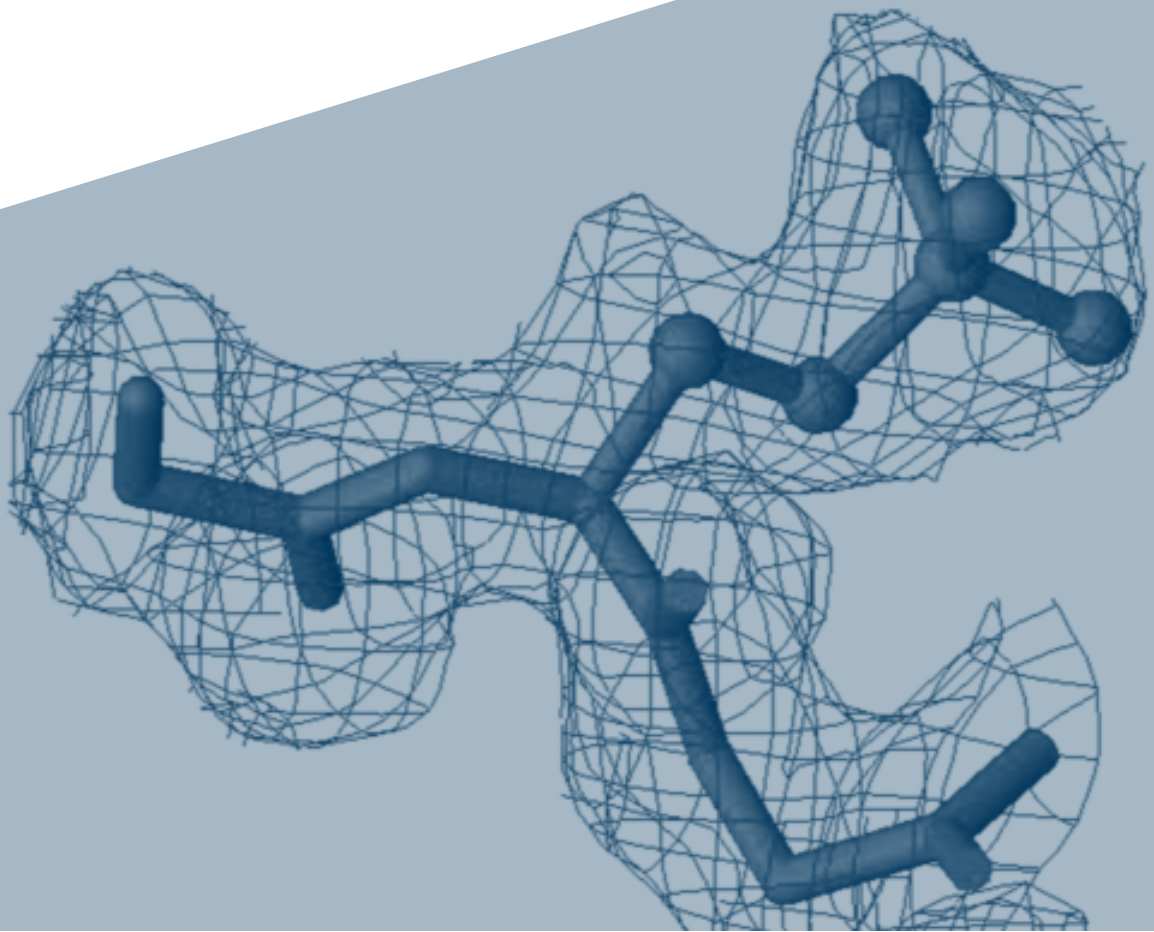
GOAL II

PREVENT OR REVERSE TYPE 1 DIABETES



Type 1 diabetes is an "autoimmune" disease that results when T cells from the body's own immune system mistakenly attack the insulin-producing beta cells in the pancreas. T cells that recognize proteins from the beta cell are normally eliminated during their maturation, but in susceptible individuals these diabetes-causing T cells migrate to the pancreas and initiate an inflammatory process that eventually destroys the beta cells. The other arm of the immune system—the B cells—produces antibodies that also recognize beta cell proteins. Although an exact role in disease progression has not been defined, these "autoantibodies" are well-established markers that predict an individual's risk of developing type 1 diabetes. Research to explore the defects in both the T and B immune cells that are associated with autoimmunity will lead to new methods to diagnose, treat, and ultimately prevent type 1 diabetes.

Another key objective of research to prevent type 1 diabetes is finding ways to generate immune tolerance—the process by which the immune system accepts a protein or other molecule as "self" and no longer mounts a destructive response against cells or tissues containing that protein. Tolerance induction can, in theory, block the autoimmune process underlying type 1 diabetes and is critical to the success of promising, new strategies to cure this disease by islet transplantation. Ideally, effective therapies to induce tolerance should selectively halt harmful immune processes without globally suppressing a patient's entire immune system.

The Special Statutory Funding Program for Type 1 Diabetes Research has sparked a major expansion of research efforts on the prevention or reversal of type 1 diabetes. Multiple, newly established clinical trial networks and research consortia will facilitate collaborations between basic and clinical investigators, promote bench-to-bedside translational research, and test new approaches for preventing the onset of disease. Investigator-initiated research has been fostered to advance the understanding of the molecular and cellular causes of autoimmunity and to explore novel therapies to prevent or reverse the fundamental immune system defects that lead to type 1 diabetes. Particular attention has been given to pilot studies that support innovative, high-impact research and that may attract new investigators to diabetes research.

Graphic
Antibody structure.

MAJOR RESEARCH CONSORTIA AND RESOURCES

With the marked increase in special statutory funds that became available in FY 2001, major research consortia, trial networks, resources, and research solicitations were launched in FY 2001 and FY 2002. Brief descriptions of the research efforts and expected outcomes of initiatives supported in whole or in part by the special funds are presented below. More detailed scientific plans are available in Appendix 3.

Type 1 Diabetes TrialNet (RFA DK01-003 and DK01-004)

TrialNet is a network of clinical centers, investigators, and core support facilities in the U.S. and Canada that supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new-onset patients and to prevent type 1 diabetes in those at-risk of developing this disease. TrialNet, which was initially funded in September 2001, is comprised of 14 clinical centers and approximately 350 recruitment sites. A solicitation to invite international participation in this effort was issued by the JDRF in 2002. A number of potential protocols testing new agents—including antigen-based therapies, antibody-based therapies, and novel immunosuppressives—are in varying stages of development. The TrialNet sponsors, NIDDK, NIAID, NICHD, JDRF, and ADA, expect this initiative to extend beyond 5 years in duration.

Immune Tolerance Network (ITN): Immunomodulation for New-Onset Type 1 Diabetes (RFP AI-DAIT-99-30)

Tolerance—the inhibition of harmful immune destruction of tissue while preserving protective immune responses—is key to prevention of autoimmune disorders such as type 1 diabetes. The ITN, an international consortium of more than 70 basic scientists and clinical investigators, is evaluating promising tolerogenic treatment regimens in four clinical areas: islet transplantation, kidney transplantation, autoimmune diseases, and asthma and allergy diseases. The state-of-the-art immune assays of the ITN, together with the network of clinical sites provided by TrialNet, afford a unique opportunity for clinical studies of new therapies for immunomodulation to prevent or delay type 1 diabetes. The ITN, which is jointly sponsored by the NIAID, NIDDK, and JDRF, began in 1999 and will extend at least through 2005.

Autoimmune Disease Prevention Centers (RFA AI00-016)

Preclinical research is key to the development of strategies for immunomodulation that can be tested through clinical networks such as TrialNet and the ITN. The Prevention Centers initiative supports a collaborative network of investigators who focus on understanding the immune mechanisms underlying autoimmune diseases, pinpointing the mechanisms and consequences of manipulating the immune response in autoimmunity, and applying this knowledge to the prevention of autoimmune disease in humans. This research aims at uncovering methods to halt the development of autoimmune diseases, such as type 1 diabetes, prior to clinical onset, by mechanisms other than global immunosuppression. The Prevention Centers were launched in 2001 with support from the NIAID, NICHD, NIDDK, the NIH Office of Research on Women's Health, and JDRF, and will continue for at least 5 years.

Trial To Reduce the Incidence of Type 1 Diabetes in the Genetically-At-Risk (TRIGR)

TRIGR, a multi-center, randomized, controlled clinical trial, will ascertain if weaning infants onto a hydrolysate of cow's milk formula *versus* standard cow's milk formula will reduce the incidence of the development of autoantibodies associated with type 1 diabetes. Anticipated enrollment is 2,370 infants at high risk for developing type 1 diabetes. The TRIGR study, which is led by the NICHD and was

initially funded in September 2001, is expected to take up to 10 years to complete. Notably, the special funds for type 1 diabetes research have been leveraged by a factor of seven by support gained from six co-sponsors—the Canadian Institutes of Health Research, the European Foundation for the Study of Diabetes, the European Union, JDRF, the Netherlands Diabetes Foundation, and industry.

Diabetes Autoantibody Standardization Program (DASP)

The presence of autoantibodies is currently the best way to predict the onset of type 1 diabetes before the appearance of clinical symptoms. DASP was formed in FY 1998 as a collaboration of the CDC with the Immunology of Diabetes Society. It seeks to improve the measurement of autoantibodies predictive of type 1 diabetes and to decrease laboratory-to-laboratory variation. In 2000, 46 laboratories in 13 countries participated in the first evaluation of autoantibody measurements. The results of extensive data analysis from this effort were distributed to participants to aid them in improving their autoantibody assays. Sets of reference samples with information on autoantibody levels were distributed to laboratories for use in further refining measurements and for comparison of new methodologies with the best existing autoantibody assays. A follow-up DASP evaluation began in 2002.

C-Peptide Standardization

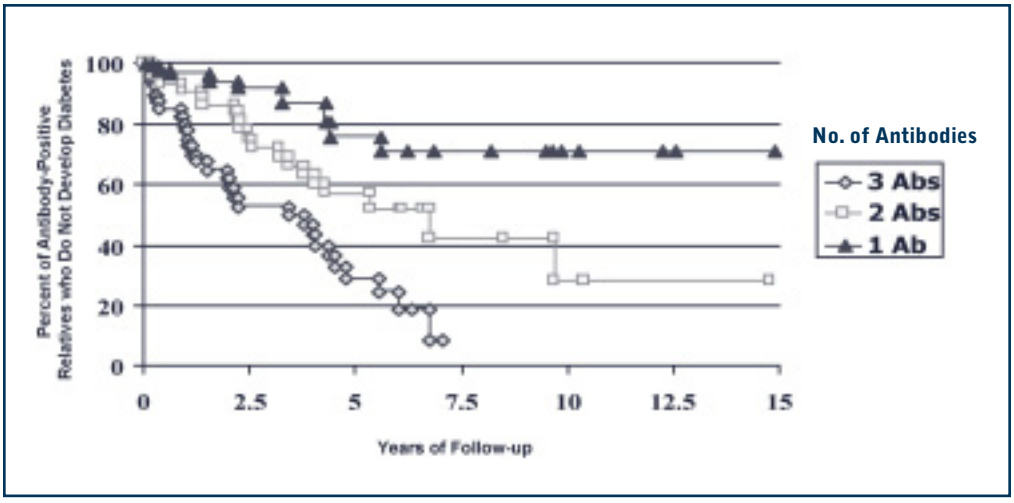
Clinical trials of agents to preserve beta cell function in new-onset type 1 diabetes will use C-peptide, a by-product of insulin production, as an outcome measure. Standardization of C-peptide assays across laboratories would facilitate the conduct of these clinical trials. In FY 2002, the NIDDK and CDC initiated a joint project for standardization of C-peptide measurement.

Data and Biosample Repository (RFP NIH-NIDDK-02-04)

In FY 2003, the NIDDK is establishing a central repository for biologic samples, such as blood, DNA, and cell lines, that are collected in the course of clinical trials. This research resource will benefit multiple research consortia and trial networks, including TrialNet, the Triggers and Environmental Determinants of Diabetes in Youth (TEDDY) consortium, the Type 1 Diabetes Genetics Consortium, and others. Researchers within these consortia and from the broader scientific community will have access to these biologic samples for peer-reviewed studies that will support and extend the primary trial objectives.

Researchers now have methods to predict with great accuracy which relatives of type 1 diabetes patients will develop the disease. This figure shows the association between the onset of disease and the presence of autoantibodies, a component of the autoimmune attack. Antibodies can potentially arise against several islet proteins. The number of proteins for which antibodies are present correlates with the risk of developing diabetes over time. The Diabetes Autoantibody Standardization Program has been established to improve the measurement of autoantibodies associated with type 1 diabetes. The accuracy and sensitivity of these assays will facilitate the conduct of clinical trials to prevent the onset of disease in at-risk individuals.

(Credit: Dr. George Eisenbarth, University of Colorado Health Sciences Center)



HIGHLIGHTS OF SCIENTIFIC DISCOVERIES

Many significant scientific advances have emerged from investigator-initiated research that began in the early years of the special statutory funding program. Highlights of these discoveries are provided here. More extensive discussion of initiatives and their research progress can be found in Appendix 3. Some grants or programs supported by the early initiatives are still in progress and the full impact of these projects on preventing type 1 diabetes may not be realized for several years. It is premature to assess accomplishments of the newly formed consortia or investigator-initiated research grants awarded in FY 2001 or FY 2002.

Understanding, Detecting, and Monitoring Autoimmunity

- Rapid assays were developed to detect anti-islet autoantibodies. These new assays will facilitate organ donor screening to identify pancreata that may be suitable for immunopathogenetic research and to aid in the identification of individuals at high risk for type 1 diabetes.

- In the NOD mouse model of type 1 diabetes, a key role was demonstrated for islet autoantibodies transmitted from a mother to her progeny in promoting autoimmune diabetes. This work may serve as a foundation for the design of prospective clinical studies aimed at determining whether the transmission of islet specific autoantibodies from human mothers to their genetically susceptible children affects the onset of type 1 diabetes.

Novel Approach To Preventing or Reversing Type 1 Diabetes

- The development of "immunologic vaccines" to prevent or delay beta cell loss using self-peptides is a newly developing field. Animal studies of the insulin B:9-23 peptide showed therapeutic promise, but led to the discovery that anaphylaxis—a severe allergic reaction—is a significant risk that will need to be monitored in clinical trials of this peptide as a treatment approach for halting the development or progression of type 1 diabetes. A potential mechanism for modifying such peptides to avoid anaphylaxis has been developed. This research will help in designing safer and more effective "vaccines" for diabetes and many other disorders as well.

New Animal Models for Type 1 Diabetes Research

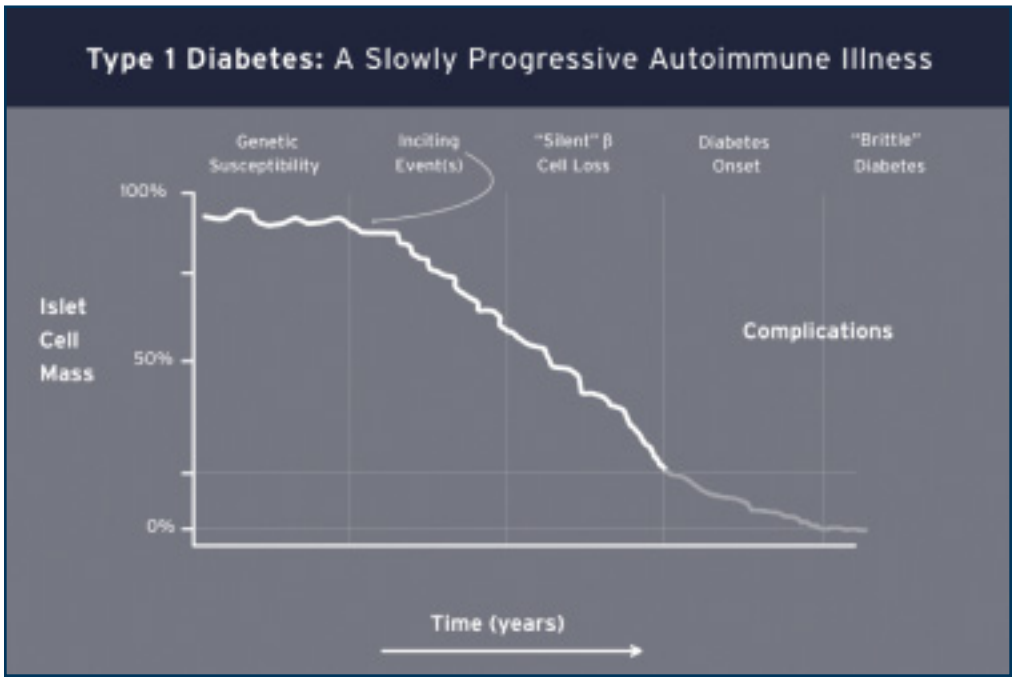
- Scientists have produced a novel, "humanized" mouse model that expresses a human histocompatibility antigen gene (HLA) and develops spontaneous diabetes due to this gene. These mice will help dissect the role played by various HLA molecules implicated in susceptibility or resistance to type 1 diabetes and provide a better model for preclinical, therapeutic studies to prevent this disease.

- IA-2 is a major autoantigen in type 1 diabetes with nearly 70 percent of newly diagnosed patients displaying autoantibodies to this protein. IA-2 deficient—"knockout"—mice have been developed and will be important research tools for understanding the potential role of these autoantibodies in triggering the autoimmune attack in type 1 diabetes. Studies in the IA-2 knockout animals have shown that these mice have significant alterations in glucose tolerance tests and insulin secretion.

Clinical Trials To Prevent or Delay Type 1 Diabetes

- Repressing the autoimmune response in susceptible individuals without globally impairing the immune system is critical to the design of therapies for type 1 diabetes. An anti-CD3 monoclonal antibody has been evaluated in a pilot clinical trial as a therapeutic agent in individuals with new-onset type 1 diabetes. Encouragingly, most of the patients in this trial maintained or improved the ability to produce their own insulin during the first year after being diagnosed with type 1 diabetes. A larger trial to extend these preliminary findings on the effectiveness of the anti-CD3 antibody in preventing type 1 diabetes is in progress. Importantly, this potent immunosuppressive agent was shown to prevent type 1 diabetes in a mouse model without also suppressing the animals' immune response to a viral infection.

- The Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) undertook two clinical trials to determine if either injected or oral insulin could prevent or delay the onset of type 1 diabetes in at-risk individuals. The DPT-1 showed no effect of injected insulin on the development of type 1 diabetes despite previous encouraging data from animal studies and a small pilot trial in humans suggesting that this could be an effective prevention strategy. Because some physicians, relying on the preliminary studies, had already been treating at-risk patients with insulin injections, the disappointing, yet definitive, results of this trial show the importance of conducting large-scale, randomized, controlled clinical trials to thoroughly validate potential therapies so that patients are not subject to ineffective and burdensome "therapies." Indeed, an editorial in the May 2002 New England Journal of Medicine, which published the DPT-1 results, characterized this trial as "a landmark attempt to intervene in the natural history of beta cell destruction before the clinical onset of diabetes."



Type 1 diabetes is a progressive autoimmune disease in which the insulin-producing beta cells, found in clusters called "islets" within the pancreas, are slowly destroyed by the immune system before the onset of clinical symptoms. Once beta cell mass falls below a critical threshold, patients require insulin therapy to regulate blood glucose levels and sustain life. The Type 1 Diabetes TrialNet and the Immune Tolerance Network are developing and testing innovative therapies to block or reverse the immune system's attack on the pancreatic islets.

(Credit: Dr. David Harlan, NIDDK)

EXTERNAL EVALUATION

This section provides commentary from leading scientific experts within the diabetes research community who assessed the accomplishments of the special statutory funding program and from researchers who participated in the use of the special funds. A complete description of the evaluation process and the use of evaluative data regarding the special funding program is available in the Assessment chapter and Appendix 2.

Advisory Panel

A panel of scientific and lay experts on type 1 diabetes research convened at the NIH in May 2002 to review the use of the special statutory funds. Comments from the advisory panel regarding initiatives related to the prevention or reversal of type 1 diabetes that were established by the special funding program include:

- The advisory panel agreed that the results of the injected insulin arm of the DPT-1 represented a significant advance by validating the biomarkers that were used to predict individual risk of type 1 diabetes and providing data that will be invaluable to the design of future research through TrialNet. Moreover, the panel was optimistic about the potential for successful immunoprevention of type 1 diabetes, including the ongoing oral insulin trial that has been subsumed within TrialNet and studies of other agents through the newly created clinical trial networks.

- The establishment of large-scale, collaborative research consortia and trial networks was strongly endorsed by the panel. The advisors identified many potential opportunities created by those programs, including TrialNet, the ITN, and the Autoimmune Disease Prevention Centers, that could facilitate the rapid development of essential research tools for the entire community. In addition, the panel reinforced the benefits of developing and maintaining close interactions between the various research consortia supported by the special funds to maximize their complementary expertise.

- The joint NIH-CDC project to standardize C-peptide assays was regarded by the advisory panel members as an extremely important and positive use of the special funds and an example of the type of standardization efforts that should be pursued in other areas of diabetes research for the attainment of more rapid clinical progress.

Extramural Grantees

Principal investigators who received grants or grant supplements related to the prevention of type 1 diabetes responded to a survey asking, in part, about the value of this grant or funding source. Representative remarks include:

- "The initial idea of the proposed studies funded by the grant was considered (even by the study section reviewers) as ambitious and risky. However, with the grant support, we were able to perform the proposed experiments and achieve the goals of the grant."

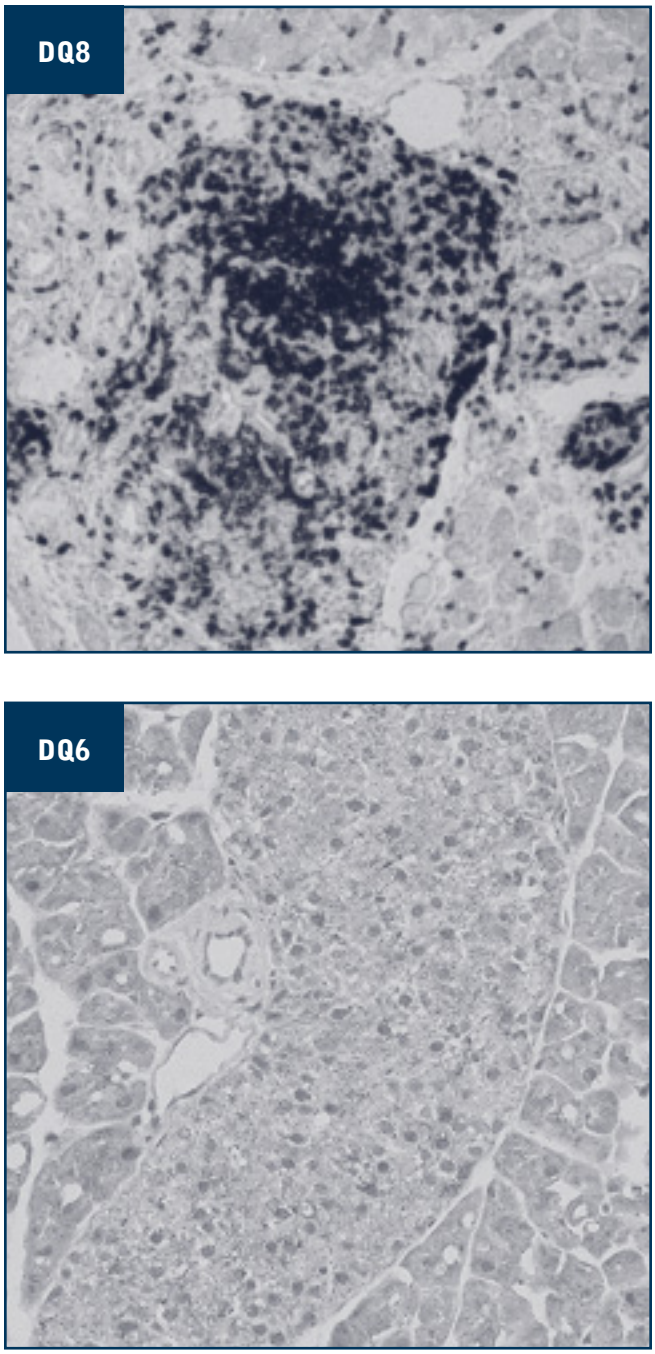
- "This funding was invaluable in permitting the initiation of a relatively short-term/high-risk project, albeit with a compelling hypothesis and logical preliminary data. The findings resulting from this work will open a novel area of clinical investigation. It is hoped that their extension to a clinical setting will provide more powerful predictive/preventive methods necessary for the elimination of type 1 diabetes."

- "I think the R21 [pilot and feasibility] mechanism was of particular value where essential, high-risk information was to be gained [through preliminary studies] that would not qualify for the R01 mechanism."

- "We have received many requests from and provided to investigators in the type 1 diabetes research community nationwide and internationally [mice developed as a result of this funding] for their 'bench-to-bedside' studies."

- "Support by this program has given me the opportunity to enter into and focus my research career on a new research problem, type 1 diabetes. It afforded me the opportunity to assemble a critical mass of investigators that work in a variety of disciplines, but often studying similar signaling mechanisms. It is my opinion that support of these types of collaborations will significantly accelerate our understanding of the cause of type 1 diabetes and will expedite the development of successful therapeutic treatments aimed at diabetes as well as other diseases."

- "The award set my career on a direction towards one active in organizing collaborations, recruiting new investigators into diabetes research, and moving scientific discovery towards preclinical and clinical application. In addition, the successful organization of this program has attracted support from the institution, state, private foundations, and individuals."



Important human HLA genes have been inserted into mouse DNA. When the human gene (DQ8) that predisposes people to type 1 diabetes is used, mice become diabetic and their pancreatic islets show evidence of attack by T cells of the immune system (*dark-stained cells in top panel*). In contrast, mice that carry the protective human gene (DQ6) do not become diabetic and their islets are free of immune cell infiltration (*bottom panel*). These "humanized" mouse models will aid researchers in uncovering the role of the HLA molecules in the destructive autoimmune process leading to type 1 diabetes. This research was supported in part by the Special Statutory Funding Program for Type 1 Diabetes Research.

(Photo Credit: Reproduced from The Journal of Experimental Medicine, 2000, 191(1): 97-104, by copyright permission of The Rockefeller University Press.)

"FRIEND AND FOE:" TACKLING THE IMMUNE SYSTEM TO DEVELOP THERAPEUTICS FOR TYPE 1 DIABETES

At the heart of the immune system is the ability to distinguish between self and non-self. Virtually every cell in the body carries distinctive molecules that identify it as self.

The body's immune defenses do not normally attack tissues that carry a self marker. Rather, immune cells and other tissues coexist peacefully in a state known as self-tolerance. But when immune defenders encounter cells or organisms carrying molecules that say "foreign," the cells of the immune system move quickly to eliminate the intruders.

Any substance capable of triggering an immune response is called an antigen. An antigen can be a virus, a bacterium, a fungus, or a parasite, or even a portion or product of one of these organisms. Tissues or cells from another individual, except an identical twin whose cells carry identical self-markers, also act as antigens; because the immune system recognizes transplanted tissues as foreign, it rejects them.

Sometimes the immune system's recognition apparatus breaks down, and the body begins to manufacture antibodies and T cells directed against the body's own constituent cells or cell components, and possibly specific organs. Such antibodies are known as autoantibodies, and along with self reactive T cells, cause autoimmune diseases.

Type 1 diabetes is an autoimmune disease, in which immune tolerance is broken by as yet unidentified environmental factors in genetically predisposed individuals. In its initial phase, which is clinically silent, T cells and other inflammatory cells invade the islets of the pancreas and eventually destroy the insulin-producing cells.

Because the pancreatic beta cells are the only cells in the body capable of making insulin, their loss results in the loss of insulin production. By the time type 1 diabetes is diagnosed, it is estimated that up to 90 percent of a person's insulin producing capacity might already be destroyed. Insulin is essential for life because it is required for control of blood sugar levels, energy storage, and metabolism; therefore, patients with type 1 diabetes must rely on externally administered insulin to survive.

Several major consortia supported by the Special Statutory Funding Program for Type 1 Diabetes Research—including the Type 1 Diabetes TrialNet and the Immune Tolerance Network—provide unprecedented opportunities to develop and test novel therapeutic approaches designed to prevent, reverse, or even cure type 1 diabetes by overcoming the aberrant autoimmune process that is central to this disease. These consortia provide the infrastructure for multidisciplinary scientific teams to undertake the major challenges associated with pursuit of this important goal.

Loss of Tolerance in Type 1 Diabetes

Early in development, a person's immune system is educated to distinguish between self—body cells and their associated proteins and other molecules—and non-self—invading organisms and toxins. The resulting lack of self-reactivity is called "tolerance." Tolerance is achieved primarily by eliminating or suppressing T cells that would otherwise react to the body's molecules.

How do these normal activities and safeguards become breached and misdirected in autoimmune diseases such as type 1 diabetes? Although exquisite, the immune system is neither static nor fool-proof. The potential remains for self-reactivity—a reactivity that may be modulated by interactions with the environment. For example, the body's cellular proteins may be altered through chemical modifications or genetic changes and suddenly acquire non-self characteristics. Alternatively, a wave of cell death, as occurs in tissue remodeling during development, might release high levels of candidate antigens in persons already prone to an autoimmune response.

Sometimes, reactivity to self—or "altered self"—is beneficial to the body. For instance, considerable data suggests that our immune systems serve as a barrier against cancer in that those cells can be recognized as abnormal and therefore subjected to destruction that is mediated by the immune system. However, when reactivity to self goes awry, the resulting autoimmune disorders can range from the killing of cells in multiple organs as in systemic lupus erythrematosus, to more specific killing as occurs in the destruction of the protective myelin protein sheaths around nerves, which results in multiple sclerosis, or the destruction of insulin-producing cells seen in type 1 diabetes. Although the targets and triggers may differ, the end result is that a healthy cell somehow sets off the same alarm bells for the body's immune defense system as a harmful invader, thereby abrogating tolerance and causing disease.

In type 1 diabetes, the loss of immune tolerance to beta cells leads to inflammation and infiltration of T cells into pancreatic islets (insulitis) followed by T cell-mediated destruction of beta cells in the islets, loss of insulin production, and frank diabetes. Concomitantly, the B cells that usually make antibodies that protect against infectious agents, start to produce "autoantibodies" that are directed against one or more beta cell proteins, including insulin itself. Patients are usually unaware of the impending disease development, which typically occurs silently over several years. However, during the period of silent progression of the disease, these autoantibodies can be detected, and this information allows identification of those at risk prior to the onset of clinically apparent diabetes.

The greatest challenge in developing treatments for type 1 diabetes lies in the fact that the autoimmune process appears to arise from a complex interplay of genetic and environmental factors. The same factors that give rise to autoimmune destruction of the beta cells also complicate efforts to treat the disease. Thus, the specter of autoimmunity looms over all efforts to combat the disease. For example, beta cell replacement therapy, currently accomplished through whole pancreas or islet transplantation, is always subject to the possibility of recurrent autoimmune attack that will target and destroy the replacement beta cells much as it did the native ones.

Any attempt to modulate the immune system to overcome autoimmunity in type 1 diabetes must recognize the immune system's critical role in combating infection and removing cancerous cells. Past therapeutic trials for type 1 diabetes—using immunosuppressive drugs such as cyclosporine, antithymocyte globulin, and prednisone—transiently improved clinical measures of disease, but the benefits were dependent upon long-term administration of potent immunosuppressive drugs that have toxic side effects. Because type 1 diabetes is typically diagnosed in childhood, it is particularly important to balance the long-term costs of immunosuppression, such as infection and susceptibility to tumors, with the benefits of preserving endogenous insulin secretion. Insulin therapy, while burdensome and imperfect, does have a proven safety profile, and glucose monitoring techniques and methods to deliver insulin are continually improving. Thus, new therapies to prevent or reverse type 1 diabetes must have a more favorable profile of risks and benefits than insulin replacement. Developing therapeutics that can re-educate the immune system to tolerate beta cells (immune tolerance induction), while causing minimal disturbance to normal immune function, is central to the permanent, complete success of any therapies to prevent, reverse, or cure type 1 diabetes.

To develop therapeutics that will induce tolerance to beta cells, researchers are focusing on three major mechanisms at work in T and B cell activation in both normal and autoimmune responses: (1) stimulatory interactions between antigens and cell surface receptors on T and B cells; (2) co-stimulatory pathways that are necessary for activation; and (3) soluble and cell-surface regulatory molecules that further modulate the immune response. Knowledge about each of these mechanisms is rapidly expanding, and each provides potential targets for intervention, many of which are being tested in preclinical models and clinical trials.

"FRIEND AND FOE:" TACKLING THE IMMUNE SYSTEM TO DEVELOP THERAPEUTICS FOR TYPE 1 DIABETES (CONTINUED)

Accelerating Therapy Development

The Immune Tolerance Network (ITN) and the Type 1 Diabetes TrialNet conduct research on novel methods to block or reverse autoimmune destruction of the pancreatic islets. ITN investigators are developing, implementing, and assessing clinical strategies and biological assays for the induction, monitoring, and maintenance of immune tolerance in transplantation and autoimmune diseases, including type 1 diabetes. The ITN is a collaborative, international consortium spearheaded by the National Institute of Allergy and Infectious Diseases (NIAID), with participation by the NIDDK and the JDRF. The ITN works in concert with the NIDDK's Type 1 Diabetes TrialNet, which provides a large consortium of 14 clinical centers and over 350 recruitment sites, a data coordinating center, and laboratory facilities to conduct rapid, preliminary clinical trials for therapies that may delay, reverse, or prevent type 1 diabetes. Formed in response to recommendations from the congressionally-established Diabetes Research Working Group, TrialNet provides an infrastructure for the testing of emerging therapies, and ensuring access to a group of patients who can be quickly identified and enrolled in clinical trials. Together, the ITN and TrialNet are focusing not just on the clinical testing of therapies, but also on broad data capture, biological sample preservation, and assay development to provide important tools and resources to other clinical researchers. Complementing these efforts, a number of NIH and CDC-supported research groups and consortia are providing improved research tools by validating and standardizing autoantibody measurements, beta cell function tests, and metabolic readouts so that diabetes researchers can more meaningfully compare results. These collaborative efforts are all directed toward streamlining clinical data analysis and assessing the efficacy of potential new therapies.

Results from a number of clinical studies have demonstrated:

- Preserving normal insulin production, even to a small degree, greatly enhances the ability of an individual with type 1 diabetes to maintain normal blood sugar control and avoid episodes of dangerously low blood sugar (hypoglycemia).

- Predicting a person's risk of developing type 1 diabetes is possible by testing genetic susceptibility, measuring anti-beta cell autoantibodies in the blood, and testing beta cell function.

Thus, researchers with an interest in type 1 diabetes now have a widening window of opportunity to detect, stall, and possibly reverse type 1 diabetes. The Special Statutory Funding Program for Type 1 Diabetes Research is facilitating the rapid and efficient conduct of promising pilot studies through consortia such as the ITN and TrialNet, NIH intramural efforts, and bench-to-bedside efforts at academic centers nationwide. While it is not possible in research to predict "breakthrough" time tables, it is safe to say that therapies designed to promote self-tolerance will move forward now with much greater speed than was possible even in the recent past. These teams continue to work to achieve the long-sought goal of restoring self-tolerance, and thereby to preserve beta cell integrity and normal insulin production. When this goal is realized, individuals who have or are prone to developing type 1 diabetes may be able to once more view the immune system as a trusted friend, and no longer as an untrustworthy foe.

PATIENT PROFILE: Michelle Kiley

Type 1 Diabetes: Mother and Child

When Michelle Kiley and her husband, Tim, decided to start their family in the mid 1990s, they were told by Michelle's physician that the chance a baby born to her would develop diabetes was about three in 100. "I was told that as long as I kept my blood sugar, or glucose, levels under control, the odds were in my favor of delivering a healthy baby, and at the same time not encountering any complications to my own health," says 30-year-old Michelle, who has had type 1 diabetes since she was a toddler. In 1996, Michelle gave birth to the couple's first daughter, Eliza. Three years later, Eliza was diagnosed with type 1 diabetes. The Kiley's second daughter, Rebecka, was born in 1998 with low blood sugar. At the age of three, Rebecka was hospitalized for a short time with elevated blood sugar and a high fever. According to Michelle, Rebecka wasn't diagnosed with diabetes because her glucose levels returned to normal after a day or so. "The doctors aren't sure why," says Michelle. At the time of this interview Michelle is pregnant with her third child. She and Tim pray every day that neither Rebecka nor their soon-to-be-born child develops diabetes. In the meantime, Michelle Kiley lives with feelings of anger, frustration, guilt, and apprehension. "The day Eliza was diagnosed with the disease was the worst day of my life," says Michelle. "That is," she adds, "unless the same thing happens to my other children."

I believe that we all have a purpose in life. Sometimes people go their entire lives without knowing their purpose. I often thought that mine was having diabetes so I could be a role model for (my daughter) Eliza. But being here today has changed my beliefs. I see that Eliza and all these children have diabetes so that WE have role models. Eliza is a brave little girl, just as all the children here today. More brave than any of us could ever be, facing this disease HEAD ON.

— *Statement of Michelle Kiley in congressional testimony during a "Children's Congress" organized by the Juvenile Diabetes Research Foundation International.*

Michelle Kiley (left), with daughter Eliza (right). Michelle has benefited greatly from many research advances, including improved methods for glucose testing, insulin delivery, and glucose regulation. Although Michelle has had type 1 diabetes for 27 years, she has not yet developed complications of the disease, and is carefully controlling her blood glucose levels in the hope of preventing complications in the future. Michelle is also hopeful that research will produce new advances to help her daughter, who also has type 1 diabetes.

(Photo Credit: Juvenile Diabetes Research Foundation International)

Living with the Odds

For her entire life, Michelle wanted nothing more than to have children of her own. "I always felt as though God put me here on Earth to be a mother. To have children was my only wish," she says. But as a young girl she was told that, due to the difficulty people with diabetes have in keeping their blood sugar levels under control, she probably wouldn't be able to bear children. It is not uncommon for mothers with poorly controlled type 1 diabetes, for example, to experience severe complications after a pregnancy, such as diabetic eye disease or kidney disease, as well as to suffer from frequent miscarriages, stillborn babies, or congenital birth defects in their newborns. Current estimates indicate that:

- Poorly controlled diabetes before conception and during the first trimester of pregnancy can cause major birth defects in 5 to 10 percent of pregnancies and spontaneous miscarriages in 15 to 20 percent of pregnancies.

- Poorly controlled diabetes during the second and third trimesters of pregnancy can result in excessively large babies, posing a risk to both mother and child.

Over the years, however, scientific advances in techniques to better control blood sugar levels made the prospect of motherhood safer for Michelle and other women with type 1 diabetes. "Glucose monitors and insulin pumps improved our ability to monitor and control our blood sugar levels," says Michelle. "I was eventually told, that, yes, I could have children. As long as I kept myself under tight control—which I did—I was told that the odds of delivering a healthy child were in my favor."

But even with a healthy delivery, there remained a small yet significant risk—the risk of diabetes developing in the child. One summer night, Eliza got up at about 2:30 a.m. and asked Michelle for water, which she had never done before. It gave Michelle the "strangest feeling," but she let it pass. The next morning, Eliza went through four cups of fluid before Michelle got the nerve to test her. "My worst nightmare was confirmed in a matter of a 15-second blood test. I diagnosed Eliza with type 1 diabetes on July 11, 1999 at home with my glucose meter," says Michelle. Having had the disease for 27 years, Michelle knew what she, her daughter, and her entire family were up against.

Type 1 diabetes is a terrible burden to patients and their families. Yet, with improvements in medical treatment—made possible by diabetes research—many women with type 1 diabetes are able to have children, manage their own diabetes during pregnancy, and remain free of complications following pregnancy. If they do develop complications at a later date, research has demonstrated that there are effective measures they can take to slow their progression.

Caring for a Young Child with Type 1 Diabetes

The night before giving the interview for this profile, Michelle says she "broke down" because she couldn't get Eliza's blood sugar under control. "Last night, I cried for an hour and a half," says Michelle. "It's my responsibility to keep Eliza healthy," she adds. "I worry that her diabetes may lead to kidney problems, loss of eyesight, or a host of other health complications."

For now, Michelle and Tim are doing everything in their power to minimize the impact of diabetes on Eliza. On her fifth birthday, Eliza received an insulin pump. She knows how to use it, and the pump is set up so that she can't overdose herself with insulin. Nonetheless, Michelle is tethered to her cell phone. "Eliza will call me from school or a friend's house and I'll help her over the phone, then have an adult check the dosage, just to be sure," says Michelle. Although Eliza has no problems with the pump or testing her own blood level, she really "hates" to have the pump catheter inserted. "The other night Tim and I literally had to pin Eliza down to change the site, with Tim having to lie across her legs to hold her down."

At the same time, Michelle has to deal on a daily basis with her own diabetes, carefully monitor her second daughter, Rebecka, who may be at risk for the disease, as well as vigilantly monitor her current pregnancy. "Tim and I are both very excited, and very nervous," says Michelle about the pregnancy. She is followed carefully by a high-risk prenatal care group. In addition to monthly appointments with her obstetrician/gynecologist, Michelle also goes for ultrasounds and sees an endocrinologist on a monthly basis. "All until the seventh month," says Michelle, "when the visits will be accelerated to every 2 weeks."

But nothing seems to relieve the long-term anguish. "I've sacrificed 27 years of my life to this disease," says Michelle. "I sometimes cry myself to sleep asking why my daughters may have to sacrifice theirs, as well... I pray that Eliza won't hate me for giving her this awful disease."

PATIENT PROFILE: Michelle Kiley (CONTINUED)

If there is anything good at all about having the disease and also having a child with diabetes, says Michelle, "it's that at least I know what to expect. I feel sorry for parents with no understanding of diabetes. There is so much for them to learn that it can be overwhelming."

Scientific Breakthroughs Over the Years

Michelle is grateful that so far she has not experienced any complications as a result of her decades-long battle with type 1 diabetes. She credits much of that to the diligence of her own parents. "On our very first date, my father handed Tim a syringe and said, 'If my daughter passes out, you need to give her this injection or she's going to die.' Of course, my father had overstated the case a bit," says Michelle, "but he wanted to impress on Tim the seriousness of my disease."

People with diabetes are at high risk for complications that can cause blindness, kidney failure, amputations, heart attack, and stroke. As a child, Michelle took part in a diabetes research study that monitored her blood glucose levels. At about the same time, the NIH-sponsored Diabetes Control and Complications Trial (DCCT) began its examination of how blood glucose levels relate to complications of the disease. The results of this crucial trial and a similar one in Europe firmly established the importance of good blood sugar control in minimizing the organ and tissue damage resulting from diabetes. Other advances over the past decade with important clinical implications include:

- The identification of genetic and immune system markers that make it possible to screen relatives of people with type 1 diabetes to see if they are at risk for the disease.
- Progress in the development of accurate, non-invasive blood glucose sensors.
- The first successful transplants of pancreatic islets—clusters of cells that produce insulin—into patients with uncontrollable type 1 diabetes.

These advances should soon join a host of other research accomplishments, such as the development of a reliable test for long-term assessment of blood glucose levels ("HbA1C test") and the introduction of the insulin pump, which have contributed to the observed increase in lifespan and improved quality-of-life of persons diagnosed with type 1 diabetes over the past 30 years.

"Science has taken us a long, long way," says Michelle, who keeps up with diabetes research. "When I was a child, we didn't have meters or insulin pumps. My bathroom always looked like a science project in progress with all the tubes and eye droppers used for urine testing. There was no way to test blood sugar levels accurately in real time, as there is today. I got one shot of insulin a day, in the morning. Today, I do as many as eight blood tests a day on myself and use an insulin pump. Even more so now with my pregnancy. That's how I stay healthy."

Hope and Expectations

For most of her life, Michelle has been hoping for a cure for type 1 diabetes, and remains determined to see one. As she puts it, "for the sake of my children, I haven't given up hope. I can't!" Because of the complex nature of the disease, a cure for type 1 diabetes has proven elusive up until now, and the Kileys–quite understandably–worry constantly about the future of their daughters and their unborn child. Fortunately, the tremendous acceleration in the pace of type 1 diabetes research in recent years, fueled in part by a burst of new technologies, is rapidly generating new insights into the causes and the course of the disease. With this expanded knowledge, researchers are improving current therapies and contributing to the development of new ones. This fast-paced research also offers real hope that families like the Kileys will see the prevention of and, ultimately, a cure for this multi-faceted disease within their lifetimes.

PATIENT PROFILE: Quinn Nystrom

One Teen's Crusade to Find a Cure for Diabetes

When Quinn Nystrom's younger brother, Will, was diagnosed with type 1 diabetes at age five, physicians assured the family that it would be highly unlikely that either of Will's two siblings would ever be diagnosed with the disease. "The doctors told us that we would be on the cover of medical journals if that ever turned out to be the case," said Quinn, who was diagnosed with type 1 diabetes at age 13, just 2 years after her brother Will. Today, at age 16, Quinn is the American Diabetes Association's National Youth Advocate. She travels around the country speaking to other young people with diabetes—as well as to physicians and U.S. Senators. Her goal: to recruit her peers and adults, especially influential adults, to be advocates for people with diabetes. "The Centers for Disease Control and Prevention (CDC) is calling diabetes the epidemic of our time," says Quinn, who, as a teen, is knowledgeable and wise beyond her years—and knows her facts. "Today, 6 percent of the population has diabetes," she adds. "And experts say that number is growing fast." Quinn's message is simple: "We need to find a cure for diabetes."

All in the Family?

Approximately one in every 400 to 500 children and adolescents has type 1 diabetes. About 80 percent of new cases of type 1 diabetes occur in families with no history of the disease. However, researchers have evidence that type 1 diabetes has genetic links, and that predisposition to diabetes can be passed down through families.

Many researchers believe that—in addition to genetic links—environmental factors, such as a virus or a reaction to cow's milk at infancy, may trigger type 1 diabetes. These hypotheses are still being tested.

Since Quinn Nystrom was diagnosed with type 1 diabetes at the age of 13, she has become a passionate advocate for diabetes research. Type 1 diabetes is one of the most common chronic diseases of childhood and the majority of new cases are diagnosed in young children and adolescents. The Special Statutory Funding Program supports multiple research initiatives to uncover the genetic and environmental triggers of this disease.

(Photo Credit: American Diabetes Association)

PATIENT PROFILE: Quinn Nystrom (CONTINUED)

According to Quinn's mother, Rachel Nystrom, the only other person in their extended family known to have diabetes is Quinn's great uncle on her father's side, who was diagnosed with type 1 diabetes at age 25 and who is now in his mid-to-late 60s. "Other than that, there is no one else," Mrs. Nystrom says. The Nystrom's oldest child, Quinn's brother Thor, has not developed diabetes. But, as the family is well aware, with diabetes, there are no guarantees.

Because of the large number of genes possibly involved and the differences in their relative contribution to the disease process, identifying those genes associated with diabetes is a major challenge for researchers. However, the National Institutes of Health (NIH) is employing a multifaceted approach to understanding the genetic factors contributing to diabetes. These efforts include research consortia, large-scale genome-wide scans, microarray technology, and animal studies.

Victim or Victor

"It's easy to get depressed when you have any kind of illness, but especially one like diabetes," says Quinn. "That's because you are reminded every second of your life that you have the disease." But Quinn has made a courageous choice. "At the end of the day," she says, "you can either choose to be the victim or the victor of your illness." Quinn has chosen to be the victor, though the decision did not come easily. After all, Quinn was diagnosed with type 1 diabetes at age 13, a transitional time for most adolescents, and one not made any easier by a serious disease such as diabetes, which requires an enormous amount of personal vigilance. "That first year was horrible; I was in total denial," she said. "Not only was I ashamed about having diabetes, I also didn't want to have to watch what I ate. Chocolate is my favorite food, and I was being told to be careful about my diet."

To add to her woes, that summer Quinn's parents enrolled her in a camp for young people with diabetes. "Can you imagine a teenager with diabetes going to a place called Camp Needlepoint?" exclaims Quinn. By her own admission, Quinn went to the camp that year kicking and screaming. "It was a physical struggle just to get me there," she says. "I told my parents that I was still healthy, I was fine, and I was not going to tie up even a part of my Summer listening to other people with diabetes."

But at Camp Needlepoint, Quinn met 14-year-old Clare Rosenfeld, the first National Youth Advocate for the American Diabetes Association (ADA). "Clare told me that I could either sit around and wait and hope that somebody, someday, finds a cure for diabetes, or I could do something about it." That message changed Quinn's life. In the Fall, she went back to school and became a one-student crusader for finding a cure for diabetes. "Instead of hiding my diabetes and being embarrassed, I made it my goal to educate my friends, classmates, and teachers. Why should I be ashamed of having diabetes? So my pancreas doesn't work, so what? What's your problem?" Quinn organized a school fundraiser, and began speaking to groups about what it's like to live with diabetes and the urgent need for a cure. Two years later she was selected as the ADA's National Youth Advocate, her friend Clare's former position.

"I learned an important lesson. If you want people to find a cure, you have to ask them," declares Quinn Nystrom.

As ADA's National Youth Advocate, during the summer of 2002 Quinn spoke at diabetes camps all over the country, flying 27,000 miles in just 3 months. She urged other children and teens with diabetes to join the fight to find a cure. "Don't wait for the grownups or the scientists or the politicians to do something," she told them. "We are the ones who live with diabetes 24/7. We are the ones who are most anxious for a cure." Quinn's take-home message to her peers is, "Turn your stumbling blocks into stepping stones and do something positive with your life."

Quinn certainly is doing something positive with hers. In her crusade to find a cure for diabetes, Quinn has met with U.S. Senators, the Speaker of the House, and Secretary of Health and Human Services Tommy Thompson, and was invited to the White House to hear President Bush announce his health and fitness campaign for young people and adults. "My Dad got to come along," says Quinn. "That was really cool."

As Quinn has learned, however, before you can begin doing something positive, you first have to face reality four-square. And when it comes to the realities that go along with diabetes, Quinn is brutally honest with herself. "No matter how well I take care of myself, I'll probably die early from this disease," she says, almost matter-of-factly. "But I'm going to do everything in my power to push that time back as far as possible." Quinn faces the future with a great deal of optimism. Unlike many others who have diabetes, Quinn has the privilege of a national platform, and because of that, she says she gets to hear a lot about possible cures. "But, I'm also a realist," she quickly adds. "I know that there's a lot more we need to do before there's a cure for diabetes."

And although Quinn speaks on behalf of all people with diabetes, there remains an unbreakable bond between her and her brother Will. "Will was diagnosed with diabetes when he was 5 years old. He wasn't even in kindergarten yet," says Quinn. "For the past 6 years, every night, he has prayed the same prayer, 'Dear God, please find a cure for diabetes.' My family has heard that same prayer more than 2,150 times. I believe that God is going to answer Will's prayers."

With her indomitable spirit and enthusiasm, Quinn is going to make sure that she and others interested in finding a cure for this insidious and deadly disease do all within their power to help those prayers come true.