

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

This report is prepared in response to Section 330B of the Public Health Service Act, as amended by the Medicare Improvement for Patients and Providers Act of 2008 (Public Law [P.L.] 110-275), which calls for the preparation of an evaluation report to the Congress on the *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program or Program)* established under that Section.*

The last decade has seen extraordinary progress in our understanding and treatment of type 1 diabetes—*Nature*, April 2010.¹

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 earned the investigators 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 and uniformly fatal disease to a chronic one.

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.²

Type 1 diabetes affects approximately 5 percent of the 18.8 million people in the United States diagnosed with diabetes.³ 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

* This report to Congress, submitted in December 2010, was supplemented with patient profiles and other ancillary material prior to printing. In order to prepare this evaluation to meet the statutory deadline, data collection on research progress was terminated in spring 2010.

¹ Reprinted by permission from Macmillan Publishers Ltd: *Nature* 464: 1293-1300, copyright 2010.

² Portuese E and Orchard T: Mortality in Insulin-Dependent Diabetes. In *Diabetes in America* (pp. 221-232). Bethesda, MD: National Diabetes Data Group, NIH, 1995.

³ Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011. Accessed from www.cdc.gov/diabetes/pubs/factsheet11.htm

effectively to insulin, and the pancreatic beta cells cannot secrete a sufficient amount of additional insulin to overcome this insulin resistance. It is important to note that 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 people with 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,⁴ heart disease risk is increased by up to 10-fold in people with type 1 diabetes compared to the general age-matched population.^{5,6} Importantly, the longer a person has type 1 diabetes, the greater the risk of developing complications, and the more severe, difficult-to-treat, and costly they can become. Especially worrisome are data showing that type 1 diabetes is being diagnosed at younger ages, suggesting that something in the environment is triggering early onset of disease in children. Early onset of type 1 diabetes can set the stage for a lifetime of living with and medically managing the disease complications.

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

Special funding for type 1 diabetes research, in the total amount of \$1.89 billion for Fiscal Year (FY) 1998 through FY 2013, was provided to the Secretary of the U.S. Department of Health and Human Services (HHS) through Section 330B of the Public Health Service Act. The

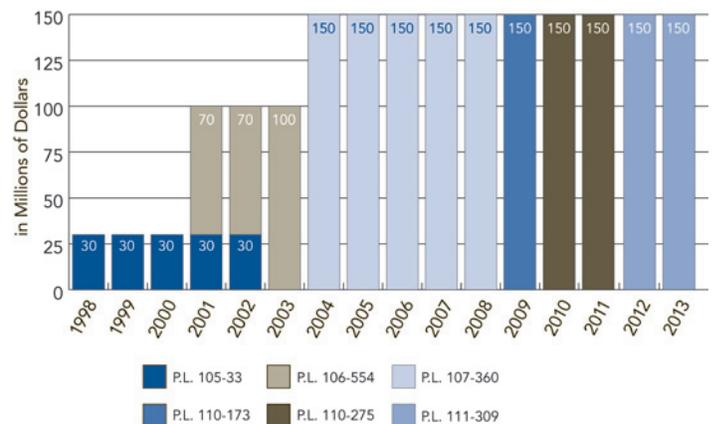


Figure 1: Special Diabetes Program Funding
Special Diabetes Program funding levels per year, Fiscal Year (FY) 1998-2011. The Special Diabetes Program was established by the Balanced Budget Act of 1997 (Public Law [P.L.] 105-33), and later extended by the FY 2001 Consolidated Appropriations Act (P.L. 106-554); the Public Health Service Act amendment relating to diabetes research (P.L. 107-360); the Medicare, Medicaid, and SCHIP Extension Act of 2007 (P.L. 110-173); the Medicare Improvement for Patients and Providers Act of 2008 (P.L. 110-275); and the Medicare and Medicaid Extenders Act of 2010 (P.L. 111-309).

Special Diabetes Program's original enabling legislation was the Balanced Budget Act of 1997 (P.L. 105-33), which was later amended by the FY 2001 Consolidated Appropriations Act (P.L. 106-554), the Public Health Service Act amendment relating to diabetes research (P.L. 107-360), the Medicare, Medicaid, and SCHIP Extension Act of 2007 (P.L. 110-173), the Medicare Improvement for Patients and Providers Act of 2008 (P.L. 110-275), and the Medicare and Medicaid Extenders Act of 2010 (P.L. 111-309) to extend the Special Diabetes Program in duration and funding levels (Figure 1).

This funding associated with the Special Diabetes Program augments regularly appropriated funds that the HHS receives for diabetes research through the House and Senate appropriations committees. The National

⁴ Laakso M: Cardiovascular disease in type 2 diabetes: challenge for treatment and prevention. *J Intern Med* 249: 225-235, 2001.
⁵ Krolewski AS, Kosinski EJ, Warram JH, et al: Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. *Am J Cardiol* 59: 750-755, 1987.
⁶ Dorman JS, Laporte RE, Kuller LH, et al: The Pittsburgh insulin-dependent diabetes mellitus (IDDM) morbidity and mortality study: mortality results. *Diabetes* 33: 271-276, 1984.

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), as well as the Centers for Disease Control and Prevention (CDC).

PURSUIT OF SIX MAJOR SCIENTIFIC GOALS

The *Special Statutory Funding Program for Type 1 Diabetes Research* and this evaluation report have been framed around 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. While significant progress has been made toward each of these Goals, research challenges still remain in each of these areas.

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

To achieve the ultimate goal of preventing and curing type 1 diabetes, it is imperative to understand the causes of the disease. A complex interplay of genetic and environmental factors underlies the development of type 1 diabetes. Not all genes that play a role are known, although many have been uncovered in recent years. For genes that are known, research is needed to elucidate the biological roles that those genes play in health and disease. Scientists think that in some people, genetic susceptibility—which can cause a person to be predisposed to the disease—is “triggered” by an environmental agent leading the body’s immune system to turn against itself. Potential environmental triggers may be infectious agents, dietary factors, environmental

toxins, and psychological stress. To date, no single trigger has been conclusively identified. Identification and study of 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. Research has suggested that preserving

patients' remaining beta cell function can have dramatic, long-term health benefits, and clinical trials are now testing the ability of agents to preserve beta cell function in people with newly diagnosed type 1 diabetes. Agents that are successful in preserving beta cell function in those newly diagnosed with type 1 diabetes can then be studied to determine whether they can prevent type 1 diabetes in those at high risk for the disease.

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 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 islet transplantation due to the toxicity associated with the required immunosuppressive drugs. Research is ongoing to improve this experimental procedure so that it may be a viable option for more patients. Scientists are also pursuing other strategies to replace beta cells, such as inducing any remaining beta cells in the pancreas to generate additional beta cells, or directing other pancreatic cell types toward becoming beta cells. For these approaches to be clinically useful, it is imperative to protect the newly formed beta cells from the same immune system attack that initially destroyed the patients' own beta cells.

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 or delay onset of 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. Linking glucose monitoring to insulin delivery—in essence, an artificial pancreas—could have a positive impact on patients' health and quality of life, and alleviate an enormous amount of patient burden.

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

Persistent elevation of blood glucose levels, despite insulin therapy, slowly damages the body's organs and can lead to life-threatening diabetes complications. Type 1 diabetes ravages nearly every part of the body: the heart, eyes, kidneys, nerves, lower limbs, mouth, and digestive and urologic systems. Insights into the underlying molecular mechanisms of these complications and new tools such as animal models and biomarkers to facilitate testing of therapeutic strategies are imperative for the development of new treatments. Until the prevention or cure of type 1 diabetes is possible, research toward preventing and treating the complications of the disease is critically important.

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; bioengineering; 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. Furthermore, the scientific community has experienced an explosion of emerging technologies that allow scientists to conduct research more efficiently and to ask questions that were previously impossible to answer. New technologies have already led to major discoveries and continue to hold great promise for advancing the type 1 diabetes research field.

SUPPORT OF RESEARCH TOWARD ACHIEVING THE SIX SCIENTIFIC GOALS

In the first years (FY 1998-2000), the *Special Diabetes Program* primarily supported initiatives to solicit research from individual independent investigators on topics of urgent and unmet research challenge. When the *Special Diabetes 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 Diabetes Program* enabled the initiation of these large, high-impact research efforts at

an unprecedented scale. 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 people with or at risk for type 1 diabetes. 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 the broad diabetes scientific community and beyond.

In addition to these major collaborative efforts, a large portion of the positive impact of the *Special Diabetes Program*-supported research comes from creative endeavors undertaken by excellent investigators working in small laboratories across the country, selected through a peer review, highly competitive process. The *Special Diabetes Program* has provided them with new key resources and solicited investigator-initiated research on topics of urgent and unmet need, such as development of artificial pancreas technology 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)."

The *Special Diabetes Program* has also served to catalyze burgeoning fields of research by bringing together scientists from across disciplines to address specific research challenges. Furthermore, the *Special Diabetes Program* has invested in training programs to ensure a future generation of clinical diabetes researchers. Overall, the funds have been deployed in a scientifically focused, but flexible, budgeting process that allows a rapid response to emerging research topics of critical importance.

HIGHLIGHTS OF SCIENTIFIC ACCOMPLISHMENTS

While important findings have already come from research supported by the Special Diabetes Program, it is anticipated that even greater benefits to the health and quality of life of people with type 1 diabetes 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.

Greatly Improved Prognosis for Americans with Type 1 Diabetes: Because of research progress over the last 2 decades, including research supported by the *Special Diabetes Program*, people with the disease are living longer and healthier lives than ever before and experiencing lower rates of disease complications. A recent study of the clinical course of type 1 diabetes concluded that starting intensive control of blood glucose as soon as possible after diagnosis greatly improves the long-term prognosis for patients. The study also found that the outlook for people with longstanding type 1 diabetes has greatly improved over the past 20 years due to a better understanding of the importance of intensive glucose control, as well as advances in insulin formulations and delivery, glucose monitoring, and the treatment of cardiovascular disease risk factors. These findings come from analyses of the long-term health outcomes for people who participated in NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and its ongoing, *Special Diabetes Program*-supported, follow-up study, the Epidemiology of Diabetes Interventions and Complications, which began in 1993. This study reinforced and extended the DCCT's initial findings that intensive blood glucose control dramatically reduces the risk of eye, kidney, and nerve damage due to diabetes. In particular, researchers found that, among DCCT participants who had received intensive glucose control during the trial, rates of vision loss and kidney failure had fallen to much lower levels than seen historically. Achieving and maintaining intensive glucose control is not easy for people with type 1 diabetes; the 21st century picture of clinical outcomes provided by this study can aid health care providers in discussing the tremendous health benefits of intensive control with their patients and reinforces the need for research to develop less burdensome approaches to help patients achieve these goals.

Newly Discovered Type 1 Diabetes Genes: Using new and emerging genetics technologies, scientists in the NIDDK-led and *Special Diabetes Program*-supported Type 1 Diabetes Genetics Consortium and their collaborators identified over 40 different genes or genetic regions that influence a person's risk of developing type 1 diabetes, bringing the total number of known regions to near 50—up from only three known genes a few years ago. Now, the challenge is to understand how those genes may influence disease development. Further research is ongoing to pinpoint the exact genes and understand their function in type 1 diabetes. Understanding the genetic underpinnings of type 1 diabetes can aid the ability to predict risk, as well as inform the development of new prevention and treatment strategies.

Adult Pancreas Cells Reprogrammed to Insulin-producing Beta Cells: Scientists in the NIDDK-led and *Special Diabetes Program*-supported Beta Cell Biology Consortium (BCBC) have made tremendous progress

in understanding beta cell biology toward the goal of developing cell-based therapies for diabetes. For example, in order to promote the formation of new beta cells, BCBC scientists are determining when and how certain pancreatic progenitor cells become “committed” to developing into specific pancreatic cell types and discovering flexibility in these cells. In one study, scientists made an exciting discovery that a type of adult cell in the mouse pancreas, called exocrine cells, can be reprogrammed to become insulin-producing beta cells. Using a genetically engineered virus and a combination of just three transcription factors, the researchers were able to reprogram some of the exocrine cells into beta cells. The newly formed beta cells produced enough insulin to decrease high blood glucose levels in diabetic mice. If the same type of approach can be developed to work safely and effectively in humans, this discovery could have a dramatic impact on the ability to increase beta cell mass in people with diabetes.

In another study, scientists uncovered plasticity in another pancreatic cell type—the alpha cell. Using genetic techniques in mice, the researchers increased the levels of a protein called Pax4, which is known to be involved in promoting cells to develop into the pancreatic beta cell type. They found that mice with high levels of Pax4 had oversized clusters of beta cells, which resulted from alpha-beta precursor cells and established alpha cells being induced to form beta cells. In addition, in a mouse model of diabetes, high levels of Pax4 promoted generation of new beta cells and overcame the diabetic state. In another study, BCBC scientists observed spontaneous conversion in beta cell-depleted mice of alpha cells to insulin-producing cells. These discoveries—that adult pancreatic cells have the potential to convert to beta cells—generate a fuller picture of pancreatic development and may pave the way toward new cell-based therapies for diabetes.

Hemoglobin A1c (HbA1c) Standardization Improves Care for People with Diabetes: HbA1c is a component of blood that is a good surrogate measure of long-term blood glucose control and, as such, reflects risk of diabetic complications. Clinical guidelines for controlling blood glucose to reduce diabetes complications set targets for control of blood glucose as assessed by this key test based on results from two landmark clinical trials: the DCCT for type 1 diabetes and the United Kingdom Prospective Diabetes Study for type 2 diabetes. To enable translation of these targets for control of blood glucose into common medical practice, the CDC and NIDDK, with support from the *Special Diabetes Program*, launched the HbA1c Standardization Program in 1998. This program improved the standardization and reliability in measures of HbA1c so that clinical laboratory results can be used by health care providers and patients to accurately and meaningfully assess blood glucose control and risks for complications. The standardization effort has been a great success and has facilitated national campaigns to improve control of blood glucose. As a result, the percentage of Americans with diabetes who had excellent glucose control increased from 37 percent in 1999-2000 to 56 percent in 2003-2004.⁷ The American Diabetes Association (ADA) built on the tremendous success of the HbA1c Standardization Program to set

⁷ Hoerger TJ, Segel JE, Gregg EW, et al: Is glycemic control improving in U.S. adults? *Diabetes Care* 31: 81-86, 2008.

treatment goals for glucose control in all forms of diabetes based on the test and has recommended HbA1c as a more convenient approach to diagnose type 2 diabetes.

New Glucose Monitoring Tools for Controlling Blood Glucose Levels: Research supported by the *Special Diabetes Program* contributed to the development of U.S. Food and Drug Administration (FDA)-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 intensive control necessary to prevent or delay disease complications. In addition, this technology, when linked to insulin delivery (known as an “artificial pancreas”), has the potential to have a further positive impact on patients’ health and quality of life, and alleviate an enormous amount of patient burden.

Novel Drugs for Treating Complications: The *Special Diabetes Program* has supported the development and clinical testing of new therapeutic agents for diabetic eye disease. For example, a recent comparative effectiveness research study, conducted by the National Eye Institute (NEI)-led Diabetic Retinopathy Clinical Research Network, found that a therapeutic called ranibizumab, in combination with laser therapy, was substantially better than laser therapy alone or laser therapy with a different drug, at treating diabetic macular edema, a swelling in the eye that often accompanies and aggravates diabetic retinopathy. Ranibizumab with laser therapy substantially improved vision among study patients, and could become the new standard of care for diabetic macular edema.

Advances in Islet Transplantation as a Therapeutic Approach for People with Type 1 Diabetes: The *Special Diabetes Program* supported the first islet transplantation trial in the United States using a procedure referred to as the “Edmonton protocol” that dramatically improved islet survival and rendered many patients insulin-free. Through the Immune Tolerance Network (ITN), which is led by the National Institute of Allergy and Infectious Diseases (NIAID), the *Special Diabetes Program* also supported the first international, multicenter trial of islet transplantation using the protocol. Additionally, research supported by the *Program* laid the foundation for an unprecedented islet transplant to an American airman, sparing him from a life-long insulin requirement after pancreatic damage from wounds suffered while serving in Afghanistan. Improved approaches to islet transplantation are important not only as an alternative to whole pancreas transplantation for treatment of type 1 diabetes but also to avoid diabetes through auto-transplantation after removal of the pancreas due to pancreatitis or injury. The *Special Diabetes 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 life-long immunosuppressive medication.

Promise of Therapies that Target Specific Lymphocytes in Preventing and Reversing Type 1 Diabetes:

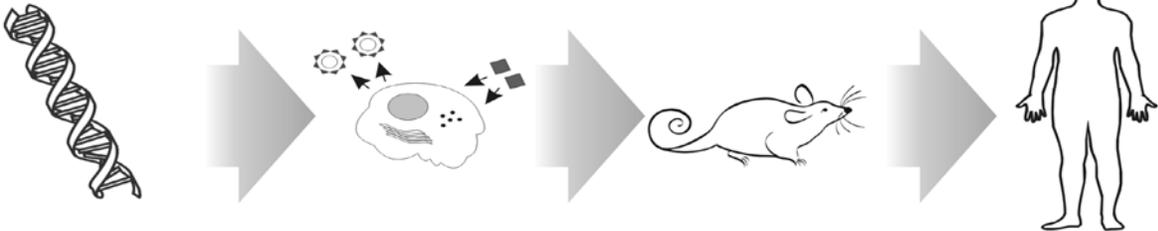
Previous clinical trials have suggested that preserving patients' remaining beta cell function can have dramatic, long-term health benefits. Researchers in NIDDK's Type 1 Diabetes TrialNet, which is supported by the *Special Diabetes Program*, reported that an immunosuppressive drug (rituximab), which destroys immune system cells called B lymphocytes, preserved the function of insulin-producing beta cells in people newly diagnosed with type 1 diabetes. Improved insulin production was maintained 1 year after the drug was administered, but the effect dissipated at 2 years. As drugs such as rituximab broadly deplete B lymphocytes, they can increase the risk of infection and therefore can have significant side effects. Nonetheless, the finding is very important because it will propel research to find drugs targeting the specific B lymphocytes involved in type 1 diabetes without the associated side effects of drugs like rituximab.

In another study, researchers in NIAID's ITN, also supported by the *Special Diabetes Program*, are building on an earlier study showing benefits of teplizumab, a humanized anti-CD3 monoclonal antibody that targets white blood cells known as "T cells" that are involved in the autoimmune attack on the beta cells. A pilot study of teplizumab showed that a single course of the antibody could delay progression of the disease over a 2-year period. The new trial is a larger follow-up study, in which two courses of the antibody are administered, 1 year apart, in an effort to extend its effects on beta cell preservation.

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

Building on findings from successful trials in newly diagnosed patients, TrialNet has developed a new paradigm: therapeutics demonstrated to be effective in new-onset patients are then tested for their prevention potential. One such prevention trial was recently launched with teplizumab, a monoclonal antibody engineered to alter the balance between destructive and protective T cells. Based on promising results in preserving beta cell function in patients newly diagnosed with type 1 diabetes, teplizumab is now being studied in relatives of people with type 1 diabetes, who are at 80 percent risk of developing type 1 diabetes over the next 5 years. This effort builds not only on the earlier success with teplizumab but also on the proven accuracy of tests to predict type 1 diabetes risk.

How Research Supported by the *Special Diabetes Program* Contributes to the Pipeline for New Therapies: The *Special Diabetes Program* supports type 1 diabetes research along a pipeline that facilitates the identification and development of new therapies. Examples of studies 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 help 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 humans to see if they are effective.</p>
			
<p>In addition to progress from investigator-initiated basic research studying underlying disease mechanisms, the Type 1 Diabetes Genetics Consortium and its collaborators have identified over 40 genes or genetic regions associated with type 1 diabetes, and The Environmental Determinants of Diabetes in the Young study completed enrollment of over 8,000 newborns and is following them until they are age 15 to study environmental triggers.</p>	<p>Studies on the immune system have led to the identification of promising agents targeting the autoimmune destruction of beta cells. The Diabetic Retinopathy Clinical Research Network identified a new therapy for diabetic macular edema that targets aberrant new blood vessel formation in the eye, a finding that was built on basic research on the molecular factors that play a role in that process.</p>	<p>Type 1 Diabetes-Rapid Access to Intervention Development and the Type 1 Diabetes-Preclinical Testing Program promote translation of research from the bench to the bedside by providing resources for pre-clinical development and testing 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>

How Type 1 Diabetes Research Benefits People with Other Diseases: Research supported by the *Special Diabetes Program* is far-reaching, benefiting not only

people with type 1 diabetes, but also people with type 2 diabetes and people 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 people with diabetes. In the same way, all people with diabetes gain from research directed at the disease complications that type 1 and type 2 diabetes share. Epidemiologic studies supported by the *Special Diabetes Program* are collecting data on both type 1 and type 2 diabetes in youth. Type 2 diabetes in youth is a growing epidemic—these data will aid the design and implementation of public health efforts to stop this alarming trend. The studies also found that children with rarer forms of diabetes are often misdiagnosed as having type 1 or type 2 diabetes and thus do not receive appropriate treatment. These results will benefit children with rarer forms of diabetes and improve their treatment. Emerging research also shows that factors in the immune system are not just important in type 1 diabetes, but are also involved in childhood type 2 diabetes and “hybrid” forms of diabetes that have characteristics of both type 1 and type 2 diabetes. Thus, research on the immune basis of diabetes broadly benefits children with diabetes.

Type 1 diabetes research also benefits people with other autoimmune diseases. Although many autoimmune diseases are rare, collectively they affect approximately 5 to 8 percent of the U.S. population.⁸ Some of the type 1 diabetes genes identified through research supported by the *Special Diabetes Program* affect the immune system and are involved in other autoimmune diseases. Therefore, understanding the genetic underpinnings of type 1 diabetes could provide insights into the genetics and pathogenesis of other autoimmune diseases. As therapies effective in type 1 diabetes may involve modulation of the immune system, these treatments could also be effective for other autoimmune diseases.

⁸ Accessed from <http://www3.niaid.nih.gov/topics/autoimmune>

Furthermore, clinical trials networks supported by the *Special Diabetes Program* are conducting “mechanistic” studies that examine how immune regulation is altered in type 1 diabetes. Understanding these defects may also shed light on other autoimmune diseases. Research could also uncover environmental triggers of celiac disease, a digestive disorder caused by autoimmunity directed at gluten proteins in wheat and other grains. Some genes confer susceptibility to both celiac disease and type 1 diabetes, and many people have both diseases. Studies supported by the *Special Diabetes Program* to identify environmental triggers of type 1 diabetes are also investigating celiac disease, which ultimately benefit patients suffering from both diseases.

PLANNING AND EVALUATION OF THE *SPECIAL DIABETES PROGRAM*

Planning Process: To ensure the most scientifically productive use of the *Special Diabetes Program* funds, NIDDK initiated a collaborative planning process that involves the participation of the relevant NIH Institutes and Centers, including the National Cancer Institute (NCI), National Center for Complementary and Alternative Medicine (NCCAM), 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), *Eunice Kennedy Shriver* 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 on Minority Health and Health Disparities (NIMHD), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), National Library of Medicine (NLM), NIH Office of Research on Women's Health (ORWH), and other NIH Institutes and Centers that are represented on the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC);⁹ and the CDC, Centers for Medicare & Medicaid Services (CMS), and other government agencies represented on the DMICC. The DMICC serves as an important venue for coordination and information sharing across the government, and DMICC members provide input on planning, implementation, and evaluation of the *Special Diabetes Program*.

The collaborative planning process also involves the two major diabetes voluntary organizations: Juvenile Diabetes Research Foundation International (JDRF) and American Diabetes Association (ADA).

Type 1 diabetes is an excellent model for a scientifically targeted and administratively 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 digestive and urologic tracts (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; the need for novel imaging technologies (NIBIB), specialized research

resources (NCRR), and data on disease incidence and prevalence in the United States (CDC); and services for pre-clinical testing of therapeutics (NCI). Thus, the *Special Diabetes Program* has catalyzed and synergized the efforts of a wide range of NIH and HHS components to combat type 1 diabetes and complications, making it a model trans-NIH and trans-HHS program.

Critical to the planning process is scientific input NIH has garnered from type 1 diabetes researchers and the broader research community. Sources of input include a variety of scientific workshops and conferences, as well as a series of planning and evaluation meetings to assess current research and future opportunities. At these planning and evaluation meetings, input was obtained from: distinguished scientists whom NIH convened in April 2000, to consider opportunities for allocations of *Special Diabetes Program* funds; a panel of scientific experts, who met in May 2002, to evaluate the use of the *Special Diabetes Program* funds and to assess opportunities for future research; a group 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 *Program* and identify future research opportunities; a panel of scientific experts who met in April 2008 to evaluate clinical research consortia supported by the *Special Diabetes Program* and indicate future research opportunities; and a group of scientific and lay experts who met in June 2009 to evaluate pre-clinical research consortia supported by the *Special Diabetes Program* and discuss future research opportunities. More information on the April 2008 and June 2009 meetings is found in the box.

⁹ For more information, please see: www.diabetescommittee.gov

Strategic planning, with broad external input, has also guided program planning. Two recent plans, “*Advances and Emerging Opportunities in Type 1 Diabetes Research: A Strategic Plan*” and “*Advances*

and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the DMICC,” are guiding type 1 diabetes research directions, including research supported by the *Special Diabetes Program*.

EXTERNAL EVALUATION OF ONGOING CLINICAL AND PRE-CLINICAL RESEARCH CONSORTIA AND NETWORKS SUPPORTED BY THE SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

Major components of this evaluation of the *Special Diabetes Program* are two *ad hoc* planning and evaluation meetings at which NIDDK convened panels of scientific and lay experts to obtain external input on the progress and future directions of ongoing research consortia and networks. Scientific judgment of these external experts on clinical and pre-clinical consortia supported by the *Special Diabetes Program* was sought at meetings in April 2008 and June 2009, respectively.

At both meetings, panelists were asked to provide input on current efforts and future directions for each consortium or network, as well as on future research opportunities outside the context of ongoing research programs. In particular, because the *Special Diabetes Program* is limited in time, the panel members were asked to provide input on future directions if the *Special Diabetes Program* is extended in time.

To frame the discussion, the panel members were asked to address questions for each consortium being evaluated, such as:

- Does the consortium address a compelling scientific opportunity?
- How might scientific progress of each consortium be improved?
- Are processes in place to modify consortium plans in response to new scientific discoveries?
- Are there opportunities to better use resources generated by the consortium to advance type 1 diabetes research?
- Are there additional opportunities for coordination of consortia with each other and with other efforts?

At the April 2008 meeting, an external panel of scientists with expertise in clinical trials, autoimmune diseases, immunology, transplantation, epidemiology, and biostatistics performed a mid-course assessment of ongoing clinical research efforts supported by the *Special Diabetes Program* and discussed possible future directions for the programs. After reviewing the clinical consortia portfolio, the panel members provided input that cut across multiple research efforts. They commended NIH and CDC on the many accomplishments that have been achieved through the clinical consortia supported by the *Special Diabetes Program* in such a short period of time and noted that the research portfolio that has been established under NIDDK’s leadership has been a very wise investment of funding.

At the June 2009 meeting, an external panel of scientific experts with expertise in beta cell biology, immunology, diabetes complications, and animal models, and a lay reviewer performed a mid-course assessment of ongoing pre-clinical research efforts supported by the *Special Diabetes Program* and discussed possible future directions for the programs. They were enthusiastic about the progress and accomplishments of the pre-clinical consortia supported by the *Special Diabetes Program*, and commended NIDDK and NIAID for their leadership of these consortia.

The input obtained at these evaluation meetings has been critically important for informing the government's program planning efforts for this time-limited appropriation. For example, at both meetings, panel members encouraged the government to enhance coordination across existing research consortia, to make the best use of existing resources and maximize research progress. One example of how coordination has been enhanced is through collaboration on a new clinical trial. Two research consortia—one with expertise in glucose monitoring technology and another with expertise in testing therapies for early treatment of type 1 diabetes—are collaborating on a clinical trial testing whether early and intensive blood glucose control at disease onset could preserve insulin production. In the trial, patients are placed on an inpatient closed-loop system and sent home with a sensor-augmented insulin pump. Thus, the combined expertise of the two consortia has been instrumental in enabling the conduct of this trial.

At the pre-clinical research meeting, the panel evaluated a consortium studying porcine to non-human primate models of xenotransplantation (solid organ, tissue, or cell transplantation between species). Panel members felt that the consortium's research was extremely valuable as an approach to relieve the shortage of solid organs for transplantation, but the research was less relevant to islet transplantation. Based on that feedback, the consortium is no longer supported by the *Special Diabetes Program*, but does continue to receive support from regularly appropriated funds for research on solid organ transplantation. Panel members at the clinical meeting felt that it was important to bolster research toward the development of an artificial pancreas. Based on this input, NIDDK developed new initiatives, with support from the *Special Diabetes Program*, to solicit research proposals from small businesses toward developing new technologies to inform development of an artificial pancreas. This example demonstrates how external evaluation led to a shift in use of the funds based on ongoing surveillance of scientific opportunities and how NIH has implemented input from the evaluation panels to enhance research supported by the *Special Diabetes Program*. The input received at these meetings continues to be invaluable as the government makes plans for future research directions.

Evaluation Process: The public laws providing funds for the *Special Diabetes Program* also mandate interim and final evaluation reports on the use of the funds. Initiatives pursued with the P. L. 105-33 funds were described in a 2000 report to the Congress.¹⁰ An interim report that describes research progress and opportunities that resulted from the *Special Diabetes Program* from FY 1998 through 2003 was published in April 2003.¹¹ Results from an evaluation of the *Special Diabetes Program* for FY 1998-2005 were submitted to the Congress in 2007.¹² The 2007 “*Evaluation Report*” described the collaborative, trans-HHS planning process that guides the use of the funds; the progress that had been achieved to date and the expected future accomplishments of the research programs and resources that had been established; and emerging research opportunities that resulted from the *Special Diabetes Program*. The final “*Evaluation Report*” presented here builds on the results reported in the 2007 “*Evaluation Report*” and describes advances, research programs, resources, and emerging opportunities that have resulted from the *Special Diabetes Program*.

Critical assessments of the planning and implementation processes, and of the scientific merit of the *Special Diabetes Program*, have been garnered through an evaluation process involving the external diabetes research community, as well as an internal review of archival data. Evaluation metrics used in this report include:

- **Research Accomplishments:** Review of scientific advances and technological developments that have had positive impacts on patients or enabled future

basic and clinical research. These data are primarily obtained from research publications, as well as from research advances included in “*Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the DMICC.*”

- **Professional Assessment:** Scientific judgment of external experts in the type 1 diabetes or related fields garnered from specific assessments of clinical and pre-clinical consortia supported by the *Special Diabetes Program* (see box earlier in chapter). Additionally, each individual consortium or project has ongoing assessment.
- **Bibliometric Analysis:** Compendium of *Special Diabetes 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 and stimulation of clinical research.
- **Input from Consortia Investigators:** Sample consortia investigators provided input on the importance and value of consortia supported by the *Special Diabetes Program*.
- **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 annual progress reports or meetings of external review committees.

¹⁰ www.niddk.nih.gov/federal/initiative.htm

¹¹ http://www2.niddk.nih.gov/AboutNIDDK/ReportsAndStrategicPlanning/Type_1_Diabetes_April_2003.htm

¹² www.t1diabetes.nih.gov/evaluation

ASSESSMENT MEASURES INDICATE THAT THE *SPECIAL DIABETES PROGRAM* HAS:

- Produced significant scientific advances with respect to each of the six overarching scientific Goals (see “Highlights of Scientific Accomplishments” earlier in this chapter), many of which were highlighted in “*Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the DMICC*” as major advances in diabetes research.
- Yielded robust scientific output with at least 2,793 scientific publications. A citation analysis found these papers cited at least 52,739 times in other publications (prior to January 1, 2010), demonstrating that research supported by the *Special Diabetes Program* is having far-reaching effects, and accelerating progress in type 1 diabetes research.
- Led to at least 38 issued patents, many of which have enabled new lines of research or have been further developed by industry for use in medical practice.
- Promoted development of resources for use by the broad scientific community, including over 40 animal models of type 1 diabetes that closely mimic various aspects of human complications of diabetes; 50 new lines of genetically engineered mice or mouse embryonic stem cells for the study of beta cell biology; 110 antibodies against markers expressed at different stages of stem cell to beta cell maturation; invaluable collections of human biological samples; databases; and protocols.
- Attracted new investigators to pursue research on type 1 diabetes: 38 percent of new research project grants (R01, R21, and DP2 mechanisms) went to new investigators, which is comparable with NIH-wide data for grant applications from new investigators.
- Fostered clinical research—over 63 percent of *Special Diabetes Program* funding supported clinical research—and propelled research progress to a point where several human clinical trials are being conducted through the infrastructure created by the *Special Diabetes Program*. Twenty-three grants supported by the *Special Diabetes Program* involved Phase III clinical trials, the final stage required before a therapy can be approved by FDA.
- Established key research programs that have been successful in providing new insights into the understanding of type 1 diabetes and its complications.
- Promoted translation of promising therapeutic agents from the 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.

