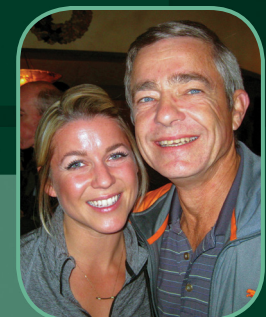
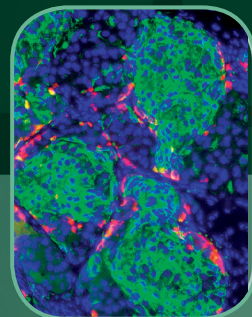
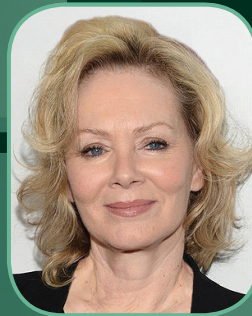


# Special Statutory Funding Program for Type 1 Diabetes Research

## *Progress Report*



## Front Cover Legend

Pictures on the cover include people and families affected by type 1 diabetes, volunteers in clinical trials supported by the Special Diabetes Program, and scientific images representing the exciting advances made in genetics, beta cell biology, and treatment of diabetic eye disease with funding from the Special Diabetes Program.

(Top to bottom; left to right)

- (1) Anastasia Albanese-O'Neill, with her husband Dan and children Cassidy and Jackson
- (2) An eye care professional examines a person's eyes for complications of diabetes, representing identification of new treatments for diabetic eye disease
- (3) Jean Smart
- (4) DNA double helix, representing the over 50 genes or gene regions associated with type 1 diabetes that have now been identified
- (5) Colby Clarizia, Frank Spesia, and researcher Dr. Steven Russell holding artificial pancreas technology
- (6) Insulin-producing beta cells (stained green) developed using a new method for large-scale production of beta cells in the laboratory. The red-stained cells are producing another hormone, glucagon, that also regulates blood glucose (sugar) levels, and the non-background blue stain indicates cell nuclei.
- (7) Ed Augustin and his daughter Jill

# Special Statutory Funding Program for Type 1 Diabetes Research

*Progress Report*





Ed Augustin and his daughter Jill

*“It’s so magnificent, a miracle, fantastic. Not only do I feel great, but my family, co-workers, friends...they’re feeling better because they don’t have to worry about me anymore.”*

Says Ed Augustin, describing how islet transplantation has changed his life. Ed participated in a clinical trial conducted by the Clinical Islet Transplantation Consortium for the treatment of type 1 diabetes in people with hypoglycemia unawareness and severe hypoglycemic events. Before the trial, Ed had frequent reactions to low blood sugar where he’d lose control and become completely disoriented, episodes that terrified not only Ed, but his family, friends, and co-workers as well.

*“Without research, there is no hope for prevention, for a cure, or for better treatments. For our family, it’s simple. Research equals hope.”*

Says Anastasia Albanese-O’Neill, talking about why it’s important for her family to participate in type 1 diabetes research studies. Research is truly a family affair: her daughter Cassidy has type 1 diabetes and participated in the SEARCH for Diabetes in Youth Study; her son Jackson is enrolled in The Environmental Determinants of Diabetes in the Young study; and Anastasia herself conducts research on the role of technology in type 1 diabetes management.



Anastasia Albanese-O’Neill, with her husband Dan and children Cassidy and Jackson



Jean Smart

*“Because of advances in diabetes care, I am standing here today.”*

Says Jean Smart in her testimony at the 2013 JDRF Children’s Congress hearing held by the Senate Special Committee on Aging. Jean described how type 1 diabetes care has dramatically changed for the better over her lifetime, including more accurate ways to test blood sugar levels and easier ways to administer insulin. Advances in diabetes management, including continuous glucose monitors and development of artificial pancreas technologies, have been supported by the *Special Diabetes Program*.

*“Participating in the bionic pancreas trial gave me true hope for a life without the everyday issues that type 1 diabetes forces upon people with diabetes. It was the first time I had felt hopeful for an (essentially) diabetes-free life since I was a little kid, and for the 5 days that I participated in the trial I was able to feel like I didn’t have diabetes. Those 5 days were easily some of the best days of my life,” says Frank Spesia.*



(L-R) Colby Clarizia, Frank Spesia, and Dr. Steven Russell

*“My time on the artificial pancreas resulted in exponentially better sugar control than I had ever been able to achieve on my own. The artificial pancreas provided a sense of confidence, security, and freedom that otherwise is difficult to find. It is very challenging to find words that sufficiently describe all that this device has provided for me already and will continue to provide once the device gains FDA approval,” says Colby Clarizia.*

Frank Spesia and Colby Clarizia were participants in a clinical trial testing artificial pancreas technology. Artificial pancreas technologies link a continuous glucose monitor to an insulin pump with a computer that calculates and instructs delivery of an appropriate amount of insulin; some systems also deliver glucagon through a second pump. This technology could relieve the burden of type 1 diabetes management, improve health, and greatly enhance quality of life.

# Achievements of the Special Diabetes Program

## Solving the Genetic Causes of Type 1 Diabetes

**Past:** In 2003, just three type 1 diabetes risk genes were known and little was understood about how these genes influenced the disease.

**Present:** More than 50 genes or gene regions associated with type 1 diabetes have been identified, and scientists are beginning to unlock how these affect the disease.

**Future:** An individual is screened at birth to determine whether they have risk genes and, if so, which risk genes they have. Based on their genetic makeup, a doctor is able to prescribe the appropriate prevention strategy to protect them from developing the disease.

## Developing Strategies to Replace Lost Beta Cells

**Past:** Researchers had just discovered loss of beta cells to autoimmunity as the underlying cause of type 1 diabetes. However, not enough was known to even consider ways to protect and replace beta cells.

**Present:** New methods for large-scale laboratory production of beta cells are being discovered, and researchers are investigating strategies to protect these cells from the autoimmune attack once implanted into people with the disease. Other approaches for regenerating beta cells are vigorously being studied, and innovative technologies for testing therapies are being developed.

**Future:** Scientists are able to generate sufficient quantities of beta cells, implant them into a person with type 1 diabetes, and protect the newly transplanted beta cells from the autoimmune attack. Alternatively, beta cells remaining in the pancreas of a person with type 1 diabetes are stimulated to replicate, or other types of pancreatic cells are stimulated to convert to beta cells to repopulate beta cell mass. These new cells are also protected from the autoimmune attack. Restoring beta cell function in a person with type 1 diabetes eliminates the need for insulin and prevents the complications of the disease.

## Creating New Devices for Blood Sugar Control

**Past:** People with type 1 diabetes had limited choices for managing their disease and no access to real-time data on their blood sugar levels, putting them at risk for life-threatening episodes of dangerously low blood sugar (hypoglycemia) and other complications of poor blood sugar control despite the significant burden on them to take care of their health.

**Present:** Better formulations of insulin and insulin administration devices, and continuous glucose monitors, a revolutionary technology that provides real-time data of blood sugar levels, are approved by the U.S. Food and Drug Administration (FDA). Artificial pancreas technologies, which link a continuous glucose monitor to an insulin pump, have demonstrated ability to improve blood sugar levels and reduce episodes of hypoglycemia, but are only available to participants in clinical studies for a limited time.

**Future:** Several artificial pancreas technologies are FDA-approved, allowing people and their healthcare providers to choose the technology that best suits their needs and lifestyle. People with type 1 diabetes are relieved of much of the burden of managing the disease and more easily achieve blood sugar levels demonstrated to prevent complications.

## Realizing New Therapies for Diabetic Eye Disease

**Past:** About 90 percent of people with type 1 diabetes developed diabetic eye disease within 25 years of diagnosis. Studies had not proven the value of laser surgery in reducing blindness.

**Present:** Laser treatment is proven to be an effective therapy to prevent progression to blindness, but the technique itself can lead to impaired vision, and it does not improve vision. Anti-VEGF therapy is shown to improve visual acuity in people with diabetic macular edema, dramatically changing clinical practice and improving quality of life for people with type 1 diabetes.

**Future:** Due to the development of new technologies to manage type 1 diabetes, people are better able to control their blood sugar levels and fewer develop diabetic eye disease. In those who do, doctors are able to personalize treatment based on the severity of their disease, providing people with options.

### Testing Novel Treatment for Kidney Disease

**Past:** About one in four people developed kidney disease within 25 years of a type 1 diabetes diagnosis. Doctors could not detect early kidney disease and had no tools for slowing its progression to kidney failure. Survival after kidney failure was poor, with 1 in 10 people dying each year.

**Present:** Blood sugar and blood pressure control and specific antihypertensive drugs prevent or delay kidney disease, but rates remain high. The inexpensive, generic medication allopurinol is being tested for kidney function preservation in people with type 1 diabetes.

**Future:** Due to the development of new technologies to manage type 1 diabetes, people are better able to control their blood sugar levels and fewer develop diabetic kidney disease. People at particular risk for kidney disease are identified early, and personalized treatment reduces the development of kidney disease.

### Improving Longevity of People with Type 1 Diabetes

**Past:** Before insulin, people with type 1 diabetes did not live beyond a year or two of diagnosis. With the discovery of insulin, many people lived into adulthood, but with markedly decreased life expectancy.

**Present:** Long-term survival of those with type 1 diabetes has dramatically improved. On average, life expectancy is 15 years less than the general population, but there have been steady gains over each successive decade. People with high socioeconomic status, with access to excellent medical care, have a life expectancy similar to the general population.

**Future:** As new products to manage the disease and/or strategies for prevention or reversal of type 1 diabetes become a reality, people with or at risk for type 1 diabetes will have normal life expectancy and improved quality of life.

## 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 individuals 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 people with type 1 diabetes 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.

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 consortia and clinical trials networks established with *Special Diabetes Program* funding; how the *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; and new therapies that have been proven effective with *Program* support and are being implemented in clinical practice. 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 a strong commitment to finding a cure for this disease and to helping others who are or may be diagnosed.

**Much of the progress in type 1 diabetes research is due to the unwavering commitment of people with diabetes, their relatives, and others at risk who participate in clinical research studies supported by the *Special Diabetes Program*.**

**The *Special Diabetes Program* is a focused research effort that has fostered unique collaborations among the Institutes and Centers of the National Institutes of Health, the Centers for Disease Control and Prevention, 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. Type 1 diabetes involves many genes that work in concert and can have both large and small effects. 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.

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

### Discovered and gained novel insights about the functions of 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 decade ago, only three genes involved in the disease were known. Today, more than 50 genes or gene regions that are involved in type 1 diabetes have been identified, in part due to an international effort led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Uncovering genetic contributors to type 1 diabetes is key to understanding the disease; to identifying individuals at risk who may benefit once a prevention strategy is discovered and who may be eligible to participate in clinical trials testing prevention strategies; and to ultimately allowing for precision medicine—where doctors can prescribe a specific prevention or treatment strategy based on the individual’s genetic makeup.

Research supported by the *Special Diabetes Program* has employed cutting-edge techniques to identify novel type 1 diabetes-associated genetic regions. Recent efforts include creation and use of the ImmunoChip, which allows comparisons of genetic risk profiles from multiple immune diseases, and gene-based pathway analysis, an approach that incorporates information about gene function to narrow gene regions to putative causal genes. Knowing the full catalog of genes that affect type 1 diabetes will enable examination of how genes associate both with susceptibility to environmental risk factors and with response to treatments.

*Special Diabetes Program*-supported scientists are now working to pinpoint the precise risk-contributing factors and to determine the functional consequences of these loci to inform the development of preventative or therapeutic strategies. For example, researchers finely mapped a gene region previously associated with risk for type 1 diabetes and discovered that the risk was associated with turning down the *DEXI* gene. Other scientists determined the specific amino acid changes in human leukocyte antigen molecules that drive type 1 diabetes risk; this may help the design of potential new therapeutic approaches. Studies of a risk candidate gene, *cathepsin H*, revealed that it is an important regulator of beta cell function, shedding light on how a risk gene affects disease progression. Rare risk variants in the *PTPN22* gene were identified, and scientists showed that one of these variants led to an altered form of the protein that competes with the normal form. These new insights into how type 1 diabetes susceptibility genes play a role in the disease may yield new therapeutic targets and opportunities to personalize therapies.

**Expanded efforts to identify environmental triggers of the disease:** The *Special Diabetes Program* also enabled major strides toward the goal of identifying environmental triggers of the disease. The Environmental Determinants of Diabetes in the Young (TEDDY) study is following over 6,000 infants at high genetic risk until they are 15 years of age, collecting dietary and health data and stool, blood, and other samples. This international, NIDDK-led study represents tremendous progress; it has amassed the most data and samples ever collected on newborns at risk for autoimmunity and type 1 diabetes, and is now analyzing over 60,000 biosamples from children who developed autoimmunity or type 1 diabetes and comparing them to carefully matched children who have not developed the disease. Studies are under way to identify biomarkers predictive



of autoimmunity and type 1 diabetes. These studies include analyses of the gut microbiome (the microorganisms that populate the digestive tract), as well as virome (studies of viruses), genes, gene expression, proteins, and metabolites (products of metabolism). Microbiome research in TEDDY is also shedding light on the broader development of the microbiome as TEDDY is one of the largest studies of the microbiome in children. TEDDY is also comparing outcomes in newborns with the same genetic risk in different regions of the United States and in Europe to elucidate the role of geographic differences. Identification of an environmental factor(s) that triggers or protects against disease can lead to a better understanding of type 1 diabetes and result in new strategies to prevent, delay, or reverse it.

Already TEDDY studies have suggested a potential association between early probiotic supplementation (prior to 1 month of age) and reduced risk of islet autoimmunity in children with the highest genetic risk of type 1 diabetes—a finding that requires further investigation. TEDDY is also demonstrating the importance of monitoring high-risk children: close follow-up of children in the study enables early detection of their type 1 diabetes, and participation in the study is associated with reduced risk of diabetic ketoacidosis—a life-threatening complication—at diagnosis.

Strategies to prevent type 1 diabetes, arising from earlier, smaller studies of environmental triggers, are also 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) is following 2,160 newborns to determine whether hydrolyzed infant formula, compared to cow's milk-based formula, decreases the risk of developing type 1 diabetes in at-risk children. Small early studies suggested that cow's milk played a role in the development of type 1 diabetes. While the larger study is still assessing the effect of cow's milk on development of type 1 diabetes, it has definitely disproved a role for cow's milk in islet autoimmunity.

**Improved methods to assess disease risk:** The ability to assess accurately those at risk for type 1 diabetes is critical for identifying individuals in the general population, so that as many people as possible can benefit if and when new prevention strategies are proven effective. Accurate risk assessment is also essential for the design of studies to prevent or delay the disease, as these studies involve children and interventions with some potential for adverse effects. The *Special Diabetes Program* has supported a broad range of research to improve methods to assess risk and, as a result, today blood tests can accurately identify relatives of people with type 1 diabetes who are at high or moderate risk of developing the disease within 5 years by the presence or absence of specific autoantibodies. In the future, risk assessment will take into account an individual's genetic makeup and their environmental exposures to determine risk even before autoantibodies appear.

Data from both TEDDY and the Type 1 Diabetes TrialNet's Pathway to Prevention Study have led to improved risk classifications and dramatically changed understanding of the development of type 1 diabetes. TEDDY data revealed that autoantibodies predictive of type 1 diabetes can occur in children as early as 3 months of age, and that the order of appearance is related to the specific types of *human leukocyte antigen* genes the child has. Data from the Diabetes Prevention Trial-Type 1 (DPT-1) showed that the rate of onset of autoimmunity declines with age; this finding led researchers to suggest that screenings to identify those at risk could start in early childhood and continue through early adolescence, a recommendation that could have clinical implications once preventative therapies

**The Environmental Determinants of Diabetes in the Young study enabled major strides toward the goal of identifying environmental triggers of type 1 diabetes, which can lead to a better understanding of the disease and may result in new strategies to prevent, delay, or reverse it. In addition, the study has amassed the most data and samples ever collected on newborns at risk for autoimmunity and type 1 diabetes, and is one of the largest studies of the microbiome in children.**

**Data from both The Environmental Determinants of Diabetes in the Young study and Type 1 Diabetes TrialNet's Pathway to Prevention Study have led to improved risk classifications and dramatically changed understanding of the development of type 1 diabetes, leading to a recommendation for a new type 1 diabetes staging classification in at-risk individuals that provides a framework for the research and development of preventative therapies.**

have been identified. The DPT-1 Risk Score has now been studied using TrialNet Pathway to Prevention Study data and has been found to improve type 1 diabetes risk classification accuracy. Researchers from TrialNet also generated data for the use of intermediate endpoints in diabetes prevention, rather than progression to the disease itself. This will allow smaller, earlier prevention trials to screen promising new therapies more rapidly.

**The Search for Diabetes in Youth study determined that an estimated 167,000 youth in the United States had type 1 diabetes in 2009, an increase of over 21 percent in 8 years.**

Data from the NIDDK-supported DPT-1, TEDDY, TrialNet, and other studies demonstrated that progression to type 1 diabetes proceeds through distinct stages, allowing identification of type 1 diabetes before symptoms appear. This forms the basis for a new recommendation from JDRF, the Endocrine Society, and the American Diabetes Association for a type 1 diabetes staging classification in at-risk individuals that provides a framework for the research and development of preventive therapies. TrialNet will begin piloting use of finger sticks to collect blood for antibody screening, which could greatly increase the number of and ease with which children are screened for risk of type 1 diabetes.

### **Collected and reported 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) and NIDDK, provided the first data on prevalence of diabetes in children in the United States in 2001. SEARCH recent data revealed that an estimated 167,000 youth (age < 20 years) in the United States had type 1 diabetes in 2009, an increase of over 21 percent in 8 years. This increase in prevalence is likely explained by an increase in the number of youth who were annually diagnosed with type 1 diabetes. Indeed SEARCH found that, from 2002 through 2012, the incidence of type 1 diabetes increased by 1.8 percent per year. Hispanic youth experienced the highest increase (4.2 percent per year). SEARCH has also demonstrated that diabetes complications are present at an early age and a short duration of diabetes, and their burden is higher in minority youth. SEARCH continues to provide critical information on patterns of care and data on development of complications in youth with type 1 diabetes. Approximately 5 million children nationwide are under surveillance each year by SEARCH to estimate incidence rates of diabetes.

### **Broad Implications of Research**

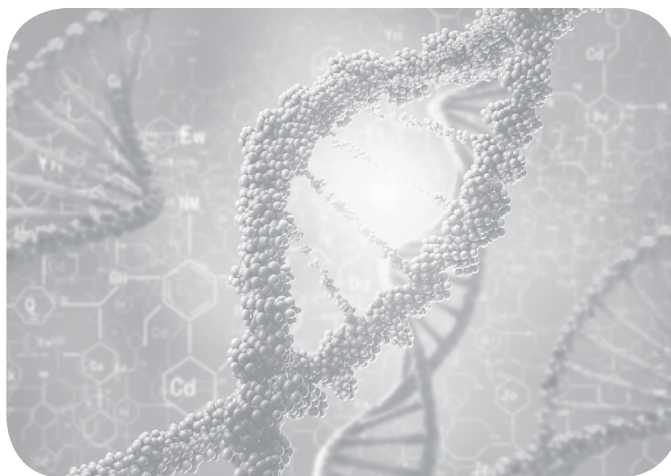
Some of the genes identified by *Special Diabetes Program* researchers affect the immune system, and are involved in other autoimmune diseases in addition to type 1 diabetes. Therefore, understanding the genetic underpinnings of type 1 diabetes could provide insights into the genetics and pathogenesis 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 1 percent of the U.S. population suffering from this disease. TEDDY researchers have reported that the risk of pediatric celiac disease is related to the child's specific genetic makeup; more than one-quarter of children with two copies of a high-risk variant in a specific group of genes develop an early sign of celiac disease by age 5. These results could have future implications for celiac disease screening in young children. TEDDY researchers also reported that the timing of first introduction to gluten is not associated with increased risk for developing celiac 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, and SEARCH data will aid the design and implementation of public health efforts to stop this alarming trend. The study also has 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 which required substantial investment of time and resources to identify at-risk newborns. To capitalize on this investment, follow-up is anticipated to continue through 2023 to study these high-risk infants through childhood and adolescence when type 1 diabetes may become manifest. A significant “omics” effort is under way to address questions related to the cause and course of autoimmunity and type 1 diabetes, including metabolomics, proteomics, and studies of the microbiome and virome. 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.
- ▶ Continued surveillance of type 1 diabetes in childhood and adolescence provides unique information about vulnerable populations and is crucial to understanding type 1 diabetes at a public health level. Additionally, because type 1 diabetes can be misdiagnosed in young adults, new research supported by the *Special Diabetes Program* will seek to determine the incidence of type 1 diabetes in this population.



## Goal II: Prevent or Reverse Type 1 Diabetes

### Research Challenges

Clinical trials have suggested that preserving a person's remaining beta cell function can have dramatic, long-term health benefits, and clinical trials with agents that modulate the immune system have shown promise in preserving beta cell function in people newly diagnosed with type 1 diabetes. In addition, the underlying causes of type 1 diabetes are becoming better understood, and new approaches to type 1 diabetes prevention are anticipated to emerge from The Environmental Determinants of Diabetes in the Young study (see Goal I).

### 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 aimed at preventing type 1 diabetes in people at risk for the disease and slowing disease progression in people who are newly diagnosed. For example, NIDDK's Type 1 Diabetes TrialNet (TrialNet) supports the development and implementation of prevention and reversal clinical trials. This involves not only clinical evaluation of new therapies to balance potential risks and benefits, but also research to understand the natural history of type 1 diabetes and identification of people at risk for the disease. To date, TrialNet has screened over 160,000 unique individuals—and screens approximately 15,000 new individuals per year—for type 1 diabetes risk to identify those eligible for participation in ongoing and planned disease prevention trials. TrialNet offers yearly re-screening for children under 18 years of age, so a total of over 250,000 screens have been conducted to date. TrialNet aims to increase and improve screening efforts to reach everyone with risk for the disease who may be eligible for participation in TrialNet trials. If successful, these high-risk, high-reward studies may inform critical future public health efforts to identify those at risk and to intervene to prevent type 1 diabetes.

Three prevention trials are ongoing in TrialNet testing the following agents: oral insulin, anti-CD3 monoclonal antibody (teplizumab), and CTLA-4-Ig (abatacept). One is based on a previous prevention study (oral insulin), and two are based on promising results in preserving beta cell function in people with newly diagnosed type 1 diabetes (teplizumab, abatacept). TrialNet evolved from the Diabetes Prevention Trial-Type 1 (DPT-1) study, which tested whether oral insulin could prevent progression from autoimmunity to type 1 diabetes in people at risk. Although there was no overall beneficial effect observed from treatment with oral insulin, there was a significant delay in development of type 1 diabetes in people with the highest levels of insulin autoantibodies; this is the basis for the TrialNet oral insulin study. In 2011, 8 years after the conclusion of the DPT-1 study, TrialNet researchers restudied the DPT-1 participants with the highest levels of insulin autoantibodies and reported that these individuals developed type 1 diabetes at similar rates whether they received the oral insulin (treatment group) or not. However, because fewer people in the treatment group developed type 1 diabetes during the trial and that benefit persisted, the overall number of people who developed type 1 diabetes 8 years later remained lower in the treatment group. The ongoing TrialNet trial will determine conclusively whether oral insulin can prevent type 1 diabetes in people with high insulin autoantibody levels.

Not only are TrialNet's studies in people newly diagnosed with type 1 diabetes potentially beneficial to participants by preserving beta cell function and making the disease easier to manage, these studies provide critical knowledge for prevention research, including safety data, discovery of novel immune and metabolic endpoints, and elucidating mechanisms of therapeutic effects. For example, TrialNet investigators reported that abatacept slowed progression of type 1 diabetes in newly diagnosed people; 2 years of monthly drug treatment maintained insulin production. Moreover, the treatment effects persisted for 1 year after the drug was discontinued. This drug has been approved by the FDA for the treatment of other autoimmune diseases, suggesting the possibility of using this therapy in combination with other agents for a more robust and prolonged effect. The positive effect and safety data of this agent in the new-onset trial enabled TrialNet investigators to test it earlier in the course of type 1 diabetes for prevention. Building on similar findings in other successful trials in newly diag-

nosed people, TrialNet also launched a prevention trial with teplizumab that targets the immune system and has been shown to improve metabolic function in people newly diagnosed with type 1 diabetes.

TrialNet continues to conduct clinical studies to improve the understanding of type 1 diabetes, such as testing interventions aimed at decreasing beta cell destruction and/or enhancing beta cell survival in people newly diagnosed with type 1 diabetes. TrialNet has completed six trials aimed at beta cell preservation in persons newly diagnosed with type 1 diabetes and has two ongoing studies (antithymocyte globulin/granulocyte-colony stimulating factor; tocilizumab). TrialNet also provides unique and important resources for the broader scientific community: access to TrialNet's accumulated data and samples, as well as to its uniquely identified at-risk population, a "living biobank." A number of ancillary studies with TrialNet participants and samples are under way to understand better the progression to the disease.

The Immune Tolerance Network (ITN), led by the National Institute of Allergy and Infectious Diseases (NIAID), is developing and testing novel therapies to induce immunological tolerance. Tolerance induction strategies re-educate the immune system so that it does not injure the body's own cells in the setting of autoimmune diseases, including type 1 diabetes. ITN has launched clinical trials in people newly diagnosed with type 1 diabetes, testing novel therapies to slow disease progression, and partnered with TrialNet on several of these. ITN recently reported that treatment with alefacept preserved insulin production in people with newly diagnosed type 1 diabetes. Participants who received the drug required less insulin and experienced fewer episodes of hypoglycemia (dangerously low blood sugar) in comparison to participants who did not. These benefits persisted for more than 1 year after the treatment ended.

**Type 1 Diabetes TrialNet has created a large and effective network to screen relatives of people with type 1 diabetes and identify at-risk individuals, and has screened over 160,000 volunteers. These individuals may be eligible to participate in TrialNet's ongoing and future prevention studies. TrialNet data and samples, as well as access to at-risk individuals, provide a unique resource for investigators to study the development of type 1 diabetes.**

## Broad Implications of Research

Although many autoimmune diseases are rare, in the United States between 14.7 and 23.5 million individuals are collectively affected by autoimmune diseases, with women disproportionately affected. As therapies effective in type 1 diabetes may involve modulation of the immune system, these treatments could also be effective for other autoimmune diseases. 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 the opportunity to advance treatments and cures for other diseases in which the immune system plays a role.

## Future Research Opportunities

Research supported by the *Special Diabetes Program* has set the stage for identifying ways to prevent or reverse 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 receive 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 disease onset. Therefore, it is critical to capitalize on successful trials in newly diagnosed people 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.
- ▶ Ongoing studies of single therapies could identify agents that may be useful in combination to provide more efficacy than seen with single agents alone. This may be especially true when combining drugs with different mechanisms of action. Therefore, it is important to support studies both of single drugs and combinations of drugs.
- ▶ TrialNet's living biobank provides a unique resource to study the progression of type 1 diabetes from appearance of autoimmunity to diagnosis of the disease. A goal of these studies is the identification of biomarkers of disease risk, disease development, or disease course to inform potential prevention and treatment strategies. Identification of biomarkers that can be used as surrogate endpoints in clinical trials is a major goal as well; such biomarkers could enable smaller, quicker clinical trials.



## 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 a person with type 1 diabetes. 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 (regeneration), or directing other pancreatic cell types toward becoming beta cells (reprogramming). 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 person's beta cells.

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

**Conducting clinical trials to improve islet transplantation:** NIAID's Immune Tolerance Network (ITN; see Goal II) completed the first multicenter clinical trial demonstrating that transplantation of pancreatic islets from a deceased donor can restore glycemic control in individuals with type 1 diabetes. To facilitate the transition of this investigational therapy into clinical practice, the NIAID and NIDDK established the Clinical Islet Transplantation Consortium (CIT). CIT has conducted eight clinical trials with associated mechanistic studies to test new strategies for improving islet transplantation, and to provide an evidence base for licensure of an islet product. CIT-07, a Phase III study of islet transplantation, enrolled 48 people with type 1 diabetes, impaired awareness of hypoglycemia (dangerously low blood sugar), and frequent severe hypoglycemia events despite expert care. At 2 years after transplantation, more than 70 percent of participants met the primary endpoint, a composite reflecting: (1) excellent glycemic control (HbA1c level less than American Diabetes Association target of 7 percent); and (2) freedom from severe hypoglycemic events, with restored hypoglycemia awareness. These impressive findings indicate that islet transplantation is an effective treatment for people who have severe hypoglycemic events refractory to the best medical care. The results of this trial will be the basis for Biologic License Applications to the FDA for licensure of Purified Human Pancreatic Islets; licensure would allow third-party reimbursement for the islet transplant procedure.

The NIDDK's Collaborative Islet Transplant Registry (CITR) is collecting and disseminating data on transplants internationally, including from the CIT and other islet transplant programs, to expedite progress and promote safety in this research field. CITR now has data from over 900 islet-alone transplant recipients and nearly 200 islet-after-kidney transplant recipients. From these data, CITR found that rates of independence from insulin administration at 3 years after islet transplant increased over time—from 27 to 37 to 44 percent in 1999–2002, 2003–2006, and 2007–2010, respectively. The transplanted islets also functioned longer in the most recent period, an important advance because even some islet function improves blood sugar control and reduces hypoglycemia, even in people who are not insulin independent. Moreover, CITR has collected data on 825 auto-transplant recipients, including children who have had their pancreas removed due to severe pancreatitis. In auto-transplantation, islets are isolated from the removed pancreas and reinfused using protocols that were developed for islet transplantation in type 1 diabetes. CITR data demonstrate that, after 1 year, 38 percent of people with auto-transplants are insulin independent, 58 percent have an HbA1c (a measure of past blood sugar control) equal to or less than 6.5 percent, and 95 percent have not had a severe hypoglycemic event. This procedure spares some of these children from lifelong diabetes; improves glucose control in those with diabetes, lessening their risk for diabetes complications; and is another example of the

**The Clinical Islet Transplantation Consortium demonstrated that islet transplantation can significantly improve blood sugar levels and protect people with type 1 diabetes from severe hypoglycemic events. The Consortium is working with FDA toward transitioning the procedure from an experimental treatment to one covered by insurers.**

benefits and broad reach of research in type 1 diabetes. Results from CIT and CTR show that islet transplantation continues to advance and that this approach significantly improves the health and quality of life of people with severe hypoglycemia.

**Scientists in the Beta Cell Biology Consortium have made numerous scientific discoveries, including the discovery of a method to produce large quantities of human beta cells in the laboratory, toward the goal of replacing lost beta cells in type 1 diabetes. To build on their success, the Human Islet Research Network was launched with the specific goals of protecting and replacing beta cells in people with diabetes.**

**Discovered new ways to produce beta cells:** The NIDDK's Beta Cell Biology Consortium (BCBC) made numerous scientific discoveries to advance understanding of pancreatic islet development and function and generated many research resources for use by the broad scientific community. Their efforts contributed to the discovery of a large-scale method to produce unlimited quantities of glucose (sugar)-responsive beta cells. Because these cells can be made from human induced pluripotent stem cells generated from adult cells, like skin cells, it is possible that scientists will be able to grow new beta cells from cells taken from a person with type 1 diabetes. This process is a promising step toward developing therapeutic cell therapies to treat type 1 diabetes and overcoming limited quantities of donor islets that have hindered islet transplantation. In addition, these cells offer a valuable new resource for investigating beta cell biology and disease modeling, as well as opportunities for drug screening and testing novel potential therapies.

BCBC scientists also made important advances in other strategies to replace lost beta cells. For example, researchers discovered that other cell types found in the pancreas—alpha cells, which produce the hormone glucagon, and delta cells, which produce the hormone somatostatin—are capable of being reprogrammed into beta cells in mice. This process could potentially be adapted to restore insulin production in people with type 1 diabetes. BCBC scientists, using cutting-edge technology, also identified a potential molecular diagnostic for the disease. In type 1 diabetes, a person's beta cells die from the immune system attack. Using the knowledge that dying cells release fragmented DNA into the blood, the researchers demonstrated that beta cells release DNA with a uniquely modified pattern that can be detected in people newly diagnosed with type 1 diabetes. This result could lead to a minimally invasive approach to monitor people at risk for the disease, and to diagnose type 1 diabetes.

Building on the success of the BCBC, the NIDDK launched the Human Islet Research Network (HIRN), a new team science program to pursue innovative strategies to protect and replace beta cells in people with diabetes. HIRN comprises four independent, but complementary, research initiatives focused on specific goals using human cells and tissues. One is focused on discovery of biomarkers of beta cell injury that will be important for testing strategies to stop beta cell destruction early in the disease process. Another is combining advances in generation of functional human pancreatic beta cells with tissue engineering technologies to develop micro-devices that will support functional human islets. A third is developing approaches to model the immunobiology of type 1 diabetes, and a fourth is investigating methods to increase or maintain functional beta cell mass.

**Gained knowledge toward protecting newly transplanted islets:** Islet transplantation therapy is also limited by the immune response to a foreign body (the newly transplanted beta cells) and the relentless autoimmune attack that caused type 1 diabetes in the first place. Currently the immune system can be tempered only by immunosuppressive medications that have significant side effects, and their long-term effects are unknown. To overcome this barrier, research on encapsulation or other strategies to protect transplanted beta cells and promote long-term survival has also been supported by the *Special Diabetes Program*. Scientists recently reported the generation of a library of variants of one of the most widely used biomaterials, alginate. Alginate has low toxicity, is inexpensive, and has been widely used as a coating for biomedical devices and drug delivery. Evaluation of the library revealed variants that led to substantially reduced immune reactions when introduced into rodents and non-human primates. Using the method to produce large quantities of beta cells described above, these scientists then encapsulated the beta cells with one of the identified alginate variants. When the encapsulated beta cells were transplanted into a mouse model of type 1 diabetes, they produced insulin and improved the animals' blood sugar levels, without the need for immunosuppression. These advances represent significant progress toward a long-term cellular therapy for 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 could lead to approaches to restore insulin production that benefits people with both forms of the disease. Results emanating from the BCBC and HIRN have the potential to inform other fields as well: discovery of a method to produce large-scale quantities of beta cells has implications in broader stem cell biology research, and the cutting-edge technology to detect fragmented DNA in the blood is being explored in other disease areas, including cancer. Additionally, progress in encapsulation research will provide new knowledge useful to bioengineering cellular implants and implanted devices to treat many different conditions. 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 safe and effective cell replacement therapy can become a reality for people with type 1 diabetes and cure their disease. Future research opportunities include:

- ▶ Outcomes from islet transplantation continue to improve. The CIT is working with the FDA toward licensure of human islets. Licensure could transition islet transplantation from an experimental therapy to a procedure covered by third-party payers.
- ▶ The newly established HIRN will build on the successes of the BCBC toward understanding how to replace the lost beta cells in the pancreas. Many significant advances are anticipated that originated with research in the BCBC and are now supported by HIRN. HIRN research will 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.
- ▶ One of the many exciting projects in HIRN is pursuing generation of an islet-on-a-chip, a miniature model of living organ tissue on a transparent microchip. An islet-on-a-chip could be used to identify therapeutics that are likely to be effective, reducing the time and money needed using current methods. This effort will join with other organ-on-a-chip initiatives at the NIH toward the development of a multi-organ network chip.
- ▶ Another new team science initiative, the Human Pancreas Procurement and Analysis Program, will bring together experts in human pancreas physiology and pathophysiology to analyze human pancreatic tissues using state-of-the-art technologies. This program will become a component of HIRN and support research to understand pancreatic function and dysfunction, the course of type 1 diabetes, and to inform strategies to increase beta cell mass.
- ▶ Newly transplanted or formed beta cells will require protection from immune system destruction. Encapsulation and other strategies to minimize the attack are being investigated.

# Goal IV: Improve Type 1 Diabetes Management and Care

## Research Challenges

People with type 1 diabetes must always walk a tightrope—balancing the immediate danger of hypoglycemia, or episodes of dangerously low blood sugar, and the long-term risk of developing complications due to high blood sugar. Many people, especially teens, are unable to achieve recommended levels of blood sugar control. There is a great need for new tools and strategies 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

**Achieved significant progress in developing artificial pancreas technologies:** The *Special Diabetes Program* supported the development of continuous glucose monitors, which reveal the dynamic changes in blood sugar levels by assessing sugar levels hundreds of times per day and displaying trends. This revolutionary technology is itself a major advance in the management of type 1 diabetes. The 2015 American Association of Clinical Endocrinologists/American College of Endocrinology consensus statement on glucose monitoring summarized data on continuous glucose monitoring use and found it has clearly upgraded the quality and safety of diabetes care, particularly for patients on intensive insulin therapy. Continuous glucose monitors are also a key component of artificial pancreas technology, which links a continuous glucose monitor to an insulin pump with a computer that calculates and instructs delivery of an appropriate amount of insulin. Artificial pancreas technology could relieve patient burden by significantly reducing the need for frequent blood sugar testing and manual insulin dosing, improving blood sugar levels, and greatly enhancing quality of life.

The *Special Diabetes Program* has supported development of improved components of artificial pancreas technology, as well as made a significant investment in studies testing its use. Rapid progress has been made in this field, moving trials from short-duration in-hospital settings to multi-day use in free-living environments. One

example of this technology is an automated “bionic” pancreas that administers both insulin and another blood sugar-responsive hormone, glucagon. Studies in preadolescent children, adolescents, and adults have shown that the bionic pancreas improves overall blood sugar levels and reduces episodes of hypoglycemia compared to conventional insulin pump therapy. Studies of another artificial pancreas technology demonstrated that unsupervised use—first overnight only and then both day and night in a second study—led to improved blood sugar control compared to conventional insulin pump therapy in adolescents. Other artificial pancreas technologies are being tested as well to determine which technology will be most beneficial to an individual’s needs.

### Launched clinical trials toward FDA approval of artificial pancreas technologies:

The *Special Diabetes Program* has and continues to support research in this field by small businesses, academic investigators collaborating with industry, and national research networks to test current systems, develop new artificial pancreas technologies, and determine how these systems may be used to improve blood sugar control, quality of life, and health outcomes. Importantly, the NIH is working closely with the FDA to lay the path toward approval of these technologies. Five projects were recently funded to support advanced clinical trials testing the outpatient safety and efficacy of different

artificial pancreas systems with the aim of improving glycemic control in children, adolescents, and/or adults with type 1 diabetes, and more projects are anticipated to be funded. These trials will include more participants than previous trials and be of a longer duration, and are expected to pave the way toward generating data to satisfy safety and efficacy requirements for approval of these systems.

**The *Special Diabetes Program*'s major investment in technology supported development of now-approved continuous glucose monitors and accelerated progress toward the development of an artificial pancreas, including improving components of the artificial pancreas, conducting studies testing use of artificial pancreas technology first in animals and then in small numbers of people, and now supporting large-scale clinical trials to generate data toward FDA approval.**

**Fostered new businesses developing diabetes management technologies:** The *Special Diabetes Program* has been instrumental in fostering new businesses developing novel technologies for management of type 1 diabetes. In addition to NIDDK small business grants that laid the groundwork for continuous glucose monitors, SmartCells, Inc., which also received support from NIDDK small business grants, made substantial progress in the preclinical development of a new formulation of insulin in which insulin release is automatically responsive to fluctuating blood sugar levels. This product has the potential to lower the risk of low blood sugar and improve glycemic control. Merck & Co., Inc. acquired SmartCells, Inc., placing this novel technology in a position to be developed to its fullest potential. Xeris Pharmaceuticals, Inc. also received a small business grant from the *Special Diabetes Program* to develop a stable, liquid, ready-to-use formulation of glucagon to prevent and treat hypoglycemia. Xeris Pharmaceuticals recently announced that it received a significant investment from investors, and reported that the glucagon formulation may be an effective option for mild to moderate hypoglycemia treatment in a small study of adults with type 1 diabetes.

***Special Diabetes Program grants to small businesses have led to the development of new technologies to improve diabetes management and fostered growth of these businesses.***

In a further example, GlySens, Inc., another small business, recently announced a significant investment from investors, which will enable expansion of clinical trials testing the first fully implanted, long-term continuous glucose monitoring system. This wirelessly-linked sensor could free users from the burden of a device worn externally and provide a means for easy and informative reporting of blood sugar levels. In this example, the initial research on this technology was supported by *Special Diabetes Program* funds to the investigator at an academic institution and later with funds to the small business. In a similar example, TypeZero Technologies has developed a computer program that runs on a mobile device linked to an insulin pump and continuous blood glucose monitor. Research that led to this technology was initially supported by *Special Diabetes Program* grants to an academic investigator, and then by small business grants. This technology was recently selected as the core analytic and control technology for one of the advanced artificial pancreas technology clinical trials mentioned above.

**Fostered behavioral research on barriers to care across the lifespan:** To ensure that advances in diabetes management fulfill their promise to improve the lives of people with type 1 diabetes, the *Special Diabetes Program* also supports research to uncover barriers to care and identify strategies to help people with the disease and their caregivers. For example, diagnosis and management of type 1 diabetes can be a highly stressful experience for parents of young children. Results from the Diabetes Research in Children Network (DirecNet), supported by the NICHD, reveal the importance of optimal blood sugar control in young children. DirecNet researchers found that continued exposure to high blood sugar levels may be detrimental to brain development in young children with type 1 diabetes, as they saw significant differences in gray matter volumes and white matter microstructure between the children with type 1 diabetes and those without the disease. The *Special Diabetes Program* is currently funding research to develop innovative and effective strategies to help families better manage diabetes and maintain good quality of life.

The Search for Diabetes in Youth Study (see Goal I) found that one in five teenagers with type 1 diabetes has poor blood sugar control, and that minority youth are significantly more likely to have poor glycemic control. These and additional data indicate that achieving the recommended levels of blood sugar control is particularly challenging in this age group. Research to develop new and better ways to improve the ability and motivation of adolescents to adhere to their prescribed treatment regimens is currently funded by the *Special Diabetes Program*. With improvements in diabetes care and management, people with type 1 diabetes are living longer, but little is known about the barriers and facilitators of good self-management in adults. The *Special Diabetes Program* is supporting research to understand how life issues—like having a family, maintaining a career, and transitioning to older age—affect diabetes management, and how technology—like continuous glucose monitors—may help older adults maintain good blood sugar control and avoid hypoglycemia.

## Broad Implications of Research

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

## Future Research Opportunities

Continuous glucose monitoring technology is revolutionizing the way people with type 1 diabetes manage their disease. It took many years between the funding of the first NIDDK grant related to the development of continuous glucose monitoring technology to clinical approval of the devices. Now, research to develop artificial pancreas technology—linking a continuous glucose monitor to an insulin pump—has made rapid progress due to support from the *Special Diabetes Program*.

- ▶ Artificial pancreas technology could help people with type 1 diabetes safely achieve the recommended levels of blood sugar control associated with preventing or delaying life-threatening disease complications, improving health and quality of life, and alleviating an enormous amount of patient burden. To further accelerate the development of artificial pancreas technology, new clinical trials are poised to test technologies in larger and longer studies that are expected to provide critical data for FDA approval.
- ▶ People of all age groups—from babies to adults—are burdened with type 1 diabetes, and each age group has different obstacles to overcome to manage their disease. Research supported by the *Special Diabetes Program* is developing strategies to help these different populations achieve good blood sugar control and enhance their quality of life.
- ▶ New technology will only be beneficial if people know how to use it, so behavioral research on how best to utilize new artificial pancreas technologies will be key toward moving this treatment strategy into practical use. The *Special Diabetes Program* also supports research on the practical aspects of implementing new technology into clinical practice, such as enhancing the usability of new technology and helping people in their decision making regarding diabetes control.



# 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. Type 1 diabetes ravages nearly every part of the body: the heart, eyes, kidneys, lower limbs, mouth, and digestive and urologic systems, and is associated with serious complications, such as heart disease and stroke, blindness, kidney failure, and lower-limb amputations. These complications greatly affect the personal health of people with diabetes and contribute significantly to the costs of health care in the United States. 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. Complications of diabetes can progress slowly but have devastating consequences. Trials of complications therapies are long, as the full benefit of treatment may not be seen for decades, 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 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 has been supported, in part, by the *Special Diabetes Program*. The DCCT established that early intensive control of blood sugar levels can reduce the onset and progression of small blood vessel complications involving the kidneys, eyes, and nerves. By continuing to follow these dedicated volunteers, researchers in EDIC demonstrated the long-lasting effects that a period of intensive control can have. For example, the initial DCCT kidney findings were based on reductions in urine protein, a sign of kidney damage but not a measure of kidney function. Two decades later, after enough time had passed for people in the study to possibly develop kidney disease, EDIC researchers found that near-normal control of blood sugar, beginning soon after diagnosis of type 1 diabetes and continuing an average 6.5 years, reduced by one-half the long-term risk of developing kidney disease, compared to conventional therapy. Similarly, EDIC researchers found that, after over 2 decades of follow-up, DCCT participants who received the intensive control therapy had fewer eye operations than those who received conventional therapy. The reduction was nearly 50 percent, and the costs of surgery in the intensive-therapy group were one-third lower than those in the conventional-therapy group.

In subsequent studies, EDIC found that intensive control could also prevent the risk of heart-related complications—the leading cause of death of people with diabetes. After 27 years of follow-up, 100 DCCT participants in the conventional therapy group had heart-related complications, which enabled EDIC researchers to analyze the risk factors associated with these complications. They found that high blood sugar levels were second only to age as associated risk factors for heart-related complications. To investigate other potential risk factors, EDIC recently launched a study in which continuous glucose monitoring data will be linked to electrocardiograms (EKG, a test that measures the heart's activity) to elucidate the possible role of hypoglycemia (dangerously low blood sugar) in heart-related complications. Improving heart health for people with type 1 diabetes holds promise to continue improving the outlook for people with the disease. EDIC also reported that people with type 1 diabetes who intensively control their blood sugar early in their disease are likely to live longer than those who do not. They found a 33 percent reduction in deaths among DCCT/EDIC participants who initially received the intensive treatment. These findings have revolutionized management of type 1

**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 and mortality.**

diabetes and translated into dramatic health benefits. Thus, the fruits of research are paying off with respect to greatly improved outcomes for people with type 1 diabetes.

**Identified new treatment for eye disease:** Blindness is a debilitating complication of diabetes. Laser treatment is an effective therapy to prevent blindness in advanced cases of diabetic retinopathy or vision loss from diabetic macular edema. Led by the National Eye Institute (NEI), the Diabetic Retinopathy Clinical Research Network (DRCR.net) showed that the anti-vascular endothelial growth factor (VEGF) drug, Lucentis®, often in conjunction with laser treatment, is a more effective treatment for diabetic macular edema than laser treatment alone. This finding dramatically changed clinical practice and quickly became a standard treatment for people with vision loss from diabetic macular edema. Building on this result, a DRCR.net comparative effectiveness trial compared safety and efficacy of three anti-VEGF drugs commonly used to treat diabetic macular edema:

aflibercept (Eylea®), bevacizumab (Avastin®), and ranibizumab (Lucentis®). The trial showed that, in people with mild visual impairment, any of the three drugs, on average, improved visual acuity and that the drugs were equally effective after 2 years. For people with worse vision at the start of the study, all three drugs improved visual acuity, but people treated with Eylea® showed greater improvement than those treated with Avastin® or Lucentis®. Improving vision with anti-VEGF therapy can make the difference between people being able to drive or not, which greatly affects quality of life.

**The Diabetic Retinopathy Clinical Research Network demonstrated that anti-VEGF therapy is a more effective treatment for diabetic macular edema than laser treatment alone. This finding dramatically changed clinical practice and quickly became a standard treatment for people with vision loss from diabetic macular edema. Additional trials demonstrated that three different anti-VEGF therapies are equally effective in people with mild vision loss—a result that will inform personalized treatment.**

These results offer important data for informing clinical decisions and personalizing treatment for diabetic macular edema and also have significant cost implications. The costs of these drugs differ widely: based on Medicare allowable charges, the per-injection costs of each drug used in this study were about \$1,850 for Eylea®, \$1,200 for Lucentis®, and \$60 for Avastin®. Many patients required 15 injections over the 2-year period. Because the study compared drugs from different companies, the NIH and *Special Diabetes Program* were in a unique position to support it, as it was unlikely to have been conducted by the pharmaceutical industry.

DRCR.net showed in a separate trial that Lucentis® was more effective than laser at improving visual acuity over 2 years for eyes with the most severe form of diabetic retinopathy (proliferative diabetic retinopathy), giving people with diabetes and their doctors the first new option for treating proliferative diabetic

retinopathy in 4 decades. Eyes treated with Lucentis® also had fewer complications from diabetic retinopathy and required less ocular surgery.

**Launched trial to test new treatment for diabetic kidney disease:** Another new clinical trial that would also not likely be supported by the private sector is the NIDDK's Preventing Early Renal Loss in Diabetes (PERL) study. PERL is testing whether the inexpensive, generic medication allopurinol, currently used for the treatment of gout, could preserve kidney function in people with type 1 diabetes who are at high risk of developing kidney disease. Despite the efficacy of blood sugar and blood pressure control and hypertension therapy in reducing the risk of diabetic kidney disease, the rates of kidney disease remain high. PERL is testing allopurinol in early loss of kidney function, a stage most likely to be responsive to therapy. The PERL trial recently completed enrollment, and results are anticipated in the next few years. If this inexpensive drug proves effective, it has the potential to be the first therapy to reduce risk for diabetic kidney disease in over 2 decades. Diabetic kidney disease is a major risk factor for heart disease in people with type 1 diabetes, underscoring the importance of studying new strategies to prevent kidney disease.

**Supported a small business's preclinical development of a novel therapeutic for diabetic nerve disease:** Through support for preclinical research from the *Special Diabetes Program*, the small business Fibrotech Therapeutics Pty Ltd. was able to develop a drug called FT011 for the treatment of diabetic kidney disease. Continual exposure to high levels of sugar in the blood can damage the kidney, resulting in fibrosis

(scarring), which can lead to kidney failure. In preclinical testing, FT011 was effective at preventing kidney fibrosis in animal models of diabetic kidney disease, and Fibrotech successfully completed this Phase Ia trial in healthy volunteers demonstrating the drug's safety and tolerability. The Phase Ib trial, which includes people with type 1 or type 2 diabetes-associated kidney disease, was launched. Fibrotech was acquired by Shire plc, a global pharmaceutical company, putting FT011 in a position to be developed to its fullest potential. The *Special Diabetes Program* enabled this small business to secure funds and data for initial clinical trials, which led to a significant investment by Shire for larger clinical trials.

**Made progress toward developing potential new treatment for diabetic ulcers:** Foot ulcers, which can lead to non-traumatic amputations, exact a significant personal toll for people with diabetes and on healthcare spending. The only FDA-approved therapies for diabetic foot ulcers were developed in the 1990s and show only modest effectiveness. Thus, there is great need for new therapeutics to prevent and treat diabetic foot ulcers. Researchers supported by the *Special Diabetes Program* reported that a transdermal, local drug delivery system, combined with the FDA-approved drug deferoxamine, significantly improved wound healing in a mouse model of diabetes. Application of this combination also prevented diabetic ulcer formation. Further research will be needed to determine whether this system shows similar results in humans, but it has great potential to transform care and prevention of diabetic ulcers.

**Gained new knowledge on why diabetic complications develop:** In addition to clinical research, the *Special Diabetes Program* supports basic research to understand how complications develop toward treating and preventing them. Though many people with type 1 diabetes will develop complications, valuable insights can be made from those who do not. Scientists are studying “Medalists”—a group of people who have lived with type 1 diabetes for at least 50 years post-diagnosis—and comparing Medalists who have experienced significant complications with those who have not. The scientists reason that the Medalists who do not develop significant complications must have factors that protect them, and that identification of these factors could help others who do develop complications. By studying cells from the Medalists, scientists revealed a role for the DNA damage checkpoint pathway and a small, circulating RNA molecule known as “miR200” in the development of complications. Additional research will determine whether this molecule could be a therapeutic target, and continuing studies of the Medalists could identify other factors that influence the development of or protect people from diabetes 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 Reference Laboratory for HbA1c 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 healthcare providers and people with diabetes to accurately and meaningfully assess blood sugar control and risks for complications. Building on this success, the American Diabetes Association recommended HbA1c as a more convenient approach to diagnose type 2 diabetes.

## 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 Standardization Program (see above), the NIH was able to launch a 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 for monitoring diabetes control.

Because researchers believe hyperglycemia (high blood sugar) 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. For example, if the PERL study (see above) demonstrates that the safe and inexpensive drug allopurinol can preserve kidney function, the drug may also be relevant to kidney protection in the larger population with type 2

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.
- ▶ 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.
- ▶ New, noninvasive approaches to assess the nerves and blood vessels in the eye could detect early subtle changes due to diabetes and facilitate clinical trials of promising new therapies by reducing the time needed to see effects. For example, researchers have developed a noninvasive, laser-based technique (corneal confocal microscopy) that images nerves in the front of the eye, and found that it is similarly effective to invasive skin biopsy for diagnosing nerve damage in people with type 1 diabetes. With support from the *Special Diabetes Program*, this approach is being further tested and developed. Another group of *Special Diabetes Program*-supported scientists demonstrated that a different imaging technique—called optical coherence tomography—showed promise as a noninvasive approach for imaging blood vessels in the eye.
- ▶ There is growing evidence that there are neurocognitive effects of type 1 diabetes, but there is limited information on if or how specific parameters—for example, age of onset, disease duration, blood sugar control, and frequency and severity of hypoglycemic episodes—may lead to changes in brain structure and function, and deficits in cognition, and on how susceptibility to these brain changes may vary across the lifespan. Opportunities now exist to study these questions due to advances in imaging and measurement technologies. This research could further understanding of how diabetes contributes to risk of Alzheimer’s disease and other forms of dementia, and is particularly important as people with type 1 diabetes are living longer.





## 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 people with the disease. 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 field.

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

**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, researchers in The Environmental Determinants of Diabetes in the Young (TEDDY) study (see Goal I) are using “omics” technologies to analyze participant samples toward the identification of causative or protective environmental factors. TEDDY scientists are also poised to take advantage of cutting-edge technologies to assess the immune profiles of participants to identify predictors of autoimmunity and progression to type 1 diabetes.

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’s 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 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 body 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. Researchers in the Human Islet Research Network (HIRN; see Goal III) are on the forefront of using and developing innovative technologies to understand human beta cells and find strategies to protect or replace lost beta cells in type 1 diabetes. For example, HIRN scientists are combining advances in beta cell biology with tissue engineering technologies to develop microdevices that support functional human islets toward screening potential therapeutics. They are also using transformational single cell analysis to examine individual cells in order to define specific cell types or states in a given population of cells to understand better the characteristics of beta cells.

**Attracted new scientists to type 1 diabetes research:** The NIDDK has employed several strategies to attract new scientists to type 1 diabetes research through support by the *Special Diabetes Program*. For example, 10 scientists who had not previously received an NIH grant successfully competed for Type 1 Diabetes Pathfinder Awards. These scientists proposed highly innovative research studies that had the potential to produce a major impact on important problems in biomedical and behavioral research relevant to type 1 diabetes and its

complications. Their research spanned a wide range of topics, from the pursuit of a vaccine to prevent type 1 diabetes to investigating methods that speed wound healing. After the end of the project period, 70 percent of the awardees had obtained independent NIH grant support, and all remained active in diabetes research. Based on the success of the Type 1 Diabetes Pathfinder program, the NIDDK recently re-issued the funding opportunity for a second round of the program. 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.

**The *Special Diabetes Program* has been employed to bring new and diverse talent to meet the specific needs in type 1 diabetes research. Programs have supported young researchers, bioengineers, behavioral researchers, and pediatric endocrinologists.**

The research progress described in this report required multidisciplinary collaborations and novel approaches. The *Special Diabetes Program* has been employed to bring new and diverse talent to meet the specific needs in type 1 diabetes research. For example, the funds have supported opportunities for bioengineers to collaborate with diabetes researchers on projects ranging from the artificial pancreas to ways to protect transplanted islets from immune system attack (e.g., encasing cells in a protective biomaterial). The *Special Diabetes Program* is also supporting the training of behavioral scientists and fostering research collaborations to conduct research relevant to improved clinical management and quality of life for people living with type 1 diabetes. Support from the *Program* has also attracted leading proteomics, metabolomics, microbiome, and biocomputational researchers to apply their expertise to the

analysis of the biosamples and data collected in TEDDY. HIRN has also brought leading beta and stem cell biologists together with experts in immunology, bioengineering, and synthetic biology.

**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, and the extraordinary clinical care demands of pediatricians specializing in childhood diabetes make it particularly challenging for these doctors to pursue research careers. This cadre of skilled researchers is critical to build upon the foundation of current basic and clinical knowledge to develop new approaches to the treatment, prevention, and cure of pediatric diabetes. Through support from the *Special Diabetes Program*, a unique program provided pediatricians with training and career development in research related to childhood diabetes. Of the 28 pediatric endocrinologists who completed the program, 27 remained in academic medicine as of 2014. Based on the success of this program, the NIDDK recently re-issued a funding opportunity to continue the program.

## **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 and artificial pancreas technology 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:

- ▶ 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 microbiomes of newborns in the TEDDY study can not only explore this possibility, but also propel metagenomic analysis to the broader study of human health.

- ▶ The recent identification of over 50 new genes and gene regions associated with type 1 diabetes (see Goal I) 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 it 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 scientists 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 cells 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*

**People with type 1 diabetes are living longer and healthier lives than ever before and experiencing lower rates of disease complications. It is important to build on the progress to date to find ways to prevent and cure the disease.**

*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 people with type 1 diabetes 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.

### 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 the earliest manifestations of damage to 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 heart attack and stroke. Subsequently, the trial demonstrated that intensive control significantly reduced chronic kidney disease and kidney failure, the need for vision-saving eye surgeries, and even death. The impact of the trial was far-reaching: it revolutionized type 1 diabetes management and led to greatly improved outcomes for people with the disease. Thirty years after the start of the trial, researchers continue to learn from following the participants of this study. Building on this success, the importance of blood sugar 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 these improvements in health were realized.

**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.**

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. Additionally, the discovery of a large-scale method to produce unlimited quantities of

glucose (sugar)-responsive beta cells in the laboratory resulted from many years of supporting basic beta cell biology research with this specific goal. These are just a few examples of the revolutionary new findings that are emerging and expected to emerge from the unique, long-term, collaborative research consortia supported by the *Special Diabetes Program*.

### 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 in the future. In the near term, artificial pancreas technologies will transform the lives of people with type 1 diabetes, making blood sugar control safer and less arduous. Finding the genes and environmental factors that contribute to type 1 diabetes may yield ways to identify those at risk at birth and safely prevent the disease, thereby eliminating new cases. New ways to restore and protect beta cells may yield a cure for those with the disease. Knowledge of the molecular pathways by which blood sugar causes cell injury may lead to the development of medicines that prevent 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), 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 (National Institute of Diabetes and Digestive and Kidney Diseases), 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); the challenges of aging with type 1 diabetes now that people with the disease are living into old age (National Institute on Aging); 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); and data on disease incidence and prevalence in the United States (Centers for Disease Control and Prevention).

The *Special Diabetes Program* supports a spectrum of research within these NIH and HHS components, making it a model of a 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 Minority Health and Health Disparities, National Center for Complementary and Integrative Health, and National Institute of Nursing Research have also participated in the *Special Diabetes Program*. Highlights of research led by NIH Institutes and Centers and the CDC include:

**National Eye Institute (NEI):** Blindness is a debilitating complication of diabetes. To fight this complication, the NEI leads the Diabetic Retinopathy Clinical Research Network (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. Research related to the immune system could inform the causes, prevention, treatment, and cure of type 1 diabetes. The NIAID-led Immune Tolerance Network (Goal II) is developing and testing novel immune therapies of type 1 diabetes. The Clinical Islet Transplantation Consortium (Goal III), co-led by the NIAID and the NIDDK, is studying new strategies to improve islet transplantation, a developing treatment for the disease.

***Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD):** Type 1 diabetes often strikes in infancy, childhood, or young adulthood. The NICHD leads the Trial to Reduce IDDM in the Genetically at Risk (Goal I), a research trial testing a possible environmental trigger of type 1 diabetes in infants.

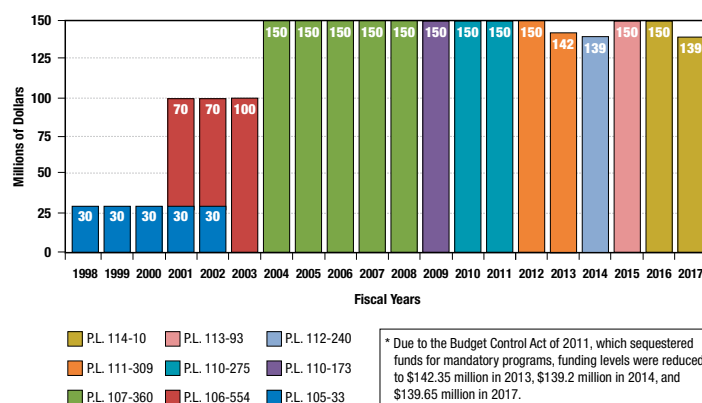
**National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK):** To identify the causes of the disease, the NIDDK leads The Environmental Determinants of Diabetes in the Young study (Goal I). Programs led by the NIDDK are also aimed at determining ways to prevent or delay onset of type 1 diabetes (Type 1 Diabetes TrialNet, Goal II); generating cures (Human Islet Research Network, Goal III); developing artificial pancreas technologies (Goal IV); and developing new talent in the research workforce (Goal VI). Critical efforts addressing the complications of type 1 diabetes are also led by the NIDDK (Epidemiology of Diabetes Interventions and Complications, Preventing Early Renal Loss in Diabetes; 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 and NIDDK's Search for Diabetes in Youth study (Goal I) provided the first data on incidence and prevalence of diabetes in children in the United States and continues to monitor whether these are changing over time.

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

Special funding for type 1 diabetes research, in the total amount of \$2.46 billion for Fiscal Year (FY) 1998 through FY 2017, 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); the Medicare Improvements for Patients and Providers Act of 2008 (P.L. 110–275); the Medicare and Medicaid Extenders Act of 2010 (P.L. 111–309); the American Taxpayer Relief Act of 2012 (P.L. 112–240); the Protecting Access to Medicare Act of 2014 (P.L. 113–93); and the Medicare Access and CHIP Reauthorization Act of 2015 (P.L. 114–10) to extend the *Special Diabetes Program* in duration and funding levels (see graph).

**Special Diabetes Program Funding:  
\$2.46 Billion over 20 years\***



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 type 2 diabetes in the United States.

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](http://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 major diabetes organizations: the JDRF, American Diabetes Association, and Leona M. and Harry B. Helmsley Charitable Trust. Sources of input include a variety of scientific workshops and conferences, as well as *ad hoc* planning and evaluation meetings in which the NIDDK convened panels of external scientific and lay experts to provide input on the *Program* and future directions. The most recent planning meeting was held in 2015. The NIDDK has also spearheaded Congressionally mandated evaluations of the *Special Diabetes Program*; the most recent one was published in January 2010. The evaluation found that the *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.

For more information on the *Special Diabetes Program*, please visit [www.T1Diabetes.nih.gov](http://www.T1Diabetes.nih.gov)

## Back Cover Legend

Logos of many of the novel and collaborative research consortia and clinical trials networks supported by the *Special Diabetes Program*, including the Beta Cell Biology Consortium (BCBC), Clinical Islet Transplantation Consortium (CIT), Collaborative Islet Transplant Registry (CITR), Diabetic Complications Consortium (DiaComp), Diabetic Retinopathy Clinical Research Network (DRCR.net), Epidemiology of Diabetes Interventions and Complications study (EDIC), Human Islet Research Network (HIRN), Immune Tolerance Network (ITN), Preventing Early Renal Loss in Diabetes (PERL), SEARCH for Diabetes in Youth (SEARCH), The Environmental Determinants of Diabetes in the Young (TEDDY), the Trial to Reduce IDDM in the Genetically At Risk (TRIGR), and Type 1 Diabetes TrialNet (TrialNet).

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