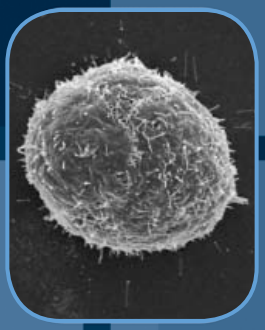
Special Statutory Funding Program for Type 1 Diabetes Research

Progress Report



Special Statutory Funding Program for Type 1 Diabetes Research

Progress Report

Charlotte Cunningham

"We had an incredibly positive experience with Charlotte's study. We were exposed to so many people who know so much about this disease—we learned so much!"

Says Lilo Cunningham, whose daughter Charlotte is participating in a trial conducted by the Immune Tolerance Network, in collaboration with Type 1 Diabetes TrialNet, to halt the destruction of the insulin-producing beta cells in people newly diagnosed with type 1 diabetes.

"The larger the pool of people they have to study, the more they can learn about combating the disease."

Says Toni Berg, explaining why it is important for families to participate in type 1 diabetes clinical research studies. Two of Toni and Rob Berg's three children have type 1 diabetes, which made the family eligible to participate in the Type 1 Diabetes Genetics Consortium. Thanks to the participation of the Bergs and over 2,800 other families, the Consortium has identified over 40 gene regions associated with type 1 diabetes.

The Berg Children

Nilia Olsen

"I would definitely recommend that others participate."

Says Sonya Olsen, whose daughter Nilia is enrolled in The Environmental Determinants of Diabetes in the Young (TEDDY), a study to identify triggers of type 1 diabetes in genetically susceptible individuals. The Olsen family moved because of Sonya's husband's military transfer, but the family has demonstrated their commitment to this important study by continuing to participate long distance.

"This technology is unbelievably helpful."

Says Leslie Burkhalter, talking about new continuous glucose monitoring (CGM) technology that her daughter, Casey, is testing as a participant in a study conducted by the Diabetes Research in Children Network (DirecNet). Casey's parents used to check her blood sugar every 2 hours at night, but they've been able to sleep better since Casey began testing the CGM.

Casey and Leslie Burkhalter

Gina Ferrari

"By giving Gina the opportunity to participate in your research study, you provided us with a tremendous training and learning experience, access to the latest technology, and made Gina feel as though she could do something important because of her diabetes."

Say Lori and Tom Ferrari, whose daughter Gina is enrolled in a study jointly conducted by Type 1 Diabetes TrialNet and DirecNet to determine whether early intensive glucose control can help preserve insulin production. The therapy includes introduction of a closed-loop system (a continuous glucose monitor linked to an insulin pump) at the onset of diabetes followed by real-time continuous glucose monitoring with use of an insulin pump.

"I believe a cure is coming, and if my family can help speed it up a bit by being part of an important study, all the better."

Says Dave Gould. Dave and his wife Ellen have eight children, four of whom have type 1 diabetes. By taking part in Type 1 Diabetes TrialNet, the family is dedicated to participating in research studies to be part of the search for a cure for type 1 diabetes.

The Gould Family

Overview of Type 1 Diabetes

Type 1 diabetes is a devastating illness that often strikes in infancy, childhood, or young adulthood, although disease onset can occur at any age. In people with type 1 diabetes, the immune system destroys 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. The cause of type 1 diabetes is not known, and there is currently no known way to prevent it.

People with type 1 diabetes, also known as juvenile diabetes, require daily insulin administration for survival. Every day, individuals with type 1 diabetes must check their blood sugar levels multiple times with finger sticks, monitor their food intake and physical activity levels, and administer insulin through repeated injections or a pump. Even the most vigilant patients are at risk for sudden, acute episodes of dangerously low or high blood sugar levels, either of which can be life-threatening in extreme cases. The constant burden of this disease greatly affects the quality of life of people with type 1 diabetes and their families.

Although life-saving, insulin therapy is not a cure. Despite efforts of patients to keep their blood sugar levels as close to normal as possible, persistent elevation of blood sugar levels slowly damages nearly all of the body's organs, including the heart, kidneys, nerves, and eyes. Diabetes complications can reduce the average life span by up to 15 years.

In addition to surveillance for diabetes across 5.5 million children, over 470,000 people—including people with diabetes, their relatives, and others at risk—have been involved in clinical studies supported by the *Special Diabetes Program.*

Seminal research findings and the development of new therapies and technologies over the last 2 decades have led to people with type 1 diabetes living longer, healthier lives than ever before. Rates of complications are lower than 30 years ago, and new technologies help manage the disease. These improvements demonstrate how research, much of which has been supported by the *Special Statutory Funding Program for Type 1 Diabetes Research (Special Diabetes Program)*, has directly improved the health and quality of life of people with type 1 diabetes.

The *Special Statutory Funding Program for Type 1 Diabetes Research*

Congress established this funding program to support scientific research on the prevention and cure of type 1 diabetes and its complications. The *Special Diabetes Program* supports many unique research programs that may not have been possible otherwise. This progress report, organized around six long-term goals for type 1 diabetes research, describes some of the major scientific advances that have been made possible by the *Special Diabetes Program*. It also describes progress made by the novel and collaborative research teams and clinical trials networks that have been established, as well as how the *Special Diabetes Program* supports type 1 diabetes research along a pipeline that has facilitated the identification and development of new therapies that are now being investigated in people. The contributions and importance of the participation of people with or at risk for type 1 diabetes in clinical research is enormous—their efforts clearly demonstrate the commitment to finding a cure for this disease and to helping others who are or may be diagnosed (see opposite page).

The *Special Diabetes Program* is a focused research effort that has fostered unique collaborations among the Institutes and Centers of the NIH, the CDC, and the broader research community, to accelerate the pace of research on type 1 diabetes.

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

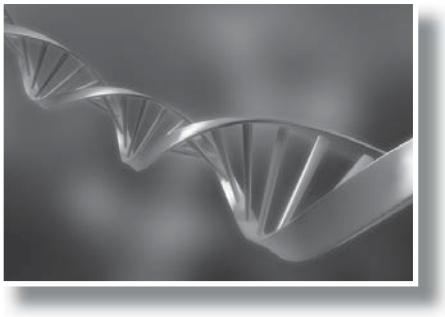
Research Challenges

To achieve the ultimate goal of preventing and curing type 1 diabetes, it is imperative to understand the causes of the disease. The development of type 1 diabetes results from a complex interplay of genetic and environmental factors. The likelihood that a person will develop the disease is higher the more closely related he or she is to someone who has type 1 diabetes. However, 80 percent of people with type 1 diabetes do not have close relatives with the disease.[1] Type 1 diabetes involves many genes that work in concert and can have both large and small effects. Researchers have made great strides in identifying these genes, but not all genes that play a role are known. If altered from their healthy state, the genes can cause a person to be predisposed to the disease. Scientists think that in some people, genetic susceptibility, "triggered" by an environmental agent, may prompt the body's immune system to turn against itself. These unknown environmental triggers may be dietary factors, environmental toxins, infectious agents, stress, or other factors. It is imperative to uncover these environmental triggers to develop approaches to prevent the disease.

Highlights of Research Progress Made Possible by the *Special Diabetes Program*

Discovered genes involved in type 1 diabetes: Research supported by the *Special Diabetes Program* resulted in an explosion of knowledge about the complex genetic underpinnings of type 1 diabetes. Just a few years ago, only three genes involved in the disease were known. Today, the Type 1 Diabetes Genetics Consortium (T1DGC) has identified more than 40 genes or gene regions that are involved in type 1 diabetes. This international effort, led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), includes 2,800 families with two or more siblings who have type 1 diabetes. Uncovering genetic contributors to type 1 diabetes is key to understanding the disease, identifying individuals at risk, developing and testing prevention strategies, and designing more specific clinical trials to test personalized interventions for patients with similar risk profiles.

In 2003, just three type 1 diabetes genes were known. Six years later, the Type 1 Diabetes Genetics Consortium has identified more than 40 genes or gene regions that are associated with the disease. This knowledge paves the way for developing new prevention and treatment strategies.



DNA double helix.

Expanded efforts to identify environmental triggers of the disease: The *Special Diabetes Program* also enabled major strides forward toward the goal of identifying environmental triggers of the disease. The Environmental Determinants of Diabetes in the Young (TEDDY) study has nearly completed its enrollment of over 7,000 infants at high genetic risk and is following these children until they are 15 years of age, collecting dietary and health data and stool, blood, and other samples. This NIDDK-led study represents tremendous progress toward amassing the most data and samples on newborns at-risk for autoimmunity and type 1 diabetes anywhere in the world. Identification of an environmental factor(s) that triggers disease can lead to a better understanding of type 1 diabetes and result in new strategies to prevent, delay, or reverse it.

[1] Dorman JS, McCarthy BJ, O'Leary LA, Koehler AN (1995). Risk Factors for Insulin-Dependent Diabetes In *Diabetes in America* (pp. 165-178). Bethesda, MD: National Diabetes Data Group, NIH.

Already, strategies to prevent type 1 diabetes, arising from earlier, smaller studies of environmental triggers, are being tested. The Trial To Reduce IDDM (insulin-dependent diabetes mellitus) in the Genetically At Risk (TRIGR), led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) completed recruitment of 2,160 newborns for a trial examining whether hydrolyzed infant formula compared to cow's milk-based formula decreases the risk of developing type 1 diabetes in at-risk children. In addition, NIDDK's Type 1 Diabetes TrialNet completed a pilot study testing effects of dietary omega-3 fatty acids on markers of risk for type 1 diabetes.

Collected national data on type 1 diabetes incidence, prevalence, and trends: Uniform national information on the percent or proportion of children with diabetes (prevalence), the rates of development of childhood diabetes (incidence), and whether these rates and the clinical course of diabetes in children and youth are changing over time, is essential to improve public health. Search for Diabetes in Youth (SEARCH), an ongoing study led by the Centers for Disease Control and Prevention (CDC), provided the first data on incidence and prevalence of diabetes in children in the U.S., reporting that an estimated 15,000 youth (age <20 years) are diagnosed with type 1 diabetes annually (incidence) and an estimated 154,000 youth in the U.S. had diabetes (type 1 and type 2) in 2001 (prevalence). Approximately 5.5 million children nationwide are under surveillance each year by SEARCH to estimate incidence rates of diabetes.

The Search for Diabetes in Youth study provided the first national data on rates of diabetes in children in the U.S., reporting that each year about 1 in 4,000 is diagnosed with diabetes. Approximately 15,000 youth develop type 1 diabetes each year.

Broad Implications of Research

Some of the genes identified by the T1DGC affect the immune system, and are involved in other autoimmune diseases as well as type 1 diabetes. Therefore, understanding the genetic underpinnings of type 1 diabetes could provide insights into the genetics and pathogenesis of other autoimmune diseases. Scientists already know that type 1 diabetes and celiac disease—an autoimmune disease where the immune system responds abnormally to dietary gluten—share many risk genes. For this reason, TEDDY is also investigating environmental triggers of celiac disease, which can benefit the one percent of the U.S. population suffering from this disease. The SEARCH study is collecting data on both type 1 and type 2 diabetes in youth. Type 2 diabetes in youth is a growing epidemic—SEARCH data will aid the design and implementation of public health efforts to stop this alarming trend. The study has also found that children with rarer forms of diabetes are often misdiagnosed as type 1 or type 2 diabetes and thus do not receive appropriate treatment. Therefore, results from SEARCH have also benefited children with rarer forms of diabetes.

Future Research Opportunities

Significant progress has been made related to genetic factors and environmental triggers of type 1 diabetes, setting the stage for pursuing future research and capitalizing on ongoing research.

- The identification of genes and gene regions associated with type 1 diabetes is an exciting finding. As the exact genes influencing disease are pinpointed, scientists can study their biological role in health and disease to find new targets for therapy for type 1 diabetes and other autoimmune diseases.
- TEDDY is a large-scale, long-term study in which follow-up is anticipated to continue through 2023. To capitalize on the substantial investment of time and resources identifying and studying at-risk newborns in TEDDY requires a long-term, coordinated study to follow these high-risk infants through childhood and adolescence when type 1 diabetes may become manifest. Identification of a dietary

or infectious cause of type 1 diabetes could have an enormously positive impact on public health through a diet change or vaccine for disease prevention.

- Ongoing trials are testing approaches to overcome possible environmental triggers of disease in at-risk children. For example, TRIGR is currently following children to determine if elimination of cow's milk formula can reduce development of type 1 diabetes.
- Now that SEARCH has completed the first baseline assessment of diabetes rates in children nationwide, the study is poised to evaluate trends in diabetes incidence and progression of the disease over time. This type of data provides unique information about vulnerable populations and is crucial to understanding type 1 diabetes at a public health level.

Goal II: Prevent or Reverse Type 1 Diabetes

Research Challenges

As the underlying causes of type 1 diabetes become better understood, strategies focused on intervening in the immune system's assault are emerging to prevent or reverse the disease. 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 to preventing the disease, it is important to identify ways to halt or reverse disease progression after onset. This could result in preservation or restoration of patients' insulin-producing capacity. Clinical trials have suggested that preserving patients' remaining beta cell function can have dramatic, long-term health benefits, and clinical trials with agents that modulate the immune system have shown efficacy in preserving beta cell function in people newly diagnosed with type 1 diabetes.

Highlights of Research Progress Made Possible by the *Special Diabetes Program*

Launched clinical trials on preventing and reversing type 1 diabetes: The *Special Diabetes Program* has enabled the establishment of unique and successful large-scale collaborative research groups and clinical trials networks to identify and test novel strategies for type 1 diabetes prevention and reversal. For example, NIDDK's Type 1 Diabetes TrialNet supports the development and implementation of clinical trials of agents aimed at preventing type 1 diabetes in people at risk for the disease and slowing disease progression in people who are newly diagnosed. To date, TrialNet has screened over 70,000 people for type 1 diabetes risk to identify those eligible for participation in ongoing and planned disease prevention trials and has launched five trials in those newly diagnosed with type 1 diabetes. In 2009, TrialNet reported that the drug rituximab preserved the function of insulin-producing beta cells. Improved insulin production was maintained 1 year after the drug was given to people newly diagnosed with type 1 diabetes. This drug has been approved by the U.S. Food and Drug Administration (FDA) for treatment of certain cancers and autoimmune disorders. Building on similar findings in other successful trials in newly diagnosed patients, TrialNet has planned a prevention trial with an agent called anti-CD3 that targets the immune system and has been shown to improve metabolic function in people newly diagnosed with type 1 diabetes. This led to the development of a new paradigm: therapeutics demonstrated to be effective in new-onset patients are then tested for their prevention potential.

TrialNet reported that the drug rituximab could preserve the function of insulin-producing beta cells in people newly diagnosed with type 1 diabetes. Previous clinical trials have suggested that preserving patients' remaining beta cell function can have dramatic, long-term health benefits.

TrialNet frequently collaborates with the Immune Tolerance Network (ITN), which is led by the National Institute of Allergy and Infectious Diseases (NIAID). The ITN is developing and testing novel therapies to induce "tolerance"— in which a short-term therapy re-educates the immune system so that it does not destroy the body's own cells—for the treatment of many autoimmune diseases, including type 1 diabetes. ITN has launched seven clinical trials in people newly diagnosed with type 1 diabetes, testing novel therapies to slow disease progression.

Improved methods to assess disease risk: Large numbers of people must be screened to identify appropriate participants for clinical trials testing type 1 diabetes prevention strategies. In a previous prevention trial (see Figure 1), scientists screened about 100,000 relatives of people with type 1 diabetes in order to enroll 372 into the study—a feat that is time- and resource-intensive. The *Special Diabetes*

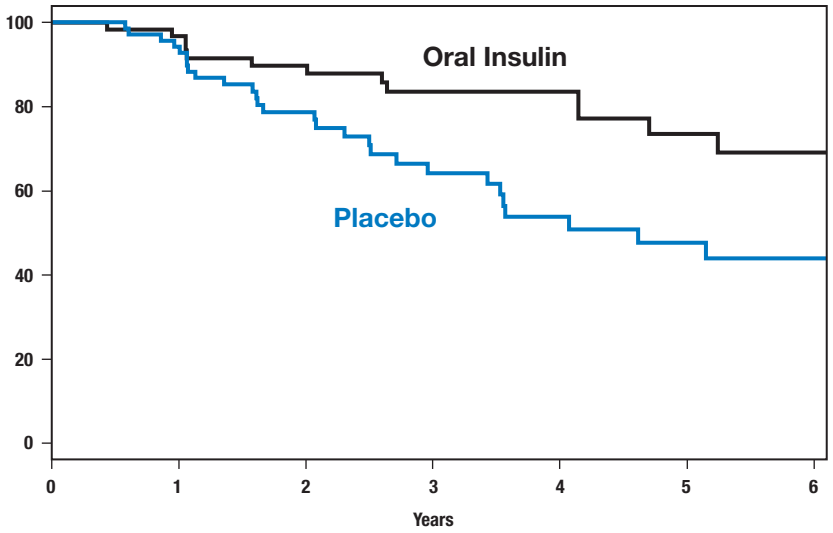


Figure 1: Type 1 Diabetes TrialNet is conducting a study to determine if oral insulin administration can prevent or delay type 1 diabetes in high-risk relatives of people with the disease who have high levels of antibodies against insulin. The trial is building on results from an earlier prevention trial that found no effect in the larger at-risk population studied but a substantial reduction in a subset of participants who had elevated levels of insulin autoantibodies, a pre-clinical marker of disease. This figure shows results from that analysis: a smaller proportion of people who received oral insulin (top line) developed diabetes than people who received placebo (bottom line) in people with high levels of anti-insulin antibodies. *Graph courtesy of Type 1 Diabetes TrialNet.*

Program supports a broad range of research to streamline this process by improving methods to assess risk and identify people who may benefit from prevention therapies. For example, research to improve predictive abilities includes studies to identify novel markers of the disease process, like the proteins recently discovered by Beta Cell Biology Consortium researchers (see Goal III); efforts to standardize measurements of these markers; and identification of new susceptibility genes (see Goal I). These efforts are not only important for improving the ability to conduct trials with fewer people, but are also critical for identifying at-risk individuals in the general population, so that as many people as possible can benefit if and when new prevention strategies are proven effective.

Created a pipeline for development of new therapeutics: Mouse models of type 1 diabetes have provided a key opportunity for pre-clinical study of potential therapeutic agents to delay or prevent type 1 diabetes. The *Special Diabetes Program* has enabled creation of national resources to distribute important mouse models, to conduct standardized pre-clinical testing of therapeutics in animal models, and to allow agents that are effective in animal models to be produced to meet the high standards required for clinical investigation.

Broad Implications of Research

As therapies effective in type 1 diabetes may involve modulation of the immune system, these treatments could also be effective for other autoimmune diseases. Although many autoimmune diseases are rare, collectively they affect approximately 5 to 8 percent of the U.S. population.[2] Furthermore, TrialNet and ITN 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. The more that is known about what goes awry with the immune system in type 1 diabetes, the greater is the opportunity that exists to advance treatments and cures for other diseases in which the immune system plays a role.

[2] http://www3.niaid.nih.gov/topics/autoimmune/

Future Research Opportunities

Research supported by the *Special Diabetes Program* has set the stage for identifying ways to prevent type 1 diabetes. Opportunities exist to build on the success to date, to make disease prevention or reversal a reality.

- There is a pipeline of promising new therapies for preventing and reversing type 1 diabetes, in large part due to basic and pre-clinical research supported by the *Special Diabetes Program*. Research opportunities exist to test these promising therapies through clinical trials networks, such as TrialNet and ITN, which have been established through support from the *Special Diabetes Program*. This ensures that the investment in basic research, as well as the investment to develop these existing networks, is fully utilized.
- Therapies demonstrated to be effective in people newly diagnosed with type 1 diabetes have the potential to prevent the onset of the disease. Therefore, it is critical to capitalize on successful trials in newly diagnosed patients and test these agents in prevention trials.
- Ongoing trials are testing approaches to prevent or slow progression of type 1 diabetes. These trials must be completed to determine if the approaches are effective.

Goal III: Develop Cell Replacement Therapy

Research Challenges

In type 1 diabetes, the body's immune system destroys the insulin-producing beta cells of the pancreas. Replacing the destroyed beta cells could be a cure for the disease. One strategy for replacing beta cells is islet transplantation, in which insulin-producing cells are taken from a deceased human donor and transferred into an adult patient. However, widespread use of this procedure is limited by several factors, including a shortage of available islets and the toxicity associated with the medicines given to prevent rejection of the transplanted cells. Scientists are also exploring other strategies to replace beta cells, such as coaxing 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.

Highlights of Research Progress Made Possible by the *Special Diabetes Program*

Launched clinical trials to improve islet transplantation: The NIAID's Immune Tolerance Network (ITN; see Goal II) completed the first multicenter clinical trial of islet transplantation, finding that restoring even partial islet function can improve a patient's post-transplant blood sugar control. Building on this success, the Clinical Islet Transplantation Consortium (CIT), collaboratively led by NIDDK and NIAID, has seven ongoing trials testing new strategies for improving islet transplantation. The NIDDK's Collaborative Islet Transplant Registry is collecting and disseminating data from the CIT and other islet transplant programs, to expedite progress and promote safety in this research field.

Contributed to unprecedented islet transplant: Research supported by the *Special Diabetes Program* laid the foundation for an unprecedented islet transplant to an American airman who was wounded while serving in Afghanistan. The airman's pancreas was damaged beyond repair by gunshot wounds, resulting in the need for removal of the entire pancreas. As complete removal of the pancreas results in insulin-dependent diabetes, the pancreas was transported from Walter Reed Army Medical Center in Washington, DC to a research team at the University of Miami. The researchers in Miami isolated and purified the islets from the airman's pancreas and sent the purified islets back to Walter Reed, where the cells were successfully infused into the patient's liver. This is the first known case of successful isolation and transplantation of insulin-producing cells following a severe trauma requiring complete removal of the pancreas. This advance is built on long-term NIDDK-supported research, including research supported by the *Special Diabetes Program*, on islet isolation, purification, and transplantation.

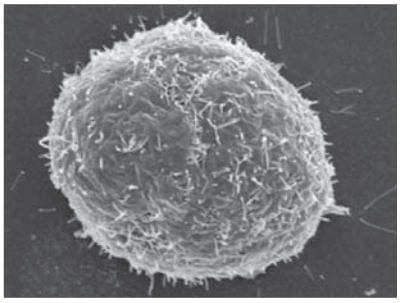
An American airman serving in Afghanistan received an unprecedented islet transplant using a procedure developed with support from the *Special Diabetes Program*.

Propelled scientific progress in beta cell biology and development: The NIDDK's Beta Cell Biology Consortium (BCBC) is studying ways to grow beta cells in the laboratory for transplantation into people and examining strategies to promote new beta cell formation in the pancreas. The BCBC has made numerous scientific discoveries and generated many research resources (*e.g.*, antibodies, mouse models) for use by the broad scientific community. BCBC scientists are making progress in understanding the steps necessary to turn stem/progenitor cells into insulin-producing cells, toward their goal of growing unlimited numbers of cells for use in people. They have also developed a mouse model in which

to study beta cell regeneration, as well as discovered that antibodies to a particular beta cell protein are an excellent marker for pre-clinical diabetes and greatly improve predictive abilities when combined with previously identified disease markers. Screening for the presence of these antibodies has already been incorporated into some ongoing clinical studies. These are just a few of the discoveries that have been made by this highly successful, collaborative group of researchers.

Scientists in the Beta Cell Biology Consortium have made numerous scientific discoveries toward the goals of growing beta cells for transplantation and promoting new beta cell formation in the pancreas.

Advanced knowledge and developed pre-clinical resources: Research conducted by two research groups led by the NIAID—the Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers) and the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG)—are advancing knowledge for the prevention and treatment of type 1 diabetes by investigating and improving animal models of type 1 diabetes. The Prevention Centers identified insulin as a primary target of the immune system's attack in a mouse model of type 1 diabetes, suggesting that autoimmune reaction against insulin may be a critical initiator of the pathway toward beta cell destruction.



Mouse pancreatic beta cell. *Image courtesy of Dr. George Harb.*

Fostered "bench to bedside" research toward goal of cell replacement therapy: The *Special Diabetes Program* vigorously supports "bench to bedside" research toward the goal of replacing insulin-producing beta cells. For example, researchers demonstrated that, in a mouse model of type 1 diabetes, treatment with an anti-inflammatory drug, called lisofylline (LSF), after islet transplantation protected the cells from recurrent destruction by the immune system. Building on these results, the CIT is now testing LSF in humans. The LSF being used in the trial was manufactured through the NIDDK's Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program, which helps scientists ready agents for testing in clinical trials. In another example, researchers in the NHPCSG demonstrated long-term survival of islets after transplantation when the animals were given a novel mixture of medicines that target the immune system. Based on these findings, the ITN approved a clinical trial to test this therapy in people with newly diagnosed type 1 diabetes, to determine if the medicines can slow progression of disease. The T1D-RAID program is generating the medicines for use in the clinical trial. These examples demonstrate how the *Special Diabetes Program* supports the discovery, manufacture, and testing of promising therapeutic agents—creating a robust pipeline of agents that have the potential to improve the health of people with type 1 diabetes.

Broad Implications of Research

Impaired function of the beta cells of the pancreas is central to both type 1 and type 2 diabetes. Thus, research on beta cell biology and development benefits people with both forms of the disease. Furthermore, the resources developed by the BCBC are not only used by members of the Consortium, but are also used by the broad scientific community, including researchers studying type 2 diabetes and pancreatic cancer. Research on islet transplantation could provide insights on transplantation of other organs, which can help people who undergo kidney, heart, liver, and other types of organ transplantation.

Future Research Opportunities

It is vital to build on the tremendous success to date so that safe and effective cell replacement therapy can become a reality for people with type 1 diabetes and cure their disease. Future research opportunities include:

- The CIT has seven ongoing trials, and it is important to complete the trials to determine which strategies work best. If safer methods for islet transplantation are discovered, more people could benefit from this promising therapy.
- Researchers have discovered many important steps needed to turn precursor cells into beta cells. With continued research, scientists will be able to grow beta cells in the laboratory, for ultimate use in clinical islet transplantation.
- BCBC and other researchers have made significant progress toward understanding how to generate new beta cells in the pancreas, but more work remains to be done. Additional research can build on these findings to identify approaches that work in people, as well as to gain a better understanding of the immune system to identify ways to protect newly formed beta cells from immune system destruction.

Goal IV: Prevent or Reverse Hypoglycemia

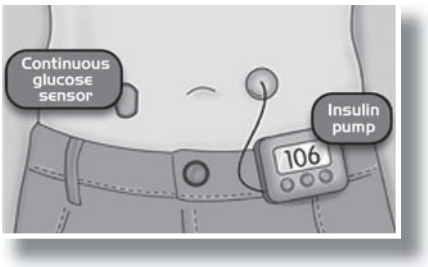
Research Challenges

Hypoglycemia, or episodes of dangerously low blood sugar, is the major obstacle to achieving the tight blood sugar control that has been proven to reduce the complications of type 1 diabetes (see Goal V). Thus, people with the disease must always walk a tightrope—balancing the immediate danger of hypoglycemia and the long-term risk of developing complications due to high blood sugar. The goal of research in this area is to help people achieve normal or near normal control of blood sugar levels with less burden and fewer episodes of hypoglycemia.

Highlights of Research Progress Made Possible by the *Special Diabetes Program*

Supported development of continuous glucose monitors and progress toward an artificial pancreas: With the knowledge that intensive blood sugar control reduces risk for diabetes complications, a high priority for research supported by the *Special Diabetes Program* has been the development of new tools to improve patients' ability to control their blood sugar levels. The *Special Diabetes Program* supported the development of recently approved continuous glucose monitors, which reveal the dynamic changes in blood sugar levels by assessing sugar levels hundreds of times per day and displaying trends. Alarms warn the patient if blood sugar becomes too high or too low. This revolutionary technology is a major advance in the treatment and management of type 1 diabetes by making it easier for patients to determine how much insulin or food they need to keep their blood sugar at healthy levels and by enhancing their ability to achieve tight blood sugar control. It is also improving the lives of parents of children with type 1 diabetes, who often wake many times a night to check their child's blood sugar levels. With a continuous glucose monitor, parents sleep better at night, knowing that the alarm will trigger if their child's blood sugar falls to dangerous levels. The *Special Diabetes Program* also supports research to "close the loop" by linking glucose monitoring to insulin delivery—what is often referred to as an "artificial pancreas." For example, grants have been awarded to small businesses to develop innovative technologies that may advance progress toward an artificial pancreas.

The *Special Diabetes Program* supported development of recent continuous glucose monitors, which are revolutionizing the way people with type 1 diabetes manage their disease.



Continuous glucose monitoring can identify variations and trends in blood sugar levels over time with much greater detail than traditional finger sticks.

Filled industry gap by testing new technology in children: A critical component to any new technology is evaluating how well it will work in the people who use it. The NICHD's Diabetes Research in Children Network (DirecNet) is filling an industry gap by testing new continuous glucose monitoring technology in children. DirecNet has yielded practical suggestions for people with diabetes and their caregivers to maintain healthy blood sugar levels more safely and effectively by managing diet and exercise.

Fostered behavioral research on utilization of new technologies: The *Special Diabetes Program* also supports research on the practical aspects of implementing new technology into clinical practice, including behavioral factors affecting use. This type of research is important to enhance the usability of new technology and help patients in their decision-making regarding diabetes control. This research will identify ways to assist patients to effectively use new technologies to benefit their health and quality of life.

DirecNet has yielded practical suggestions for people with diabetes and their caregivers to maintain healthy blood sugar levels more safely and effectively by managing diet and exercise.

Launched clinical trials to test new technologies: DirecNet is collaborating with Type 1 Diabetes TrialNet on a clinical trial testing whether early and intensive blood sugar control can protect patients' remaining insulin-producing beta cells from the toxic effects of high blood sugar. The trial participants are placed on a closed-loop system, linking blood sugar monitoring and insulin delivery, to intensively manage their blood sugar levels shortly after disease onset.

Broad Implications of Research

People with type 1 or type 2 diabetes must control their blood sugar levels to reduce their risk of developing disease complications. Thus, continuous glucose monitoring technology—and ultimately an artificial pancreas—may help people with both forms of the disease improve diabetes control and avoid the deadly consequences of hyperglycemia. Hypoglycemia is common in people with type 2 diabetes who are treated with insulin and other diabetes medications. Thus, new knowledge gained on ways to prevent or reduce hypoglycemia will help people with both forms of diabetes.

Future Research Opportunities

Continuous glucose monitoring technology is revolutionizing the way that patients manage their disease. It took many years between the funding of the first NIDDK grant related to the development of continuous glucose monitoring technology and clinical approval of the devices. Now, the pace of research to close the loop is more rapid due to support from the *Special Diabetes Program*.

- It is critical to go a step further and close the loop by linking glucose monitoring to insulin delivery—an artificial pancreas. An artificial pancreas could have a positive impact on patients' health and quality of life, and alleviate an enormous amount of patient burden. Importantly, artificial pancreas technology could help patients safely achieve the tight blood sugar control associated with preventing or delaying life-threatening disease complications. Thus, this technology has high potential to reduce patient burden and improve long-term health outcomes. To further accelerate the development of an artificial pancreas, there is close coordination among the National Institutes of Health (NIH), the Juvenile Diabetes Research Foundation International (JDRF), and the FDA. The NIH and JDRF fund research in this area, and the FDA advises researchers as they develop new technologies needed to make the artificial pancreas a reality and assists them as they design studies to evaluate safety and effectiveness.
- As new technologies are developed, it is important to continue to conduct behavioral research to help understand factors affecting its use. People of all age groups—from babies to adults—are burdened with type 1 diabetes, and each age group has different obstacles to overcome in managing their disease. New technology will only be beneficial if people know how to use it, so research on how best to utilize new artificial pancreas technology will be key toward moving this treatment strategy into practical use.

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

Research Challenges

Persistent elevation of blood sugar 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. In the U.S., diabetes is the leading cause of new cases of blindness in working age adults, nontraumatic lower limb amputations, and kidney failure.[3] Heart disease risk is increased by up to 10-fold in people with type 1 diabetes compared to the general age-matched population.[4] Type 1 diabetes is estimated to shorten the average life span by 15 years.[5] Until the prevention or cure of type 1 diabetes is possible, intensified research toward preventing and treating the complications of the disease is critically important.

Highlights of Research Progress Made Possible by the *Special Diabetes Program*

The *Special Diabetes Program* enabled the establishment of large-scale collaborative research groups that seek to understand and treat the complications of diabetes. Trials of therapies for complications are long and expensive, so few are conducted by the private sector. The *Special Diabetes Program* uniquely enables these trials, which have led to dramatic improvements in the lives of people with type 1 diabetes.

Demonstrated importance of intensive blood sugar control to prevent heart-related complications: The Epidemiology of Diabetes Interventions and Complications (EDIC) study is an ongoing follow-up effort to the NIDDK's landmark Diabetes Control and Complications Trial (DCCT) and is supported in part by the *Special Diabetes Program*. The DCCT demonstrated that intensive control of blood sugar levels can have long-lasting effects toward reducing the onset and progression of small blood vessel complications involving the kidneys, eyes, and nerves. In subsequent studies, EDIC found that intensive control could also prevent heart-related complications—the leading cause of death among people with diabetes. These findings have revolutionized management of type 1 diabetes and translated into dramatic health benefits. DCCT/EDIC and other researchers recently reported that improved control of blood sugar beginning as soon as possible after diagnosis can greatly improve the long-term prognosis of type 1 diabetes and result in reduced rates of complications. Thus, the fruits of research are paying off with respect to greatly improved outcomes for people with type 1 diabetes.

Research supported in part by the *Special Diabetes Program* has shown that improved control of blood sugar beginning as soon as possible after diagnosis can greatly improve the long-term prognosis of type 1 diabetes and result in reduced rates of complications.

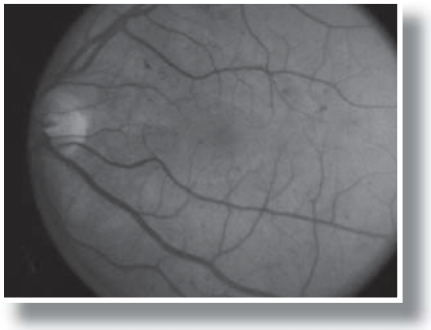
Improved blood sugar tests: An important component of achieving intensive control is the availability of the HbA1c blood test, which provides information about an individual's average blood sugar levels for the past 2 to 3 months. The *Special Diabetes Program* supports the CDC's Reference Laboratory for HbA1c

[3] Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: U.S. DHHS, CDC, 2008.
[4] Krolewski AS, et al. *Am J Cardiol*. 59:750-755, 1987; Dorman JS, et al. *Diabetes*. 33:271-276, 1984.
[5] Portuese E, Orchard T (1995). Mortality in Insulin-Dependent Diabetes In *Diabetes in America* (pp. 221-232). Bethesda, MD: National Diabetes Data Group, NIH.

and the National Glycohemoglobin Standardization Program (NGSP), which have been great successes and 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 sugar control and risks for complications. Building on this success, the American Diabetes Association recently recommended HbA1c as a more convenient approach to diagnose type 2 diabetes.

Launched clinical trials to combat diabetic retinopathy: Blindness is a debilitating complication of diabetes. Laser photocoagulation is an effective therapy to prevent progression of diabetic retinopathy to blindness, but the technique itself can lead to impaired vision. Thus, new therapeutic options are needed and are being tested in the Diabetic Retinopathy Clinical Research Network (DRCR.net). Led by the National Eye Institute (NEI), DRCR.net is facilitating multicenter clinical research on diabetic retinopathy, diabetic macular edema, and other associated conditions, and has launched 15 studies. One DRCR.net study demonstrated that intravitreal steroids, although effective in reducing diabetic macular edema, had considerable side effects and that standard laser treatment is still the treatment of choice. DRCR.net is also investigating intravitreal anti-vascular endothelial growth factor drugs and results from a major trial comparing this treatment with laser or the combination of laser and intravitreal steroids will be available in mid-2010.

DRCR.net is providing rapid, efficient, and thorough evaluation of treatments for diabetic retinopathy through community-based and university-based sites, as well as through collaborations with industry.



Human eye with retinopathy—a complication of type 1 and type 2 diabetes.

Identified genetic factors involved in diabetic complications: The *Special Diabetes Program* also supports studies of genetics related to diabetes complications. For example, studies from DCCT/EDIC led to the identification of a gene associated with HbA1c levels, which could be used to identify people at risk for poor blood sugar control. NIDDK's EDIC and Family Investigation of Nephropathy and Diabetes (FIND), and the JDRF's Genetics of Kidneys in Diabetes Study (GoKinD) have identified genetic factors that predispose people with diabetes to—or protect them from—developing complications in various organs. Identification of genes associated with diabetes complications could greatly improve understanding of the disease process, as well as provide targets for therapy.

Broad Implications of Research

Standardization of HbA1c testing is important for all forms of diabetes and is critical to early diagnosis, intensive control, reduced risk of complications, and improved outcomes. Building on the efforts of the CDC-led standardization program (see above), the NIH was able to launch a new campaign highlighting the importance of using accurate methods to test HbA1c in people who have sickle cell trait or other inherited forms of variant hemoglobin. This campaign assumes increased importance as HbA1c is used for diagnosis of diabetes as well as monitoring diabetes control.

Because hyperglycemia damages the eyes, kidneys, and nerves by the same molecular mechanisms in type 1 and type 2 diabetes, the important scientific and clinical accomplishments that emerge from research on complications may benefit individuals affected by both forms of diabetes. Studying complications of diabetes also provides new knowledge about many diverse organ systems including the heart, eyes, kidneys, and nerves. This additional knowledge could aid in preventing and treating diseases related to these tissues in the absence of diabetes.

Future Research Opportunities

Diabetes complications are a debilitating consequence of the disease, and future research can build on progress to date to ameliorate them.

- DRCR.net is actively pursuing the identification and design of important clinical trials that not only encompass a broad diversity of promising new therapeutic approaches, but also address the full spectrum of people with diabetic eye disease.
- The identification of genes associated with diabetes complications is an exciting finding. To capitalize on these results, scientists are studying the biological role of these genes in health and disease. Additional research on these genes and identification of new genes may allow physicians to predict which patients are at risk for developing specific complications, paving the way toward personalized prevention and treatment approaches.
- Research to identify biomarkers for early detection of cardiovascular disease and kidney disease may allow more intensive treatment to be targeted to people at risk for development of these complications.
- Through support from the *Special Diabetes Program*, researchers are already using animal models to test potential new therapies for the nerve damage that predisposes to amputation. Research to develop new animal models of diabetes complications will allow expanded testing of novel therapeutics for a broader range of complications.

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

Research Challenges

Type 1 diabetes affects many organ systems and involves diverse areas of science. Thus, it is imperative to pursue a broad range of research to have the greatest impact on the health of patients. Toward that end, it is important to recruit researchers with different areas of expertise and to promote collaboration to conduct research on type 1 diabetes. Furthermore, in recent years, 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.

New technologies applied to type 1 diabetes research have led to major scientific advances, including the identification of numerous genes associated with disease, the development of continuous glucose monitors, and progress toward imaging islets and autoimmunity in the pancreas.

Highlights of Research Progress Made Possible by the *Special Diabetes Program*

The *Special Diabetes Program* has enabled the development of research programs to attract creative and skilled scientists to study type 1 diabetes and to empower them by increasing access to cutting-edge tools and technologies. This research has generated significant progress. For example, using new genetics technology, the T1DGC has identified over 40 genes or gene regions associated with type 1 diabetes (see Goal I). Researchers supported by the *Special Diabetes Program* also contributed to the development of continuous glucose monitoring technology (see Goal IV), which is revolutionizing diabetes management.

Fostered research using "omics" technologies: Researchers supported by the *Special Diabetes Program* are using "omics" technologies to generate a system-wide picture of all of the molecules in a cell and how they are affected by type 1 diabetes. This includes determining the sequences and expression of all genes in a certain cellular context (genomics), mapping out all interactions of different proteins and how they are modulated in disease (proteomics), and following the path of all metabolic intermediates (metabolomics). For example, a new initiative supports research on "fine mapping" the newly discovered type 1 diabetes gene regions and studying the function of the genes. Researchers are using proteomics to elucidate beta cell function and to identify new proteins on the beta cell that may be targets of the immune system's attack. Research supported by the *Special Diabetes Program* demonstrated that, in mice, the trillions of bacteria that live in the gut may protect against the immune system attack that causes type 1 diabetes. Thus, knowledge stemming from the NIH Human Microbiome Project, which is identifying and characterizing the microorganisms found in the body, can be utilized to explore this fascinating new insight into type 1 diabetes. In fact, the samples that are being collected by TEDDY (see Goal I) could be analyzed with new technologies emerging from the Human Microbiome Project, to uncover potential environmental triggers of disease.

People have 10 times more microbial cells than human cells. Research supported by the *Special Diabetes Program* is investigating the role that bacteria in the gut and nose may play in the development of type 1 diabetes.

Supported research using new and emerging technologies: In other new and emerging technologies and areas of science, research supported by the *Special Diabetes Program* suggests that manipulating dendritic cells of the immune system is a promising strategy to prevent, delay, or reverse type 1 diabetes. Scientists are using small interfering RNA technology to identify target genes that promote type 1 diabetes and developing strategies for therapeutic application of small interfering RNA to turn off genes of interest. Also, bioengineers are working on artificial pancreas technology, and also trying to find ways to protect transplanted islets from immune system attack (*e.g.*, encasing cells in a protective barrier).

Attracted new scientists to type 1 diabetes research: The NIDDK recently employed a novel strategy to attract new scientists to type 1 diabetes research, through support by the *Special Diabetes Program*. Ten scientists who had not previously received an NIH grant successfully competed for Type 1 Diabetes Pathfinder Awards for highly innovative research studies. Their research spans a wide range of topics, from the development of a vaccine to prevent type 1 diabetes to methods that speed wound healing. Encouraging new researchers to study type 1 diabetes brings fresh talent to the field and promotes the careers of young scientists poised to make a difference in public health.

Supported the next generation of scientists: There is a long process of training and career development before a new independent investigator is ready to obtain grant support and lead a research laboratory. Through support from the *Special Diabetes Program*, a cadre of pediatricians specializing in childhood diabetes received such research training and career development. In 2009, the NIDDK utilized funding from the American Recovery and Reinvestment Act to build on that training infrastructure and conduct a summer research program for medical students. The diabetes-related research of the students was quite broad and ranged from basic laboratory studies to clinical studies to translational research involving epidemiology and health sciences research. Thus, the NIDDK has built on the infrastructure enabled by the *Special Diabetes Program* to support the next generation of diabetes researchers.

Broad Implications of Research

Technologies developed in the context of type 1 diabetes research can also advance research on other forms of diabetes as well as inflammatory and autoimmune diseases, which may share similar underlying mechanisms. Collaborations among bioengineers and pediatricians forged for the development of continuous glucose monitoring technology and an artificial pancreas will not only benefit people with all forms of diabetes but may also serve as a springboard for the application of engineering expertise to other biologic problems. Attracting new and talented scientists to research on type 1 diabetes may start them on a journey of discovery with far-reaching implications for medical research—a result that is a benefit to all people.

Future Research Opportunities

There are tremendous opportunities to use new technologies that have emerged in recent years toward prevention, treatment, and cure of type 1 diabetes:

- Unlike taking an X-ray to see a broken bone, there is no way to see to what extent the pancreas has been damaged in type 1 diabetes. Imaging inflammation, a response to the immune system attack,

holds promise as a means to allow scientists to visualize the extent of pancreatic damage and, potentially, to see directly if a therapy is effective. This could lead to smaller, shorter, and less expensive trials for both type 1 and type 2 diabetes, but additional research will help to achieve the goal of clinical use.

- Recent insights about the possible role of gut bacteria in protecting against type 1 diabetes are intriguing and prompt the question of whether bacteria-based treatments could prevent or treat the disease. Application of newly developed technology to study the microbiome of samples collected from newborns in the TEDDY study can explore this possibility, as well as propel metagenomic analysis to a broader study of human health.
- The recent identification of over 40 new genes and gene regions associated with type 1 diabetes opens the door to future research to understand how those genes influence disease. With application of small interfering RNA and other new technologies, the function of these genes in specific cells can be probed to develop novel prevention and treatment strategies.
- Historically, scientists have looked at individual genes or proteins to understand how they influence disease. This has been a useful strategy and led to revolutionary progress and new treatment approaches, but could be limiting—like looking at one piece of a puzzle. The era of "omics" technologies now provides researchers an opportunity to understand how networks of cellular components work together to produce a state of health and to identify key players that go awry in disease. Applying these "omics" technologies to type 1 diabetes gives us a chance to see the entire puzzle, facilitating a greater understanding of disease. For example, applying genomics/proteomics technologies to biosamples from people at risk for type 1 diabetes might be used to identify environmental triggers.
- Additional opportunities include: research in "biocomputing" to develop algorithms to link insulin pumps and glucose sensors; efforts to deliver genes and/or proteins to reprogram other cell types into beta cells; studies isolating distinct populations of immune cells (T cells) and determining their molecular signatures to identify people at risk; and further research utilizing small interfering RNA technology to study and potentially treat type 1 diabetes.

Summary

As described in this progress report, the *Special Diabetes Program* has contributed to significant and accelerated scientific progress that has made a tremendous impact on the health and quality of life of people 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. The outlook for people with type 1 diabetes has never looked better. However, disease management to reduce risk for complications places an enormous burden on patients and their families, so it is important to build on the progress to date to find ways to prevent and cure the disease. Research supported by the *Special Diabetes Program* sets the stage for doing just that.

The clinical course of type 1 diabetes mellitus, including its treatment, metabolic outcomes and long-term clinical complications, has changed dramatically in the past 20 years—*Archives of Internal Medicine*, July 2009

A Long-Term Investment in Research

Scientific progress does not happen overnight. Particularly for chronic diseases, a long-term investment in research can pay major dividends. For example, the landmark Diabetes Control and Complications Trial (see Goal V) began in 1983, but because it can take years or decades for diabetes complications to develop, it was not until 1993 that sufficient time had passed for the trial to prove that intensive blood sugar control reduced the risk of complications of the eyes, kidneys, and nerves. Because cardiovascular complications take even longer to develop, it was not until 2005—over 20 years since the start of the trial—that intensive control was found to reduce the risk for those complications. Although this trial took over 2 decades, its impact was far-reaching: it revolutionized type 1 diabetes management and led to greatly improved outcomes for people with the disease. Building on this success, the importance of glycemic control has been extended to type 2 diabetes, and multiple classes of medications for type 2 diabetes have been approved. It was only through this long-term investment in research, which included support by the *Special Diabetes Program*, that improvements in health were realized.

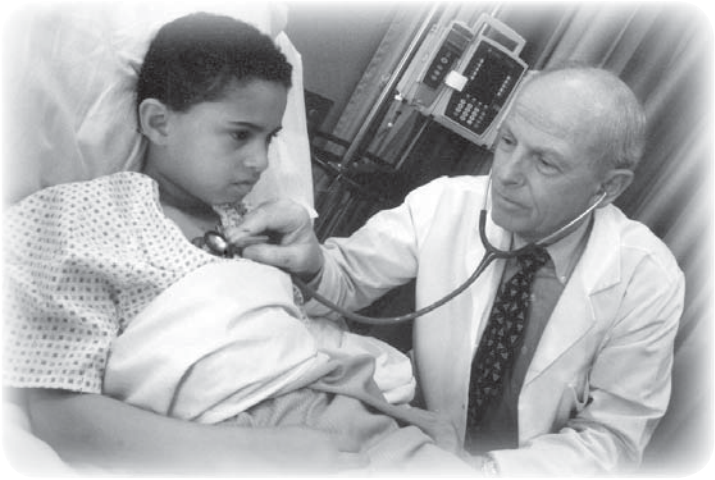
Similarly, many long-term efforts supported by the *Special Diabetes Program* are poised to contribute unprecedented new knowledge about type 1 diabetes. For example, TEDDY is following newborns until age 15, and is scheduled to continue until 2023. This long-term study can lead to the identification of environmental triggers of disease, which may in turn provide opportunities to develop interventions, such as a vaccine, to prevent the disease. This is just one example of the revolutionary new findings that are expected to emerge from the unique, long-term, collaborative research consortia supported by the *Special Diabetes Program*.

With continued research, it is possible to imagine that people could lead a life free of the burden of type 1 diabetes and its complications.

The Future of Type 1 Diabetes

With the remarkable progress already achieved through support from the *Special Diabetes Program*—and the promise of future research—we can speculate as to what type 1 diabetes may look like a few decades from now. By finding the genes and environmental factors that contribute to type 1 diabetes, researchers will have developed ways to identify those at risk at birth and safely prevent the disease, thereby eliminating new cases, and also developed ways to restore beta cell function in those with the disease. Knowledge about biological pathways controlling beta cell development will have led to ways to promote

growth of new beta cells in people with type 1 diabetes, and insights into the immune system will have made it possible to intervene in the immune attack to protect those new beta cells from destruction—effectively curing the disease. Knowledge of the molecular pathways by which blood sugar causes cell injury will have led to the development of medicines that prevent and repair the damage, preventing life-threatening disease complications. With continued research, it is possible to imagine that people could lead a life free of the burden of type 1 diabetes and its complications.



Special Statutory Funding Program for Type 1 Diabetes Research: Supporting Research Across NIH and HHS

Type 1 diabetes is a systemic disease that requires a multidisciplinary research approach and therefore is addressed by multiple components of NIH and the U.S. Department of Health and Human Services (HHS). The disease involves the body's endocrine and metabolic functions (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]) and immune system (National Institute of Allergy and Infectious Diseases); complications affecting the heart and arteries (National Heart, Lung, and Blood Institute), eyes (National Eye Institute), kidneys and urologic tract (NIDDK), nervous system (National Institute of Neurological Disorders and Stroke, National Institute of Mental Health), and oral cavity (National Institute of Dental and Craniofacial Research); the special problems of a disease diagnosed primarily in children and adolescents (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development); complex genetic (National Human Genome Research Institute) and environmental (National Institute of Environmental Health Sciences) factors; the need for novel imaging technologies (National Institute of Biomedical Imaging and Bioengineering); data on disease incidence and prevalence in the U.S. (Centers for Disease Control and Prevention); development of research resources (National Center for Research Resources); and services for pre-clinical testing of therapeutics (National Cancer Institute).

The *Special Diabetes Program* supports a spectrum of research within these NIH and HHS components, making it a model trans-NIH and trans-HHS program. In addition to the components listed above, the NIH Office of Research on Women's Health, NIH Office of Dietary Supplements, National Institute on Aging, National Center on Minority Health and Health Disparities, National Center for Complementary and Alternative Medicine, and National Institute of Nursing Research have also participated in the *Special Diabetes Program*. Selected highlights of research led by NIH Institutes and Centers and the CDC include:

National Eye Institute (NEI): In the U.S., diabetes is the leading cause of new cases of blindness in working age adults. To fight this debilitating complication, the NEI leads the Diabetic Retinopathy Clinical Research Network (see Goal V), a multicenter clinical research consortium on diabetic retinopathy, diabetic macular edema, and other associated conditions.

National Institute of Allergy and Infectious Diseases (NIAID): In people with type 1 diabetes, the immune system destroys the insulin-producing beta cells within the pancreas. Therefore, research related to the immune system could inform the causes, prevention, treatment, and cure of type 1 diabetes. The NIAID-led Immune Tolerance Network (see Goal II) is developing and testing novel immune therapies of type 1 diabetes. The Clinical Islet Transplantation Consortium (CIT; see Goal III), co-led by NIAID and NIDDK, is studying new strategies to improve islet transplantation, a potential cure for the disease. The NIAID's Cooperative Study Group for Autoimmune Disease Prevention (see Goal III) and Non-Human Primate Transplantation Tolerance Cooperative Study Group (see Goal III) are researching ways to modulate the immune system to protect beta cells, whether a patient's own cells or newly transplanted islets.

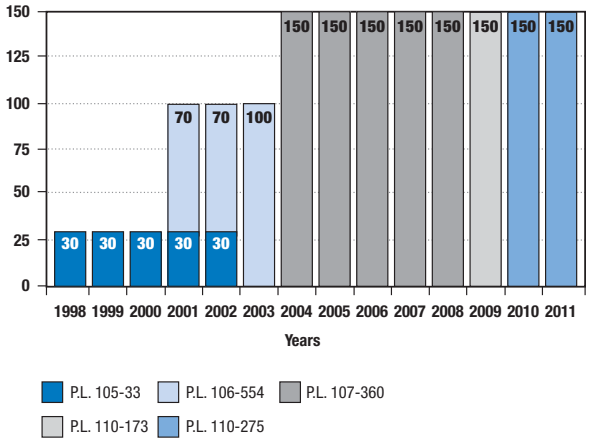
***Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD):** Type 1 diabetes often strikes in infancy, childhood, or young adulthood. NICHD leads the Diabetes Research in Children Network (see Goal V), which is testing new continuous glucose monitoring technology in children. NICHD also leads the Trial to Reduce IDDM in the Genetically At Risk (see Goal I), a prevention trial testing a possible environmental trigger of type 1 diabetes in infants.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): To identify the causes of the disease, the NIDDK leads the Type 1 Diabetes Genetics Consortium (see Goal I) and The Environmental Determinants of Diabetes in the Young (TEDDY; see Goal I). Programs led by the NIDDK are also aimed at determining ways to prevent or delay onset of type 1 diabetes (Type 1 Diabetes TrialNet; see Goal II) or to develop cures (Beta Cell Biology Consortium, CIT; see Goal III). Critical efforts addressing the complications of type 1 diabetes are also led by the NIDDK (Epidemiology of Diabetes Interventions and Complications, Family Investigation of Nephropathy and Diabetes; see Goal V).

Centers for Disease Control and Prevention (CDC): Uniform national information on people with type 1 diabetes is essential to improve public health. The CDC's Search for Diabetes in Youth study (Goal I) provided the first data on incidence and prevalence of diabetes in children in the U.S. and continues to monitor whether these are changing over time. The CDC also leads the Reference Laboratory for HbA1c and the National Glycohemoglobin Standardization Program, which have improved the standardization and reliability in measures of HbA1c (see Goal V).

Overview of the Special Statutory Funding Program for Type 1 Diabetes Research

www.T1Diabetes.nih.gov



Special funding for type 1 diabetes research, in the total amount of $1.59 billion for Fiscal Year (FY) 1998 through FY 2011, was provided to the Secretary of HHS through Section 330B of the Public Health Service Act. The original enabling legislation was the Balanced Budget Act of 1997 (Public Law [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); and the Medicare Improvement for Patients and Providers Act of 2008 (P.L. 110-275) to extend the *Special Diabetes Program* in duration and funding levels (see graph). In parallel with the *Special Statutory Funding Program for Type 1 Diabetes Research*, Congress established the *Special Diabetes Program for Indians* (SDPI), administered by the Indian Health Service, to address the growing problem of diabetes in those communities. The SDPI has led to substantial improvements in diabetes care in the population with the highest rates of diabetes in the U.S.

The *Special Diabetes Program* augments regularly appropriated funds that HHS receives for diabetes research. The NIDDK 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 NIH and the CDC.

Collaborative planning process: To ensure the most scientifically productive use of the funds from the *Special Diabetes Program*, the NIDDK initiated a collaborative planning process that involves the participation of numerous federal agencies represented on the statutory Diabetes Mellitus Interagency Coordinating Committee (www.diabetescommittee.gov). Also critical to the planning process is input that the NIDDK has garnered from type 1 diabetes researchers, the broad research community, and the two major diabetes voluntary organizations: the Juvenile Diabetes Research Foundation International and the American Diabetes Association. Sources of input include a variety of scientific workshops and conferences, as well as a series of planning and evaluation meetings in which the NIDDK convened panels of external scientific and lay experts to provide input on the *Special Diabetes Program* and future directions. The NIDDK has also spearheaded evaluations of the *Special Diabetes Program*, the most recent one published in August 2007 (www.t1diabetes.nih.gov/evaluation). The evaluation found that the *Special Diabetes Program* produced significant scientific advances, attracted new scientists to type 1 diabetes research, propelled research progress to a point where several human clinical trials are being conducted through infrastructure created by the *Special Diabetes Program*, and established key research programs that are providing new insights into the understanding of type 1 diabetes and its complications.

Collaborations among research programs: The research supported by the *Special Diabetes Program* spans a broad array of scientific areas, but also has common elements. To maximize research progress, the NIDDK facilitates coordination among research consortia with both overlapping and distinct interests. Coordination helps to prevent duplicative work by promoting the sharing of resources and methodology, and facilitating cross-disciplinary approaches and the pursuit of novel research directions.

Credits

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