ▶ Identify and Optimize the Detection of Immunologic, Genetic, and Metabolic Markers of Type 1 Diabetes

#### **Immunopathogenesis**

- ▶ Understand the Interplay Between Early Environmental Encounters and the Immunoregulatory Defects That Results in Beta Cell Destruction in Human Type 1 Diabetes
- ▶ Advance Basic Understanding of Facets of the Human Immune Response (e.g., Regulatory T Cells, Innate Immunity) That Have Recently Been Appreciated as Key Mediators of Beta Cell Destruction

#### **Clinical Trials**

- ▶ Identify an Intervention Capable of Long-term Reversal of Recent Onset Type 1 Diabetes Without Concomitant Short- or Long-term Adverse Effects
- ▶ Develop a Safe and Universal Means for the Primary Prevention of Type 1 Diabetes

### **Goal III: Develop Cell Replacement Therapy**

Islet transplantation has engendered tremendous hope as a possible cure for type 1 diabetes. This therapeutic strategy replaces the insulin-producing beta cells destroyed by the immune system, thereby eliminating or reducing the need for insulin administration. However, to make this strategy a viable option for most patients, it is imperative to overcome the numerous obstacles that still exist, such as the shortage of available islets and the need for less toxic methods to prevent islet rejection and the recurrence of autoimmunity. Research on both beta cell biology and clinical islet transplantation can help to overcome these and other barriers. Key research objectives in this area are:

#### **Islet Transplantation**

- ▶ Develop Novel Strategies and Infrastructure That Support Advancing Pancreas Procurement and Islet Processing
- ▶ Develop Improved Methods To Assess Islet Beta Cell Viability and Function That Predict Early Islet Function After Transplant
- ▶ Investigate the Use of Porcine Islets as an Alternate Source of Islets for Transplantation
- ▶ Improve Islet Transplant Procedures
- ▶ Develop Novel Methods To Accurately Assess the Post-Transplant Islet Mass
- ▶ Harness New Understanding of the Immune System To Develop Improved Clinical Monitoring and Immunotherapies

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

- ▶ Grow a Renewable Supply of Pancreatic Beta Cells That Can Be Transplanted into Patients
- ▶ Understand How Mature Beta Cells Are Maintained and Replenished in the Adult Pancreas
- ▶ Develop Strategies To Regenerate Beta Cells Through Replication or Neogenesis

#### **Goal IV: Prevent or Reduce Hypoglycemia in Type 1 Diabetes**

Hypoglycemia is a distressing, acute complication of type 1 diabetes. Low blood glucose impairs brain and other bodily functions, including defenses against future hypoglycemia episodes, causing a vicious cycle of recurrent events. Understanding how the brain and body work together to sense and adjust glucose levels, as well as research to improve and link glucose monitoring and insulin delivery, could help scientists develop strategies to prevent hypoglycemic episodes and improve patients' quality of life. Key research objectives in this area are:

##### **Brain and Peripheral Nervous System Mechanisms of Hypoglycemia**

- ▶ Define the Mechanisms and Modulators of Metabolic Sensing
- ▶ Elucidate Brain Alterations in Response to Hypoglycemia
- ▶ Develop New Strategies To Prevent or Reverse Hypoglycemia-Associated Autonomic Failure

##### **Clinical Interventions To Prevent or Reduce Hypoglycemia**

- ▶ Control Hypoglycemia Through Behavioral Therapies
- ▶ Close the Loop: Develop the Tools Required for an Artificial Pancreas

#### **Goal V: Prevent or Reduce the Complications of Type 1 Diabetes**

Persistent elevation of blood glucose can lead to life-threatening disease complications. Research has dramatically demonstrated that intensive control of blood glucose levels can prevent or delay the development of these complications. However, because of the limitations and difficulties of current therapies for achieving good glucose control, as well as the threat of hypoglycemia associated with intensive control, patients rarely achieve recommended glucose levels. Future research strategies will build upon the existing approaches to control diabetes, as well as develop novel approaches to break

the link between high glucose and chronic complications. Key research objectives in this area are:

##### **Molecular Mechanisms of Common Pathways in Diabetic Complications**

- ▶ Identify Molecular Pathways of Hyperglycemia Damage
- ▶ Clarify Mechanisms Linking Fuel Utilization and Heart Disease
- ▶ Understand the Systems Biology of Diabetic Complications

##### **Metabolic Memory**

- ▶ Discover the Molecular Mechanisms of Metabolic Memory

##### **Genetic Factors**

- ▶ Identify Genes Conferring Susceptibility and Resistance to Diabetic Complications

##### **Animal Models**

- ▶ Develop More Human-like Animal Models of Diabetic Complications

##### **Biomarkers and Surrogate Endpoints To Facilitate Clinical Trials**

- ▶ Identify Biomarkers or a Combination of Biomarkers for Earlier Detection of Cell and Tissue Damage
- ▶ Validate Surrogate Endpoints for Assessing the Progression of Complications in Clinical Trials

##### **Therapies To Improve Patient Health**

- ▶ Identify Therapeutics That Prevent or Reverse the Development and Progression of Diabetic Complications
- ▶ Mitigate Psychosocial Complications and Comorbidities of Diabetes To Improve Quality of Life
- ▶ Combine New Technology for Diabetes Management with Behavioral and Translational Research

## **Goal VI: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes**

Continued research progress depends on attracting and training a workforce of scientists with diverse expertise to conduct research on type 1 diabetes and its complications. In addition, the harnessing of new and emerging technologies sets the stage for innovative discoveries that can bring tremendous benefits to patients. Key research objectives in this area are:

### **Engaging Talented Scientists**

- ▶ Recruit Expertise from Diverse Fields
- ▶ Design Incentives That Reward Research Innovation
- ▶ Train New Scientists in Clinical Type 1 Diabetes Research

### **Development and Application of New Technologies**

- ▶ Develop Noninvasive Imaging Technologies To Monitor Type 1 Diabetes
- ▶ Promote Application of Advances in Bioengineering to Type 1 Diabetes
- ▶ Foster Application of Gene Delivery and Gene Silencing Technology To Develop New Therapies for Type 1 Diabetes and Its Complications
- ▶ Apply New and Emerging Technologies in Functional Genomics, Proteomics, and Metabolomics to Type 1 Diabetes Research
- ▶ Improve the Power of Diabetes Research by Utilizing Computational Biology and Bioinformatics
- ▶ Apply New Technology to the Development of Improved Animal Models for the Study of Type 1 Diabetes

## **NIH Support for Type 1 Diabetes Research**

Research toward achieving the six overarching Goals has been accelerated by the *Special Statutory Funding Program for Type 1 Diabetes Research*. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) administers this

special appropriation on behalf of the Secretary of the Department of Health and Human Services (HHS), in collaboration with multiple other NIH Institutes and Centers, and the Centers for Disease Control and Prevention (CDC). The *Special Funding Program* has allowed the creation of unique, collaborative, and innovative research consortia and clinical trials networks to increase understanding about the prevention, treatment, and cure of type 1 diabetes. Initiatives supported by the program are different in size, scope, duration, and nature from other type 1 diabetes efforts supported through regular NIH appropriations. The *Special Funding Program* enabled the initiation of most of these large-scale, high-impact efforts, at a scientifically optimal scale of operation. Importantly, the research efforts that have been supported to date have spurred numerous future opportunities that could dramatically improve the lives of patients with type 1 diabetes. Type 1 diabetes research is also supported by regularly appropriated funds to HHS.

## **Implementation: Guiding Future Research Efforts**

The Strategic Plan reflects a dynamic planning process that involves collaboration among numerous stakeholders to ensure that research progress is regularly assessed and that new and emerging opportunities are identified. The statutory Diabetes Mellitus Interagency Coordinating Committee will continue to play a key role by assessing progress toward attaining the goals and objectives described in the Plan, which was developed under its auspices. The NIH will also continue to solicit broad external input from the scientific, lay, and patient advocacy communities to inform its planning efforts. The NIH will use the research objectives described in the Strategic Plan as a scientific guidepost to improve current treatment strategies and to identify ways to prevent or cure type 1 diabetes and its complications.



## Process for the Development of the Type 1 Diabetes Research Strategic Plan

### Origin

One of the recommendations emanating from a January 2005 *ad hoc* planning and evaluation meeting focused on large scale efforts made possible by the *Special Statutory Funding Program for Type 1 Diabetes Research* was that the NIH should initiate a broad review of the entire state-of-the-science with respect to type 1 diabetes and its complications. In response to this recommendation, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) launched a new strategic planning effort for type 1 diabetes research.

### Collaborative Planning Process

This Strategic Plan was developed through an open and inclusive planning process, with oversight by the statutory Diabetes Mellitus Interagency Coordinating Committee, and leadership by the NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases. The Committee, chaired by the NIDDK, includes representation from NIH components involved in diabetes research, as well as from other relevant federal agencies.

To develop the scientific chapters of the Strategic Plan, Working Groups were convened to identify recent scientific advances and research objectives for Goals I-V. Goal VI, "Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes," was addressed by all Working Groups because it is an interdisciplinary goal that applies across type 1 diabetes research. The Working Groups were composed of a diverse and talented group of individuals who are committed to propelling progress in type 1 diabetes research. They were chaired by scientists external to the NIH, with membership that included extramural scientists, NIH representatives, patients, and representatives from patient advocacy groups.

Public comment was solicited prior to publication by the posting of the draft plan on a website created for the planning effort ([www.T1Diabetes.nih.gov/plan](http://www.T1Diabetes.nih.gov/plan)).

### Organization of the Strategic Plan

The Strategic Plan was framed around the six overarching scientific goals of type 1 diabetes research. One version of the Plan was developed for patients with type 1 diabetes, their family members, and the public. It contains a description of how research addressing each goal could benefit people living with type 1 diabetes and their family members, as well as profiles of patients and scientists. Another version of the Plan was developed for the scientific research community. While tailored to different readers, both versions highlight key recent scientific advances that have accelerated research and/or benefited patients' health, and identify the most compelling opportunities and objectives for research.

Both versions of the Plan contain a summary of major research objectives. Research objectives are specific research directions that can be pursued over the next decade, within available NIH resources, to realize the goal of each chapter. In some cases, these objectives intersect with one another and may be dependent upon one another for progress. For example, identifying environmental triggers of type 1 diabetes (Goal I) will help to inform future disease prevention strategies (Goal II). Also, “Attract New Talent and Apply New Technologies” (Goal VI) is important for every area of type 1 diabetes research. The Strategic Plan describes a coordinated, multifaceted approach for significantly advancing research to combat type 1 diabetes.

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The background consists of a white triangular shape pointing to the right, set against a solid red background. The text is positioned within the white triangle.

**APPENDIX 7: ACRONYMS  
AND ABBREVIATIONS**

## ORGANIZATIONS

ADA	American Diabetes Association	NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
AHRQ	Agency for Healthcare Research and Quality	NIBIB	National Institute of Biomedical Imaging and Bioengineering
CDC	Centers for Disease Control and Prevention	NICHD	National Institute of Child Health and Human Development
CIHR	Canadian Institutes of Health Research	NIDCR	National Institute of Dental and Craniofacial Research
CMS	Centers for Medicare & Medicaid Services	NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
DHHS	Department of Health and Human Services	NIEHS	National Institute of Environmental Health Sciences
EFSD	European Foundation for the Study of Diabetes	NIH	National Institutes of Health
FDA	Food and Drug Administration	NIMH	National Institute of Mental Health
FOCIS	Federation of Clinical Immunology Societies	NINDS	National Institute of Neurological Disorders and Stroke
HRSA	Health Resources and Services Administration	NINR	National Institute of Nursing Research
IDS	Immunology of Diabetes Society	NLM	National Library of Medicine
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine	OBSSR	Office of Behavioral and Social Science Research
JDRF	Juvenile Diabetes Research Foundation International	ODS	Office of Dietary Supplements, NIH
NASA	National Aeronautics and Space Administration	OER	Office of Extramural Research, NIH
NCI	National Cancer Institute	OMB	Office of Management and Budget
NCMHD	National Center on Minority Health and Health Disparities	ORWH	Office of Research on Women's Health, NIH
NCRR	National Center for Research Resources	USPTO	U.S. Patent and Trademark Office
NDF	Netherlands Diabetes Foundation		
NEI	National Eye Institute		
NHGRI	National Human Genome Research Institute		
NHLBI	National Heart, Lung, and Blood Institute		
NIA	National Institute on Aging		
NIAID	National Institute of Allergy and Infectious Diseases		

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AMDCC	Animal Models of Diabetic Complications Consortium <a href="http://www.amdcc.org">www.amdcc.org</a>	ITN	Immune Tolerance Network <a href="http://www.immunetolerance.org">www.immunetolerance.org</a>
BCBC	Beta Cell Biology Consortium <a href="http://www.betacell.org">www.betacell.org</a>	MGC	Mammalian Gene Collection <a href="http://mgc.nci.nih.gov">http://mgc.nci.nih.gov</a>
CIT	Clinical Islet Transplantation Consortium <a href="http://www.isletstudy.org/">www.isletstudy.org/</a>	MMPC	Mouse Metabolic Phenotyping Centers <a href="http://www.mmpc.org">www.mmpc.org</a>
CITR	Collaborative Islet Transplant Registry <a href="http://www.citregistry.org">www.citregistry.org</a>	MMRRC	Mutant Mouse Regional Resource Centers <a href="http://www.mmrrc.org/">www.mmrrc.org/</a>
DASP	Diabetes Autoantibody Standardization Program <a href="http://www.idsoc.org/committees/antibody/dasphome.html">www.idsoc.org/committees/antibody/dasphome.html</a>	NGSP	National Glycohemoglobin A1c Standardization Program <a href="http://www.ngsp.org">www.ngsp.org</a>
DCCT	Diabetes Control and Complications Trial	NHPCSG	Non-Human Primate Transplantation Tolerance Cooperative Study Group
DirecNet	Diabetes Research in Children Network <a href="http://public.direc.net/">http://public.direc.net/</a>	NRSA	National Research Service Award
DPT-1	Diabetes Prevention Trial-Type 1	SEARCH	Search for Diabetes in Youth Study <a href="http://www.searchfordiabetes.org">www.searchfordiabetes.org</a>
DRCR.net	Diabetic Retinopathy Clinical Research Network <a href="http://www.drcr.net">www.drcr.net</a>	T1DGC	Type 1 Diabetes Genetics Consortium <a href="http://www.t1dgc.org">www.t1dgc.org</a>
EDIC	Epidemiology of Diabetes Interventions and Complications <a href="http://www.bsc.gwu.edu/bsc/studies/edic.html">www.bsc.gwu.edu/bsc/studies/edic.html</a>	T1DR	Type 1 Diabetes Mouse Resource <a href="http://www.jax.org/t1dr/">www.jax.org/t1dr/</a>
FIND	Family Investigation of Nephropathy and Diabetes <a href="http://genepi.cwru.edu/FIND/">http://genepi.cwru.edu/FIND/</a>	T1D-RAID	Type 1 Diabetes-Rapid Access to Intervention Development <a href="http://www.T1Diabetes.nih.gov/T1D-RAID/index.shtml">www.T1Diabetes.nih.gov/T1D-RAID/index.shtml</a>
GoKinD	Genetics of Kidneys in Diabetes Study <a href="http://www.gokind.org/access/home.html">www.gokind.org/access/home.html</a>	TARP	Trans-Institute Angiogenesis Research Program <a href="http://www.tarp.nih.gov">www.tarp.nih.gov</a>
ICR	Islet Cell Resource Centers <a href="http://icr.coh.org/">http://icr.coh.org/</a>	TEDDY	The Environmental Determinants of Diabetes in the Young <a href="http://www.teddystudy.org">www.teddystudy.org</a>
IHWG	International Histocompatibility Working Group <a href="http://www.ihwg.org">www.ihwg.org</a>	TrialNet	Type 1 Diabetes TrialNet <a href="http://www.diabetestrialnet.org">www.diabetestrialnet.org</a>
		TRIGR	Trial to Reduce IDDM in the Genetically at Risk <a href="http://www.trigr.org">www.trigr.org</a>

## OTHER ACRONYMS AND ABBREVIATIONS

ABCC	Administrative and Bioinformatics Coordinating Center	IA-2	protein tyrosine phosphatase-2
ACE	angiotensin converting enzyme	IDDM	insulin-dependent diabetes mellitus
AGE	advanced glycation endproducts	IMPAC II	Information for Management, Planning, Analysis, and Coordination
ATP	adenosine triphosphate	IMSR	International Mouse Strain Resource
BMI	body mass index	INS	insulin gene
CBP	Collaborative Bridging Project	IRB	Institutional Review Board
CGMS	continuous glucose monitor system	LDL	low-density lipoprotein
ChIP	chromatin immunoprecipitation	LSF	lisofylline
CL	Cytotoxic lymphocyte	MHC	major histocompatibility complex
CRISP	Computer Retrieval of Information on Scientific Projects	MMTT	mixed meal tolerance test
CVD	cardiovascular disease	MODY	Maturity Onset Diabetes of the Young
DCs	dendritic cells	MRI	magnetic resonance imaging
DKA	diabetic ketoacidosis	mRNA	messenger RNA
DMICC	Diabetes Mellitus Interagency Coordinating Committee	MRS	magnetic resonance spectroscopy
DNA	deoxyribonucleic acid	NHP	non-human primate
DRWG	Diabetes Research Working Group	NIP	Nutritional Intervention To Prevent Type 1 Diabetes Study
DSG	15-deoxyspergualin	NOD	non-obese diabetic
DSMB	Data and Safety Monitoring Board	OCR	oxygen consumption rate
EAB	External Advisory Board	ODN	oligodeoxyribonucleotide
EAC	External Advisory Committee	PBMC	peripheral blood mononuclear cells
ESAC	External Scientific Advisory Committee	PEDF	pigment epithelium-derived factor
ES cell	embryonic stem cell	PERV	porcine endogenous retrovirus
ESRD	end-stage renal disease	PET	positron emission tomography
EU	European Union	PI	Principal Investigator
FACS	fluorescence activated cell sorting	PKC beta	protein kinase C beta
FY	Fiscal Year	PL	Public Law
GAD	glutamic acid decarboxylase	PPAR-alpha	peroxisome proliferator-activated receptor-alpha
GMP	good manufacturing practices	PTPN22	protein tyrosine phosphatase N22 gene
GST	glucagon stimulation test	RAGE	receptor for advanced glycation endproducts
HAAF	hypoglycemia-associated autonomic failure	RFA	Request for Applications
HbA1c	Hemoglobin A1c	RFI	Request for Information
HIPAA	Health Insurance Portability and Accountability Act	RFP	Request for Proposals
HLA	human leukocyte antigen	RNA	ribonucleic acid
		ROS	reactive oxygen species

SBIR	Small Business Innovation Research	SNP	single nucleotide polymorphism
SC	Steering Committee	STTR	Small Business Technology Transfer
SDF-1	stromal cell derived factor-1	TNF	tumor necrosis factor
siRNA	small interfering RNA	VEGF	vascular endothelial growth factor





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