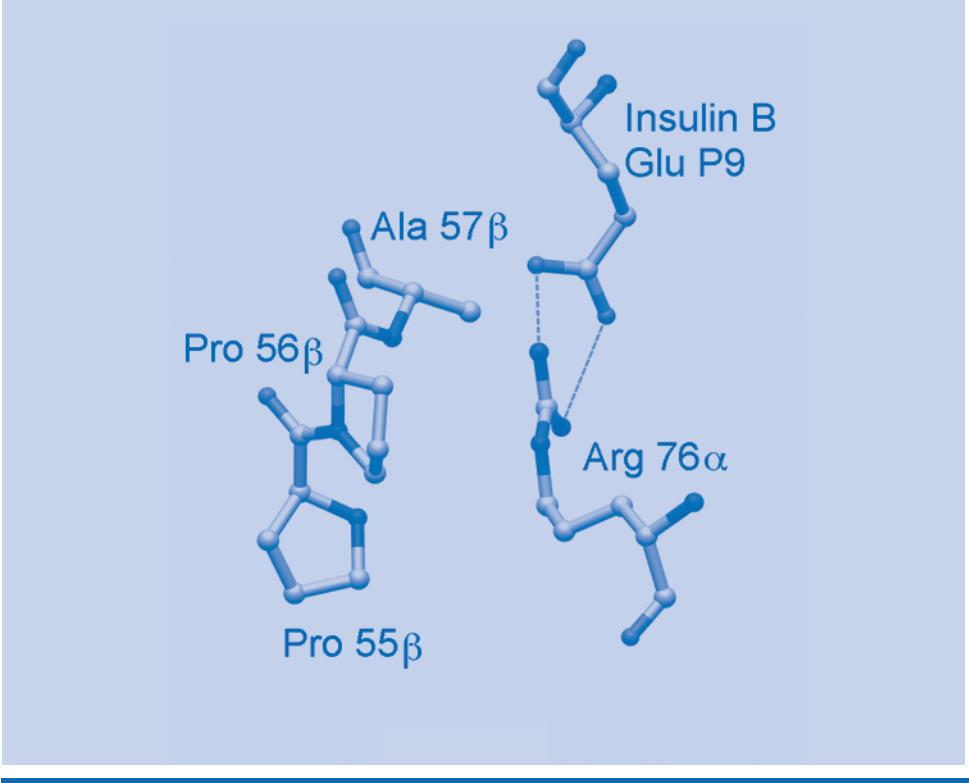


GOAL II:

PREVENT OR REVERSE TYPE 1 DIABETES

Why It Is Important To Prevent or Reverse Type 1 Diabetes

- Understanding Regulation of the Immune System
- Improving Screening for Type 1 Diabetes Risk
- Slowing the Immune Attack and Prolonging Pancreatic Function
- Reversing Type 1 Diabetes
- Enhancing Animal Models
- Developing a Safe and Universal Means for Primary Prevention

Patient Profile

- Jodie and Dillon Distel: Participating in Clinical Research To Fight Against Type 1 Diabetes

WHY IT IS IMPORTANT TO PREVENT OR REVERSE TYPE 1 DIABETES

Parents of children at risk for developing type 1 diabetes often ask: "Can research help my child lead a life free of this disease?" Those who are newly diagnosed ask: "If my body is still making some insulin, what can I do to prolong this or fully restore the ability to make it?"

Insulin treatment is essential for the survival of patients with type 1 diabetes, but it is not a cure. For the rest of their lives, patients must carefully watch their food intake, monitor their blood glucose levels, and try to control their levels with externally administered insulin. More serious than the inconvenience and discomfort of this treatment regimen is the danger of acute, life-threatening episodes of low blood glucose and the very high probability of chronic, disabling complications. To end these problems, researchers seek to short-circuit the underlying autoimmune disease process—that is, to thwart the immune system's misguided destruction of insulin-producing pancreatic cells.

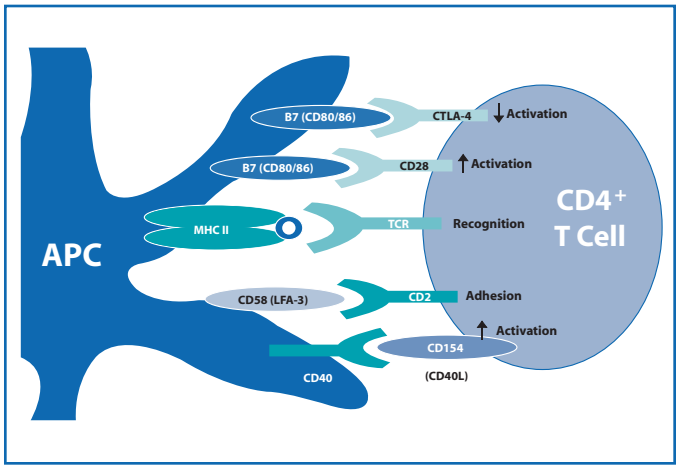
Because the genetic and environmental causes of type 1 diabetes are not well understood, strategies to prevent or reverse the disease are currently focused on intervening in the immune system's assault. These strategies must be two-pronged: they must squelch autoimmunity in people who are at risk for or already have the disease, while maintaining or restoring the patient's own insulin-producing capacity. (Goal III addresses another approach for reversing the disease by transplanting insulin-producing cells obtained from donor pancreatic tissue or regeneration of beta cells.)

Of course, the immune system provides critical protection against infection, so it is vital for any approach that modifies its activities to be as selective as possible in damping down just those processes that lead to autoimmunity. This delicate balancing act will be achieved by leveraging knowledge about the immune system in general, combined with insights into disease causation, in order to devise new diagnostic, treatment, and prevention strategies. Success will depend in large measure on building upon research advances and pursuing opportunities for uncovering the roots of this disease. Fortunately, research on type 1 diabetes has already advanced to the point that some new prevention and reversal strategies can be tested even in the absence of complete knowledge of disease causation.

Major progress has also been achieved through the identification of antibodies that are produced in type 1 diabetes when the immune system attacks the body's insulin-producing cells. These antibodies are, therefore, markers of type 1 diabetes. They have been shown to be detectable well before the loss of insulin production and the diagnosis of clinically overt disease. Tests of these antibodies in the siblings of patients with type 1 diabetes can predict with great accuracy whether they too will develop the disease in a few years. This predictive tool, coupled with other new technologies, has given researchers the remarkable ability to design and conduct primary prevention clinical trials in type 1 diabetes. A major research goal is to expand this type of predictive tool beyond its current, limited use in first-degree relatives of patients with type 1 diabetes.

Understanding Regulation of the Immune System

The immune system is made up of numerous different cell types that, when functioning properly, interact with one another to respond to various threats. Certain of these cells act to regulate the function of others. A central feature of that regulation is a process called "tolerance," recognition of self, which prevents the immune system from attacking the body's own cells. Tolerance is, therefore, a major focus of research on all autoimmune diseases, and scientists are making important strides in understanding how it works. Studies in special mouse and rat strains that have a genetic predisposition to type 1 diabetes have been insightful and will continue to contribute significantly to this research. While many forms of white blood cells play important roles in the autoimmunity of type 1 diabetes, researchers are homing in on the functions of one cell type, the T cell, which is thought to be instrumental in the autoimmune process, due to its destructive capacity combined with its potential to affect immune responses. For years, researchers have struggled to determine which beta cell proteins are key targets of autoimmune attack. Several published studies now support the notion that the insulin



T cells are thought to play a key role in the autoimmune processes that damage insulin producing beta cells. T cell activation requires two signals from an antigen presenting cell (APC): (1) the presentation of a peptide bound to class I or class II molecules of the major histocompatibility complex (MHC); and (2) binding of "costimulatory molecules" (such as B7) to receptors on the T cell. A possible therapeutic approach to preventing or reversing type 1 diabetes is to prevent T cell activation. One potential approach is to identify a way to block the second costimulatory signal.

(Image courtesy of Dr. George Eisenbarth and reprinted with the kind permission of Springer Science and Business Media. From Eisenbarth, S. "Primer: Immunology and Autoimmunity." Type 1 Diabetes: Molecular, Cellular, and Clinical Immunology. Ed. George S. Eisenbarth. Online Edition Version 2.5. Accessed at: www.uchsc.edu/misc/diabetes/oxch1.html. Copyright © 2004 Eurekah.com and Kluwer Academic/Plenum Publishers. All rights reserved.)

molecule itself is an important, potentially type 1 diabetes-initiating target of the immune system, although several other proteins may also play a role.

Improving Screening for Type 1 Diabetes Risk

Delaying or preventing type 1 diabetes can only be an effective strategy if health care providers are able to identify patients in the early stages of autoimmunity. Research has progressed to the point at which it is increasingly possible to identify people at risk for type 1 diabetes in the earliest stages of the disease, when a significant fraction of their insulin-producing cells is still alive and functioning. Current screening strategies look for proteins called autoantibodies, which characterize the autoimmune attack. Tests for genetic variants associated with type 1 diabetes are also incorporated into the screening process. With more precise genetic markers, screening methods that are currently applied only to relatives of patients with type 1 diabetes could conceivably be enhanced to predict and monitor disease risk in the entire pediatric population or the general population. Such genetic risk assessment would also shed light on other autoimmune diseases that often occur in patients with type 1 diabetes, including celiac disease, Addison's disease, and rheumatoid arthritis. As these screening tools are developed, the psychological impact of at-risk status and the most appropriate manner for communicating risk must be considered.

For those identified to be at risk based on antibodies and genetic susceptibility, monitoring the progression of disease and the effects of potential therapy is critically important. To this end, innovative clinical research studies will be made possible through a better understanding of facets of the immune response (e.g., regulatory T cells, innate immunity), which have recently been appreciated as key mediators of beta cell destruction. For example, it is important to understand cells that regulate the immune response, to develop better assays to measure the autoimmune response, and to find ways to measure the mass and function of insulin-producing cells. Tests of T cell function are under development as useful tools for monitoring autoimmunity. New imaging methods are also in development to detail the immune process in the pancreas. These methods may not only be excellent screening tools, but may also help scientists better understand the biology of autoimmunity.

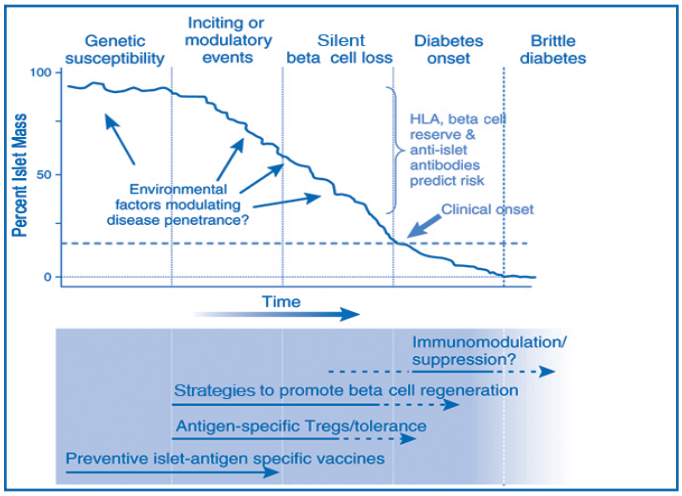
Slowing the Immune Attack and Prolonging Pancreatic Function

A more thorough understanding of genetic factors and environmental exposures underlying type 1 diabetes could lead to novel preventive approaches. At present, however, knowledge of causative factors is incomplete, and, therefore, strategies to prevent or reverse the disease are directed largely toward modulating the autoimmune process. A treatment that slows the immune attack and prolongs pancreatic functioning would be a great boon to patients because it could delay progression to diabetes and help those with the disease achieve better blood glucose control with less risk of hypoglycemia. Researchers are now testing several promising treatment regimens based on this approach. Particularly exciting research involves an agent known as anti-CD3, which has been shown to preserve metabolic function when administered to people with recent onset type 1 diabetes. With time, it is hoped that this, or other agents, will become proven components of a cure for type 1 diabetes by promoting disease reversal.

Reversing Type 1 Diabetes

For patients who have already developed type 1 diabetes, reversing or slowing beta cell loss is a key goal because prevention is no longer possible. Suppressing autoimmunity must

be a crucial component of any treatment designed to reverse type 1 diabetes in affected individuals. Once this suppression is accomplished, it may in principle be possible for patients to regrow pancreatic tissue. Indeed, data from the landmark Diabetes Control and Complications Trial suggest that some patients with type 1 diabetes maintain a limited capacity to produce their own insulin long after onset of disease. Additional recent research suggests that most people with type 1 diabetes, regardless of the length of their disease, may still have beta cells. These findings could mean that some beta cells are escaping the immune attack, and that their activity could possibly be bolstered. Alternatively, and perhaps more likely, the pancreas may be able to sometimes counter autoimmunity through a limited capacity for regeneration, although not nearly to a sufficient degree to actually offset beta cell losses. Unfortunately, many drugs that are known to be effective in suppressing the immune system (most commonly used in transplant patients) are actually harmful to beta cells, and may prevent regeneration. Therefore, researchers are attempting to develop new medications that are gentler and better targeted to the immune cells most directly responsible for beta cell autoimmunity. Medical approaches to stimulating beta cell development and function are addressed in Goal III.



Type 1 diabetes is a progressive autoimmune disease in which beta cells of the pancreatic islets are depleted by the immune system before the onset of clinical symptoms. Researchers suggest that a single intervention may not be completely effective; combinatorial therapies may be required. The proposed type of combinatorial therapies differs depending on the stage of the disease.

(Image courtesy of Dr. David Harlan and adapted with permission from Harlan DM and von Herrath M. Nature Medicine, 11: 716-718, 2005.)

Progress would be furthered by the conduct of multiple clinical trials, based on sound infrastructural support and incorporating standardized design and outcome measures. Trials would assess not only drug efficacy, but also safety considerations, particularly the safety of agents that modulate or suppress the immune system. Once individual drugs are shown to be useful, it would also be beneficial to determine whether combination therapies offer improved outcomes. Additional studies could evaluate whether the preservation of insulin production in recently diagnosed patients offers short- and long-term clinical benefit with respect to complications, particularly eye, kidney, and nerve disease.

Enhancing Animal Models

Additional animal models are needed to accelerate the study of relevant immune mechanisms and potential interventions. While spontaneous animal models of type 1 diabetes have been very useful in understanding the mechanisms underlying development of the disease, some strategies that prevent it in animals have not proven successful in humans. Thus, mouse models that mirror the disease in humans with greater fidelity than do current models could be derived and tested for their utility to serve as surrogates for investigating new therapies aimed at combating autoimmunity. Such work would enhance the development of safe compounds for later testing in patients with type 1 diabetes.

Developing a Safe and Universal Means for Primary Prevention

Vaccination programs have dramatically cut rates of infectious diseases, such as measles, rubella, diphtheria, tetanus, mumps, and polio. These examples clearly show how prevention is more efficient and effective than treatment. With improved identification of environmental factors that modulate autoimmunity, potential targets for vaccination could be revealed for prevention of type 1 diabetes in humans.

Jodie and Dillon Distel:

Participating in Clinical Research To Fight Against Type 1 Diabetes

Jodie Distel had just given birth to her son, Dillon, at St. Joseph's Hospital in Denver, Colorado, when she was asked if she would like to participate in something called the Diabetes Autoimmunity Study in the Young, or DAISY. The study, she was told, would initially involve a fairly simple test: Blood from her newborn son's umbilical cord would be screened for genes that could indicate whether he was at high risk for developing type 1 diabetes.

"I didn't know very much about the disease," says Jodie, "but I figured that if taking part in the study might benefit someone else's child or my own son, that it was okay with me." She signed up for the study on the spot.

Within a week after Dillon's birth, Jodie was taken totally by surprise to learn that test results indicated that Dillon was at high risk for developing type 1 diabetes. Later, Jodie recalls, study staff alerted her that it was extremely likely that Dillon would have the disease by the time he was 8 years of age. In fact, exactly 3 days after his seventh birthday, Dillon was formally diagnosed as having the disease.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Jodie. Now, looking back, she adds that, "Participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

What Is DAISY?

DAISY is one in a group of epidemiological studies that researchers are pursuing to better understand the underlying causes of type 1 diabetes. The study is based at the University of Colorado Health Sciences Center in Denver. Marian Rewers, MD, the lead investigator for the study, says, "With DAISY, we have two primary objectives. One is to find out what causes [type 1] diabetes; the other is to find ways to prevent it."

To those ends, DAISY researchers are following two groups of children at risk for type 1 diabetes. One group was identified through screening a general population of newborns—which is how Jodie and Dillon got involved in the study. The other group consists of children who have a parent or sibling with type 1 diabetes.

"I had no idea before taking part in the study that diabetes would be a factor in our lives," says Jodie. Now, looking back, she adds that, "Participating in DAISY is probably the best thing I've ever done for Dillon and his future!"

Children who participate in DAISY are followed until they receive a clinical diagnosis of type 1 diabetes or until age 15, whichever comes first. Follow-up includes interviews with the parents to determine a child's diet and exposure to certain viruses, as well as periodic blood tests for three different antibodies against insulin-producing pancreatic islet cells, starting at 9 months of age. Like the initial genetic screening, the antibody tests are used to predict risk of developing type 1 diabetes. The presence of antibodies indicates that the autoimmune process has

begun. Dillon's blood tests were negative for antibodies against the insulin-producing islet cells until he reached the age of 2, at which time he began showing an elevated level of one antibody. Subsequently, his blood was tested more frequently, every 3 to 6 months. At three-and-a-half years of age, he began showing an elevated level of two antibodies. Other markers for diabetes began to change as well. Over time, Dillon's levels of a marker called hemoglobin A1c (HbA1c) began to show an upward trend. Finally, his blood sugar levels became elevated. On December 13, 2004, Dillon was diagnosed with type 1 diabetes. He started on a low dose of insulin, and is currently doing very well. As of January 2006, he has never been hospitalized for diabetes-related conditions. With only about one-quarter of the insulin dose it usually takes at his age, physicians are currently able to keep Dillon's levels of the HbA1c marker at a level consistent with improved long-term health outcomes in people with type 1 diabetes.

By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

Dillon's case appears to support previous observations that early diagnosis helps, to some degree, to preserve the body's insulin production. This may be in part due to avoiding a condition called diabetic ketoacidosis (DKA), a dangerous metabolic condition caused by profound insulin deficiency. Prior to diagnosis, many patients with undetected type 1 diabetes will develop DKA, which, if untreated, places them at risk of diabetic coma and death. However, the severe metabolic disturbance of DKA is not only life-threatening, but it also further damages any residual insulin-producing cells. Thus, early detection helped Dillon to avert both DKA and DKA's negative impact on his already compromised ability to produce insulin—and, by doing so, likely contributed to his need for less aggressive insulin therapy at diagnosis.

The benefits of early detection and preservation of the body's capacity to produce insulin can last many years. In the landmark Diabetes Control and Complications Trial, for example, participants who had preserved insulin secretion not only had better blood sugar control and lower insulin requirements, but also had a 50 percent lower risk of eye complications and a 65 percent lower risk of severe hypoglycemia, or low blood sugar (a risk patients face as a result of insulin treatment).

Thus, early detection of type 1 diabetes can provide both immediate and longer-term health benefits. "Dillon is in a much better situation than if we had not participated in the study," says Jodie. In addition to testing a child's blood for antibodies and elevated sugar levels, the families of the children who participate in DAISY are educated about what to expect in the way of symptoms, how to do blood sugar tests at home, and more.

As part of the DAISY research efforts, "one of the best things we do is to educate families, from the time their child's screening indicates high risk, straight through to diagnosis, if that should end up being the case," says Michelle Hoffman, RN, the clinical coordinator for DAISY.

Benefits of the DAISY Study

Since December 1993, the DAISY study has screened more than 33,000 newborns in the Denver, Colorado, area for genetic markers that would indicate high risk for type 1 diabetes. Of those, the study has followed more than 2,000 children whose genetic screenings indicated that they were at high risk for developing the disease. Of those, 143 children developed islet cell autoimmunity—a condition present in the majority of cases of type 1 diabetes, although people with islet cell autoimmunity do not always progress to onset of the disease. Of those 143, 48 have developed type 1 diabetes.[2]

"It should be noted," says Dr. Rewers, "that 90 percent of children in the United States diagnosed with type 1

[2] These numbers are current as of December 2005.

diabetes are hospitalized at the onset of the disease, and nearly one-third of those enter the hospital with DKA." According to Dr. Rewers, approximately 100 children die each year of DKA. However, of the 48 children in the DAISY study who went on to develop full-blown type 1 diabetes, only one—an 11-month-old infant—needed to be hospitalized at disease onset.

Therein lies one of the benefits for participants in the DAISY study: By participating in research studies that follow children from birth who are at high risk for type 1 diabetes, both the parents and children are better prepared if and when a child experiences onset of the disease.

Jodie lived for 7 years with the hope that Dillon would never be diagnosed with type 1 diabetes. However, when the diagnosis came, she was knowledgeable. "Because of the DAISY program, I think Dillon and I were prepared to handle Dillon's being diagnosed, and I think we had to go through far less than any other child and family who do not have the benefit of learning and recognizing early indications of this life-changing disease," she says. "From day one, I was told what symptoms to look for, and I mentally prepared myself for this day and how I would help Dillon from that day."

Because diabetes is an insidious disease, "most families are blindsided; they don't know what to look for to recognize onset of the disease," says Dr. Rewers. "When eventually diagnosed, the overwhelming majority of these children end up in the hospital, and many are fighting for their lives—at great emotional expense to themselves and their families, and financial expense to our society." He adds, however, that until researchers can discover and develop prevention strategies to arrest disease onset, they do not currently recommend extending screening programs outside of the research setting.

Research Findings

In addition to refining ways to recognize a genetic predisposition to diabetes and to pursue effective family follow-up, DAISY has been responsible for a number of significant findings. "For example," says Dr. Rewers, "by closely following these children, we've been able to rule out quite a few environmental factors once suspected as triggers for the onset of diabetes."

DAISY has also opened up new areas for investigation. For example, researchers are currently investigating whether the introduction of baby cereals may have something to do with the onset of inflammation in the pancreas that leads to diabetes. "We've discovered through DAISY that if babies at increased risk of type 1 diabetes first eat cereal regularly in their diets before 4 months of age, or after 6 months, their risk of islet autoimmunity is four to five times higher than if they begin eating cereal between 4 and 6 months of age," says Dr. Rewers. (The current American Academy of Pediatrics recommendation is to breast-feed babies and begin introducing iron-enriched solid foods, such as cereal, beginning at 6 months of age, if the child is ready [17].) For children who have a specific genetic marker that is known to strongly predispose individuals to type 1 diabetes, the risk appears to be even greater. According to Dr. Rewers, "These children have an overall increased risk of islet autoimmunity six times higher if fed cereal before age 4 months, and twelve times higher if cereal is delayed beyond 6 months, than if they are started on cereal at age 4 to 6 months." Research is ongoing to tease out the answers to this and other challenging issues regarding possible causes of type 1 diabetes and factors contributing to its onset.

> ***"The more brain power contributing to this effort, and the better we can coordinate our work and findings, the greater the chances of our discovering ways to more quickly develop prevention strategies for type 1 diabetes," says Dr. Rewers.***

TEDDY—A Collaborative Effort

In addition to DAISY, other studies have contributed

many important insights to advance research on environmental factors in type 1 diabetes. However, there are limitations to smaller studies, such as the number of patients that can be recruited in a given location. To overcome these limitations, the NIH spearheaded the launch of a long-term, international, collaborative effort to identify environmental triggers of type 1 diabetes. Begun in 2002, this effort is called "The Environmental Determinants of Diabetes in the Young," or TEDDY. Funded by the *Special Statutory Funding Program for Type 1 Diabetes Research* (see www.T1Diabetes.nih.gov), TEDDY consists of six centers in the United States, Finland, Sweden, and Germany. The creation of the TEDDY consortium allows for: a coordinated, multidisciplinary approach; collection of data and information in a standardized manner; greater statistical power than can be achieved in smaller studies; and the creation of a central repository that includes data and biological samples for use by the scientific community.

Researchers participating in TEDDY—including the Denver investigators who have conducted DAISY—are recruiting newborns who are genetically predisposed to developing type 1 diabetes. They are screening newborns from the general population, as well as newborns who have parents or siblings with the disease. The children will be followed until they are 15 years old or until they develop islet autoimmunity or type 1 diabetes. This long-term study will amass the largest data set and samples on newborns at risk for type 1 diabetes anywhere in the world.

"The more brain power contributing to this effort, and the better we can coordinate our work and findings, the greater the chances of our discovering ways to more quickly develop prevention strategies for type 1 diabetes," says Dr. Rewers.

TEDDY is currently enrolling patients. TEDDY enrollment sites in the United States are located in Georgia, Florida, Colorado, and Washington. For more information on enrolling in TEDDY, please see: www.niddk.nih.gov/fund/diabetesspecialfunds/t1d_ctcr/study.asp?StudyID=121