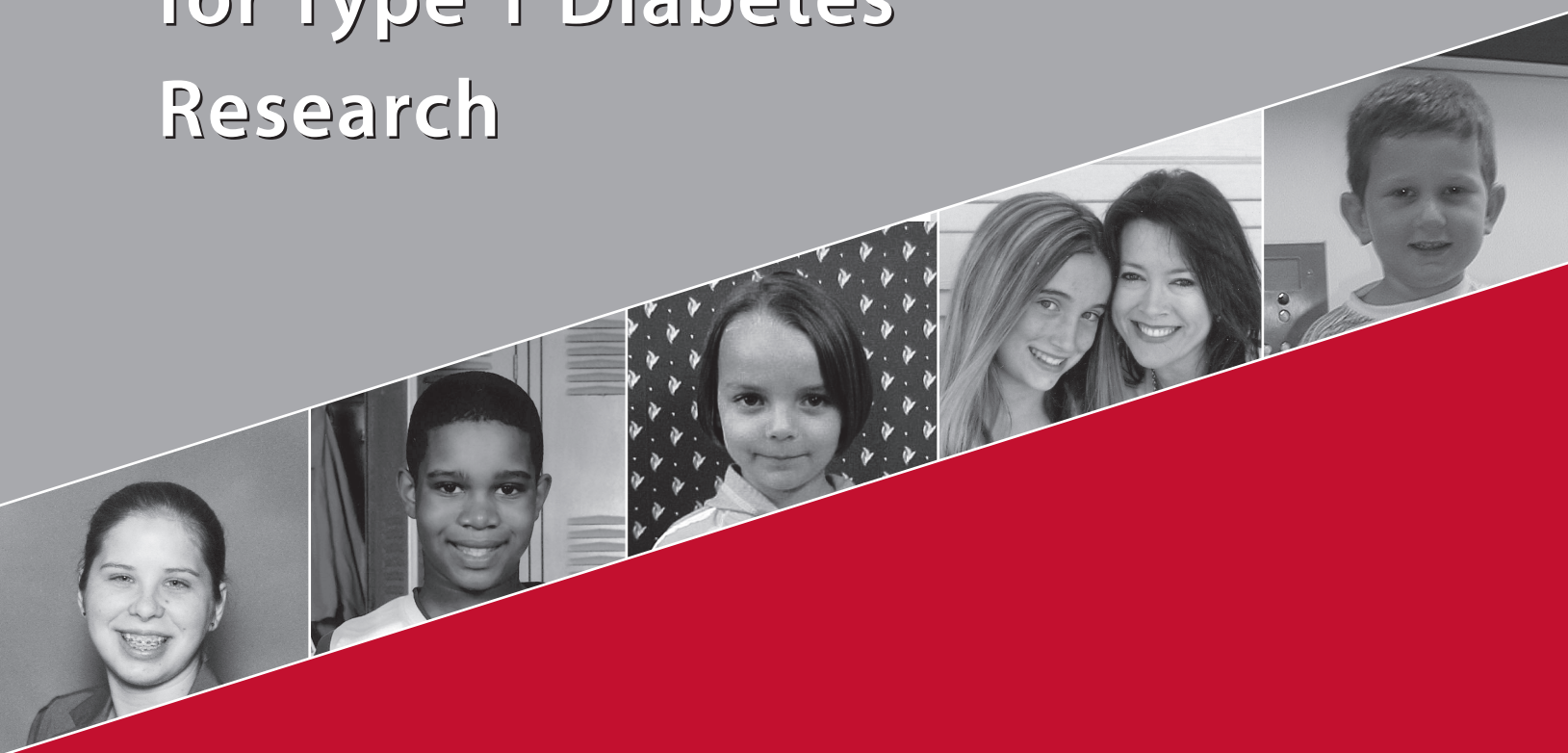
EVALUATION REPORT:
EXECUTIVE SUMMARY

Special Statutory Funding Program for Type 1 Diabetes Research



EVALUATION REPORT:
EXECUTIVE SUMMARY

Special Statutory Funding Program for Type 1 Diabetes Research

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.[1]

Type 1 diabetes affects an estimated 5 to 10 percent of the 14.6 million people in the United States diagnosed with diabetes.† 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,[2] heart disease risk is increased by up to 10-fold in type 1 diabetes patients compared to the general age-matched population.[3, 4] 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.

† 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)

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

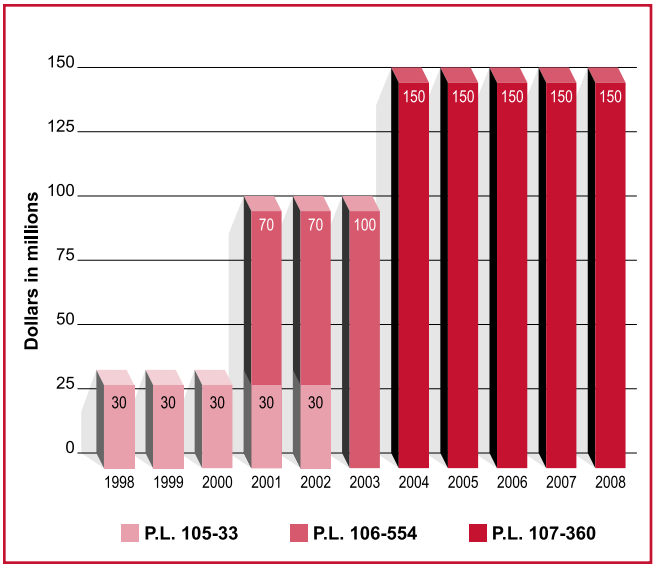


Figure 1: *Special Funding for Type 1 Diabetes Research*. *Special Program* funding levels per year, FY 1998-2008. The *Program* was established by the Balanced Budget Act of 1997 (Public Law [P.L.] 105-33), and later extended and augmented by the FY 2001 Consolidated Appropriations Act (P.L. 106-554)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

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.[3, 4]

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.

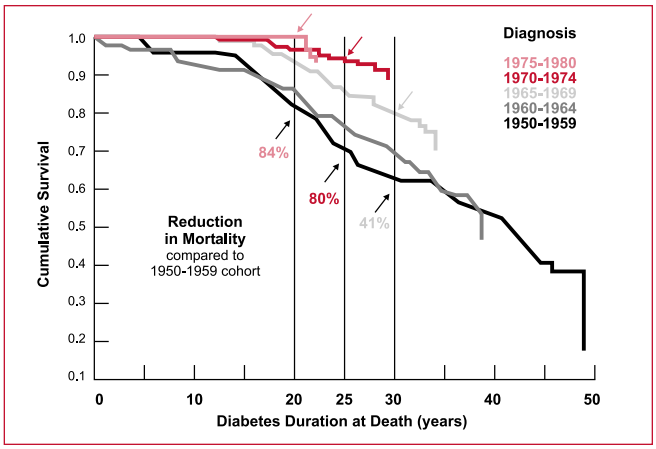
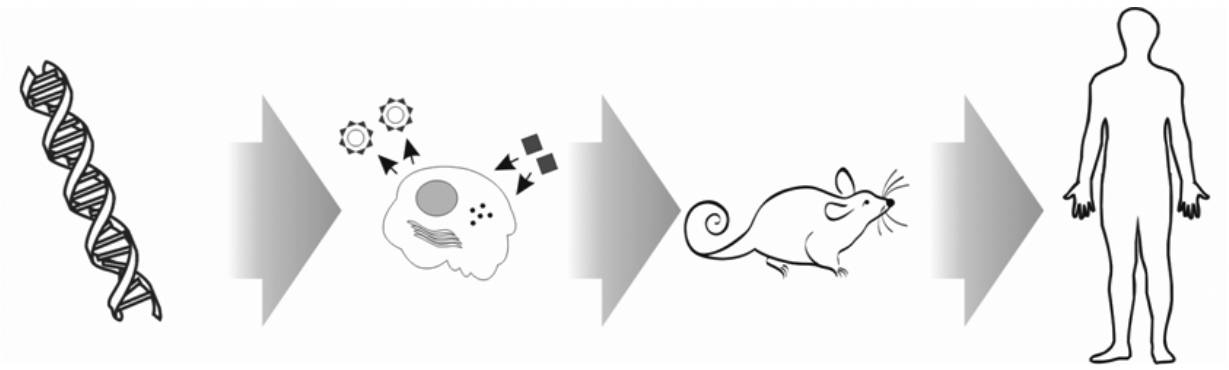


Figure 2: People with Type 1 Diabetes are Now Living Longer, Healthier Lives: Scientists examined the rates of premature death and complications 20-30 years after diagnosis with type 1 diabetes in Western Pennsylvania. Each line shows a survival curve for a group diagnosed over a 5-year interval. Compared 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
Research to identify genes, environmental triggers, and underlying mechanisms of disease development helps scientists find targets for therapy.	Knowledge about molecular pathways permits identification of drugs or other interventions to act on those pathways and intervene in the disease process.	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.	After pre-clinical development, agents are ready to be tested in human patients to see if they are effective.
			
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.	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.	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.	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.

PURSUIT OF SIX MAJOR SCIENTIFIC GOALS

The 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). 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/). 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*.

REFERENCES

1. Portuese E, Orchard T (1995). Mortality in Insulin-Dependent Diabetes. In *Diabetes in America* (pp. 221-232). Bethesda, MD: National Diabetes Data Group, NIH.
2. Laakso M (2001). Cardiovascular Disease in Type 2 Diabetes: Challenge for Treatment and Prevention. *J Intern Med.* 249:225-235.
3. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC, Rand LI, Christlieb AR, Bradley RF, Kahn CR (1987). Magnitude and Determinants of Coronary Artery Disease in Juvenile-Onset, Insulin-Dependent Diabetes Mellitus. *Am J Cardiol.* 59:750-755.
4. Dorman JS, Laporte RE, Kuller LH, Cruickshanks KJ, Orchard TJ, Wagener DK, Becker DJ, Cavender DE, Drash AL (1984). The Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Morbidity and Mortality Study. Mortality Results. *Diabetes.* 33:271-276.

US Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes & Digestive & Kidney Diseases

NIH Publication No. 05-5769
August 2007