

# Extraordinary Opportunity:

## Autoimmunity and the Beta Cell

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Type 1 diabetes is an autoimmune disease in which the immune system attacks the insulin-producing beta cells of the pancreas. The beta cell is also central to the development of type 2 diabetes. First, the beta cell must meet the increased requirement for insulin during the period of insulin resistance that typically precedes development of type 2 diabetes. Ultimately, it is the failure of the beta cell that precipitates the onset of type 2 diabetes.

In pursuing the Extraordinary Opportunity presented by research on “Autoimmunity and the Beta Cell,” the DRWG urged emphasis on understanding the autoimmune basis of type 1 diabetes, development and clinical testing of methods for replacing beta cell function, and intensification of research on beta cell biology. The DRWG urged the NIH to exploit important discoveries from the fields of immunology and cell and molecular biology in order to find ways to prevent or block development of diabetes and to develop beta cell replacement therapies. Since issuance of the DRWG Strategic Plan, the NIH has made strides in all these areas.



*Photo: JDRF.*

Children with type 1 diabetes and their families participate in the “Children’s Congress” of the Juvenile Diabetes Research Foundation International (JDRF).



Photo: Richard T. Nowitz, for NIDDK.

Researchers conduct an islet transplantation procedure. Islet transplantation has become a promising research avenue, which could lead to a cure for type 1 diabetes.

## Understanding and Preventing Type 1 Diabetes

The DRWG's Strategic Plan underscored that understanding, at the molecular level, how immune system function is altered in type 1 diabetes is key to developing therapies to prevent or reverse this disease. Each step in the process of activation of the immune system provides a potential target for intervention.

Thus, it is imperative to learn how the immune system is triggered to attack and destroy insulin-producing pancreatic cells in this form of diabetes and the mechanisms by which autoimmunity, once initiated, is perpetuated. The availability of animal models for type 1 diabetes has facilitated such studies, but major challenges remain in unraveling the mechanisms by which immune dysregulation leads to beta cell destruction. This fundamental understanding is critical to developing new strategies to prevent the disease in people who are predisposed

to develop it, as well as new treatments to slow or reverse beta cell destruction in those already affected.

Ongoing studies in animal models and in humans have shed new light on the underlying causes of type 1 diabetes and have suggested promising avenues for exploration in diabetes therapy. For example, we now know that the cells of the immune system that target and destroy insulin-producing cells are active long before diabetes becomes clinically evident. In fact, the immune

process usually reduces insulin production well before diabetes symptoms become apparent. Recent clinical trials have shown that we can predict with accuracy the likelihood that an at-risk individual will develop type 1 diabetes over the next five years, based on a pattern of genetic markers, antibodies to components of the beta cell in the blood, and measurement of stimulated insulin secretion. The proof of this concept came from a recently completed component of the NIH-funded Diabetes Prevention Trial for Type 1 Diabetes (DPT-1). In this trial, individuals considered to be at high risk for developing type 1 diabetes received low dose insulin injections in an effort to prevent development of diabetes. Although the study did not demonstrate a benefit for this therapy in pre-diabetic patients, it did show that it was possible to accurately identify individuals at very high risk for progression to type 1 diabetes and it set the stage for future studies through a new clinical trial network, the Type 1 Diabetes TrialNet. The ability to recognize the onset of autoimmunity before damage is sufficient to cause diabetes and to identify individuals likely to progress to diabetes will be essential for the design of future clinical trials to prevent type 1 diabetes.

We have also learned from follow-up studies of participants in the Diabetes Control and Complications Trial (DCCT) that type 1 diabetes patients with minimal but measurable beta cell function do better than those with undetectable beta cell function. Very low levels of insulin production, although not sufficient to spare the need for insulin injections, result in fewer complications of diabetes than are seen in patients who make no insulin at all. This finding tells us that, even after onset of type 1 diabetes, efforts to preserve residual beta cell function are warranted.

## TESTING APPROACHES TO PREVENT OR SLOW TYPE 1 DIABETES IN A NATIONAL DIABETES CLINICAL TRIALS NETWORK—TYPE 1 DIABETES TRIALNET

As previously noted, we now have the ability to identify relatives of patients with type 1 diabetes who are at specific levels of increased risk for type 1 diabetes and the ability to measure residual beta cell function in new onset diabetes. Moreover, it appears that preservation of beta cell function is likely to confer better and easier control of diabetes and reduced risk of diabetes complications. These observations form the basis for efforts to undertake a systematic series of clinical trials to prevent progression to type 1 diabetes in family members of those with type 1 diabetes and to preserve beta cell function in patients with new onset type 1 diabetes and residual beta cell function. Among current intervention strategies are protocols that target cells of the immune system, or their bioactive products (the so-called “immunotherapies”). For example, immune cells communicate with each other and with their environment by releasing soluble mediators known as cytokines. By interrupting this intercommunication, or by inhibiting the release of toxic products from these cells, researchers may be able to break the cycle of immune reaction and damage that leads to the devastation of insulin-producing beta cells in type 1 diabetes.

To capitalize on the research opportunities presented by this knowledge, the NIH has implemented one of the major recommendations of the DRWG: creation of a national network of cooperative clinical groups, called the Type 1 Diabetes TrialNet. Each clinical site combines expertise in immunology and clinical diabetes, as well as

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support for clinical trial coordinators and patient recruitment personnel. A coordinating center provides expertise in trial design and management. The TrialNet will collaborate with a complementary effort, the Immune Tolerance Network, described later in this report, which provides state of the art methods for measurement of immune parameters and broad immunology expertise extending to multiple autoimmune disorders. The TrialNet is thus ideally constituted to conduct clinical trials of new prevention-oriented strategies in those at risk for diabetes and also to test strategies to preserve beta cell function in new onset type 1 diabetes patients.

TrialNet will facilitate rapid, preliminary testing of emerging therapeutic strategies. Those that prove most promising in small studies aimed at preserving beta cell function in patients with new onset diabetes can then be moved quickly into larger scale prevention trials. The nationwide TrialNet will efficiently identify and enroll eligible participants in these trials. Many of the agents to be tested in the TrialNet are derived from our expanding knowledge of immunology and the autoimmune disease process. New methods for promoting immune tolerance and modulating the immune process are being evaluated in animal studies, and then, the most promising new approaches are moving forward to clinical trials. These include antigen-specific, cytokine-based, or antibody-based immunotherapies. TrialNet will also be a valuable resource for efforts to find genes and other factors that predispose people to developing type 1 diabetes and for studies of the development of type 1 diabetes in those at risk. To gain maximum benefit from the resources supported by TrialNet, researchers may place genetic and other biological samples and data from participating patients in repositories for use by many investigators. Thus, this multi-faceted TrialNet will be an extremely valuable resource for the entire diabetes research community.

## FINDING FACTORS THAT TRIGGER THE DEVELOPMENT OF AUTOIMMUNE DIABETES IS CRITICAL FOR INTERVENTION

In type 1 diabetes, unknown environmental factors combine with genetic susceptibility to destroy the insulin-producing beta cells. To address this key gap in current knowledge about what causes type 1 diabetes, the NIH is initiating a concerted research effort to identify infectious agents, dietary components, or other environmental factors that may contribute to the initiation of autoimmunity directed at the beta cell.

This effort builds upon our ability to identify—at birth—genetic patterns that put individuals at increased risk for diabetes. It also builds upon what we have learned about identifying early signs of autoimmunity. This initiative will involve a multi-center study following high-risk newborns in an attempt to identify environmental factors associated with the onset of autoimmunity. To facilitate this effort, the NIH is creating a multi-disciplinary consortium with expertise in genetics, immunology, infectious disease, epidemiology, and biostatistics. Investigators in this consortium will seek to stimulate the development of novel technologies and/or improvements in established technologies to identify infectious organisms that may play a role in chronic diseases such as type 1 diabetes. The study requires a substantial long-term research commitment to permit investigators to follow these newborns through puberty, a time of high risk for onset of type 1 diabetes.

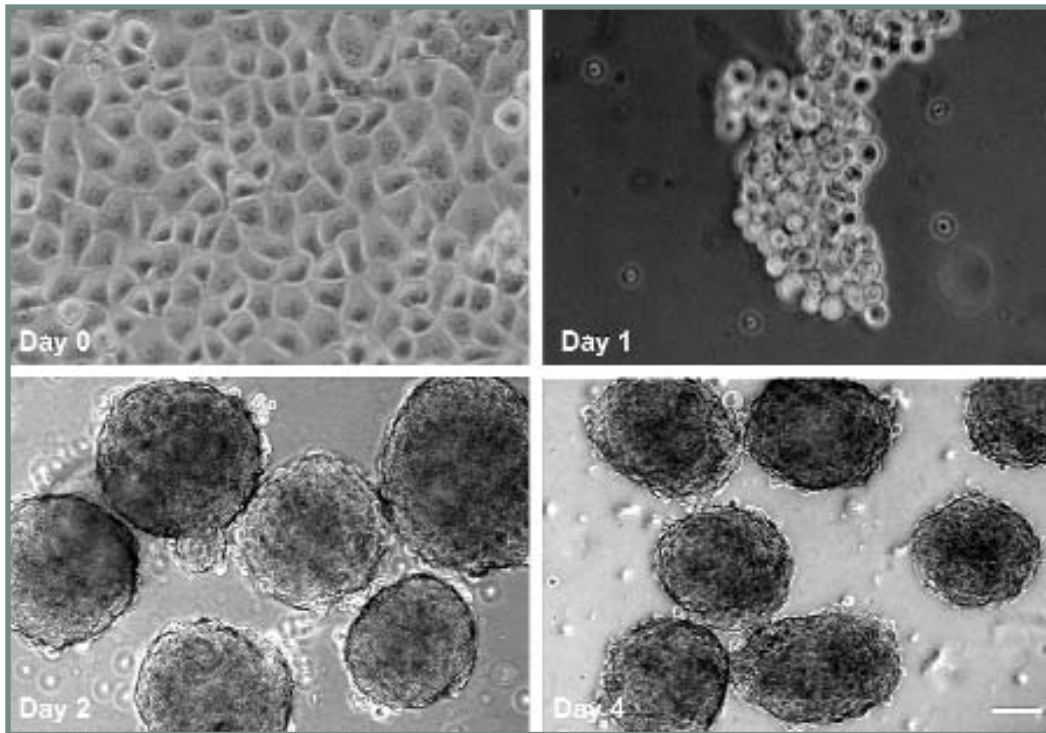
## ▶ INTENSIFYING RESEARCH TO UNDERSTAND THE IMMUNOLOGICAL BASIS OF TYPE 1 DIABETES

An understanding of the immunological basis of type 1 diabetes is the foundation for the development of new therapies. Several components of islets have been established as important targets for the T cell lymphocytes that attack and destroy the beta cell. The therapeutic potential of one such target, insulin itself, is now being tested in a multi-center clinical trial through the Type 1 Diabetes TrialNet. Animal studies are ongoing to explore the therapeutic potential of specific fragments of the insulin molecule, as well as multiple other recently characterized antigens implicated in type 1 diabetes. Successes in these studies will foster bench-to-bedside studies to translate emerging experimental concepts into therapies specifically for type 1 diabetes. Newly developed technologies include “Elispot assays,” to identify specific cytokines and cytokine-producing cells, and “MHC-tetramers,” to identify antigen-specific populations of T cells. Assays such as these create opportunities for understanding the mechanisms by which potential interventions exert their effects to prevent beta cell destruction.

New research is exploring gene therapy approaches to use the antigen or epitope specificity (the site on a molecule against which an antibody will be produced) of the immune system for diabetes protection strategies. One possible approach involves genetic manipulation to express autoantigens that may reduce the inappropriate immune-mediated destruction of beta cells while not compromising normal immune system activity. Other gene therapy

approaches flow from a new understanding of the immune basis of disease. These approaches include the use of T cell homing technologies to deliver immune suppressive factors to the site of inflammation. Because several different types of immunoregulatory T cells have been identified in animal models, it is essential to gain a complete understanding of the types and functions of regulatory cells that participate in human type 1 diabetes.

The DRWG emphasized that identification and characterization of the autoantigens that are targets for the autoimmune destruction of beta cells may hold the key to specifically modifying the immune response in type 1 diabetes. Thus, it urged complete mapping of T cell specificity of autoimmune response to major pancreatic islet cell proteins. Research in this area will foster the identification and characterization of molecular targets for tolerance induction and clarify the molecular events responsible for the loss of tolerance to self-antigens. To build upon these anticipated advances, the NIH has solicited “Innovative Grants on Immune Tolerance.” The newly formed Autoimmune Diseases Prevention Centers will also expand this knowledge base.



Over a 4-day period, specially cultured cells from the human pancreatic duct aggregate and express proteins characteristic of islets. Researchers are studying pancreatic duct cells as a possible source of insulin-producing cells. Bar represents 20 micrometers.

Photo: Dr. Marvin Gershengorn and Dr. Anandwardhan Hardikar, NIDDK.

## EXPANDING KNOWLEDGE ABOUT THE AUTOIMMUNE DISEASE PROCESS

The NIH supports a broad range of research to understand, treat, and prevent autoimmune diseases, such as type 1 diabetes. Whatever is learned about the underlying causes and mechanisms of autoimmunity in one of these diseases may be highly relevant to the others. A number of cooperative groups have been established to facilitate research into causes of and cures for autoimmunity. The International Histocompatibility Working Group (IHWG), described in the previous chapter of this report, is pursuing the

development, standardization, and distribution of reagents used to identify human leukocyte antigens (HLA). Patterns of HLA expression are among the most important biomarkers for tracking susceptibility to a variety of autoimmune diseases, including type 1 diabetes. The Autoimmune Diseases Prevention Centers will develop and test new strategies to prevent autoimmunity in multiple autoimmune disorders, including type 1 diabetes. Finally, the Autoimmunity Centers of Excellence are designed to integrate basic, pre-clinical, and clinical research in autoimmunity and to conduct clinical trials of therapies designed to modulate immune responses.



## PROMOTING IMMUNE TOLERANCE AS A WEAPON AGAINST AUTOIMMUNE DISEASES

During their development, cells of the immune system are educated by the body to recognize foreign proteins, or antigens, while at the same time the cells are taught to ignore, or tolerate, normal cells and self proteins. This latter state of “immune tolerance” is the safeguard that prevents the body’s immune system from harming itself. This is the safeguard that invariably fails in type 1 diabetes and other autoimmune diseases. A broad-based research effort focused on preventing and reversing this process is being conducted through the Immune Tolerance Network (ITN), an international consortium to test promising new therapies for inducing or enforcing immune tolerance. The ITN will evaluate therapies designed to prevent transplant rejection, to moderate asthma and allergies, and to test treatments for several autoimmune diseases, including type 1 diabetes. One focus of the ITN will be the development of assays and the identification of biomarkers to measure the induction, maintenance, and loss of immune tolerance in each of these diseases. This effort will complement the TrialNet and the initiative to identify environmental triggers of type 1 diabetes, described previously. It will also enhance research to discover novel molecular mechanisms of immune tolerance and their application to disease.

## ANIMAL MODELS FACILITATE CLINICAL STUDIES

Although no single animal model perfectly mimics a human disease, the availability of animal models for type 1 diabetes, such as the NOD mouse and the BB rat, has facilitated not only studies of disease pathogenesis, but also development of potential approaches to prevent or delay disease development. Among the newer models created for these purposes are mice genetically manipulated to express human HLA. These “humanized mouse models” have helped to delineate the role played by various HLA molecules that confer susceptibility or resistance to type 1 diabetes, as demonstrated in human studies, and may be useful for testing new therapies. T cell receptor-transgenic mice have also provided valuable information about the processes by which T cells are activated and involved in beta cell destruction. A new generation of animal models, reagents, and assays has created a wealth of expanded research opportunities. One enormous opportunity is the development of markers for immune activity that are now being applied in clinical studies.

One concept that was originally explored in animal models has now been translated into studies in recent onset type 1 diabetes patients. This involves the use of suppressive immunotherapy in which specific antibodies dampen the inflammatory process that occurs in and around pancreatic beta cells. In this case, antibodies directed against one of the molecules on the lymphocyte surface, CD3, are used to

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block immune cell activation and immune cell mediated destruction of pancreatic islets. Another form of suppressive immunotherapy being tested in the NOD mouse delivers regulatory proteins to the site of inflammation to dampen or modify the destructive actions of immune cells. Further research in animal models of type 1 diabetes is essential to gain a complete understanding of the types and functions of regulatory cells that actually participate in human disease and to learn precisely how the activity of these cells can be modulated. This will facilitate the design of rational therapies that are specifically tailored to prevent or control immune cell function in type 1 diabetes.

Recent studies in animal models have raised the exciting possibility that a “vaccine,” if properly designed, may be able to prevent type 1 diabetes. Normal islet proteins (autoantigens) can be targets of immune cell activity in the diabetic pancreas. When these autoantigens are used to “vaccinate” pre-diabetic animals, the animals fail to develop diabetes. This finding suggests a potential therapeutic benefit for vaccines consisting of a combination of human islet autoantigens. These autoantigens could be administered as proteins, as in a classical vaccine, or introduced into patients by gene transfer techniques. In some cases, the efficiency of vaccines could also be enhanced when antigens or autoantigens are introduced with specific cytokines. After additional safety studies, these findings in animal models will be tested in humans.

## ▶ NON-INVASIVE IMAGING OF BETA CELL MASS, FUNCTION AND INFLAMMATION

Moving research from the laboratory to animals and then to application to patients would be greatly facilitated by development of “surrogate markers.” Surrogate markers allow researchers to monitor the course of a disease—often before clinical symptoms arise—and also can provide them with an early indication of an intervention’s effectiveness. For type 1 diabetes, such markers could include measures of toxic immune cell infiltration into the pancreas, or assessment of beta cell damage before the cell loss is so severe that insulin production is impaired. If physicians could directly visualize the beta cells in the pancreas, they would be able to identify more readily those individuals whose beta cells were becoming compromised and who were thus on the way to becoming diabetic. Such techniques would also help to monitor islet transplant patients to ensure that their new islets are thriving. The NIH has sought to foster development of these imaging techniques because of their potential for use as surrogate markers. Already, promising results have been achieved with efforts to visualize islets using labeled drugs or antibodies as “tags” to “light up” beta cells selectively and thus make it possible for researchers to image these cells. One research team injected healthy and diabetic mice with a radioactive monoclonal antibody that binds selectively to the surface of beta cells and facilitates the imaging of these cells. When the researchers subsequently removed the pancreata from these mice, they found that the amount and spatial distribution of radioactivity imaged in the excised pancreas correlated well with the actual beta cell mass. The ability to measure beta cell mass would be particularly useful for monitoring responses to therapy in clinical trials designed to stop the progression to overt diabetes, or to preserve beta cell function in newly diagnosed diabetes.



## Replacing Beta Cell Function Through Islet Transplantation

Given the importance of good blood glucose control—but the difficulties, risks, and limitations of using insulin injections to achieve it—the DRWG emphasized the need to intensify clinical research on islet transplantation therapy to restore natural insulin production to type 1 diabetes patients.

The DRWG's Strategic Plan cited the impressive demonstration by the NIH's Diabetes Control and Complications Trial (DCCT) that improved control of blood glucose levels in type 1 diabetes patients can prevent or delay the onset of complications that damage the small blood vessels of the eyes, nerves, and kidneys. However, the DRWG emphasized that current means for attaining such control are not optimal and that research should be directed toward development of better methods. Finger sticks for measurement of blood glucose and self-injection of insulin multiple times daily are tedious and painful, especially for children and adolescents, and can only partially replicate normal glucose regulation. In addition, multiple self-injections, as well as continuous insulin injection devices, can be associated with an increased risk of dangerous episodes of low blood glucose (hypoglycemia), which, if not caught in time, can lead to coma and death.

Islet transplantation would give patients the benefits of blood glucose control without the drawback of external insulin administration. However, much more information is needed about the long-term effects of drugs used to prevent rejection and recurrent autoimmunity. The DRWG recommended the expansion of research efforts directed at identifying and testing safe and effective immunosuppressive and immunomodulatory regimens. It also recommended the establishment of a national system for the preparation and distribution of islets.

### NEW IMMUNOSUPPRESSIVE REGIMENS IMPROVE ISLET TRANSPLANT SUCCESS

Tremendous new opportunities have emerged in the field of islet transplantation since the DRWG issued its Strategic Plan. The use of this experimental therapy was revolutionized in 2000 when researchers in Edmonton, Alberta, Canada, pioneered the use of new techniques, including a steroid-free immunosuppressive regimen, in small numbers of patients. Their protocol resulted in 85 percent of their patients being free of insulin injections for one year, and 60 percent of them being insulin-free for two years. Prior to these studies, insulin independence was observed in fewer than 10 percent of patients one year after transplantation. Opportunities now exist to extend the success of the Edmonton protocol with further improvements in immunosuppressive medications. The Edmonton protocol required two donor pancreata for each islet transplant recipient. New approaches could potentially decrease the number of needed donor islets. Studies are under way to develop and test methods of achieving immune tolerance so as to eliminate the need for lifelong immunosuppression in islet transplant recipients.



The goal of restoring normal insulin production and blood glucose control in patients with type 1 diabetes could become a reality through islet transplantation research.

*Photo: Richard T. Nowitz, for NIDDK.*

## ► PURSUING ISLET TRANSPLANTATION AS A POTENTIAL CURE FOR TYPE 1 DIABETES

With the recent achievement of promising results in islet transplantation research—and the interest expressed by multiple medical centers to test this therapeutic approach—the NIH has intensified support for such clinical studies and for the production of human islets for this purpose, consistent with DRWG recommendations. The NIH intramural program began a series of islet transplant procedures in a small number of adult patients with severe type 1 diabetes. The Immune Tolerance Network (ITN) began the first multi-center clinical trial of this technique. Complementing these efforts, the NIH expanded regular research grant support to a range of independent investigators in the extramural community to step up their work on islet transplant approaches.

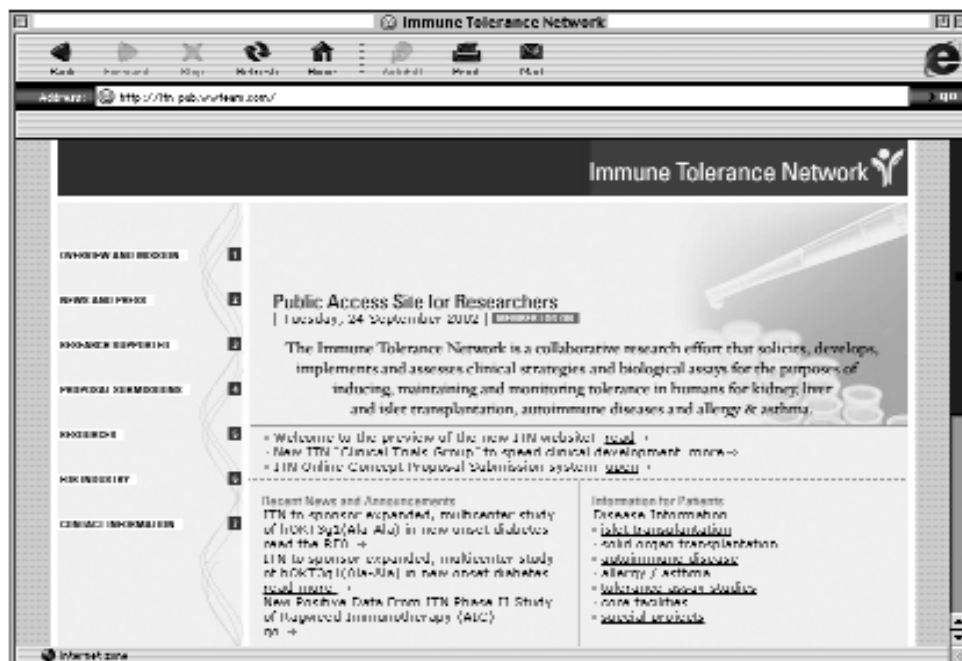
To enhance islet availability, the NIH established ten Islet Cell Resource Centers around the country in order to provide clinical-grade islets to the transplantation community and to facilitate improvements in the islet isolation procedure. Opportunities exist to improve islet transplantation techniques by avoiding or reducing dependence on freshly isolated islets—a dependence that can make transplantation logistically difficult. Previously, there had been a very short window of time after harvesting a pancreas in which to isolate islets successfully. However, in a recent advance, researchers have been able to culture islets in a manner that maintains their viability and function for longer periods of time, thus providing the ability to ship islets to regions throughout the country. This extended viability offers greater flexibility in using islets and increases their availability to patients who could be transplanted.

With the increased number of islet transplantations being performed in research settings— involving multiple approaches to immunosuppression and islet isolation—a means of capturing the resulting data was critical. To this end, the NIH established the Collaborative Islet Transplant Registry to ensure the optimal collection and utilization of the data being generated in the various clinical trials as a way of facilitating evaluation of the safety and efficacy of various approaches to islet transplantation. The NIH continues to support the “Pancreas Transplant Database” as a means of gathering and assessing information on whole pancreas transplantation procedures.

## DEVELOPING IMMUNE TOLERANCE METHODS TO ENHANCE ISLET TRANSPLANTATION

Current organ and tissue transplantation in humans requires the use of immunosuppressive medications to prevent rejection of the trans-

plants. However, these drugs have significant undesirable side effects. An important research objective is to avoid or minimize a patient’s lifelong dependence on costly and potentially toxic immunosuppressive drugs following islet transplantation. Thus, a major goal in transplantation research has been to develop immune tolerance—the means by which rejection of transplanted organs or tissue can be avoided without the life-long commitment to immunosuppressive drugs. To further develop tolerance approaches for islet transplantation in animal models most closely related to humans, the NIH has established a Non-Human Primate Immune Tolerance Cooperative Study Group. Researchers have developed a successful tolerance procedure for islet transplantation in a non-human primate model. The NIH is now initiating clinical trials to evaluate potential tolerance approaches in human islet transplantation through the Immune Tolerance Network and individual research projects.



## Establishing a Replenishable Supply of Islets for Therapy

Recent advances in islet transplantation therapy now offer hope that—with additional clinical trials demonstrating safety and efficacy—this approach could become a medical treatment for the estimated one million Americans with type 1 diabetes. However, even with the availability of safe and effective methods for transplantation, an additional obstacle must be overcome. Only a few thousand human pancreata are currently available each year from which islets can be obtained for transplantation.

Before islet transplantation could be offered to all who might benefit, the supply of islets for transplantation would need to be greatly increased. The DRWG recognized that tissue supply is a major limiting factor in development of islet transplantation as a therapy for type 1 diabetes. To address this problem, the DRWG recommended expanded research on the mechanisms controlling islet cell growth and development and the mechanisms involved in glucose regulation of insulin secretion from beta cells.

The shortage of islets for transplantation could be addressed by coaxing undifferentiated progenitor cells, called stem cells, to develop into pancreatic beta cells that would be useful in transplantation. The nature and source of the stem cells from which insulin-producing beta cells develop during normal growth and development of the pancreas are poorly defined. By understanding this devel-

opment process, researchers may be able to recapitulate normal development of beta cells in tissue culture using stem cells obtained from the patient or from other human donors. The results could lead to the development of an unlimited supply of islets for transplantation, and to novel therapies designed to stimulate beta cell growth *in vivo*. If a person's own stem cells could be coaxed to develop into islets, then the risks of immune reaction to foreign tissues and many of the other potential problems encountered with the transplantation of tissue would be reduced. Another important potential source of beta cells for transplantation is the availability of human embryonic stem cell lines that have been approved as meeting established criteria for NIH-funded research. Thus, replacement or regeneration of beta cells damaged in diabetes through cell-based therapies is a significant research opportunity that holds great promise for future treatments.

## ▶ USING STEM CELLS OR EXTRA-PANCREATIC TISSUE TO PRODUCE INSULIN-PRODUCING CELLS

The diabetes research community sees enormous potential in the use of mouse and human embryonic stem cells and tissue-specific adult multipotential progenitor cells in deriving a host of differentiated cell types, including insulin-producing beta cells. However, the molecular features of both embryonic and multipotential adult stem cells are poorly understood in both undifferentiated and differentiated states.

Researchers have yet to learn the instructive signals needed to efficiently induce large numbers of undifferentiated stem/progenitor cells to become fully functioning beta cells. A research opportunity thus exists to develop procedures for identifying, purifying, expanding, and assessing populations of pancreatic stem/progenitor cells that have the capacity to self-renew and generate differentiated islet cell types. Before the potential of cell-based therapy can be fully realized, researchers will need to undertake a systematic comparison of the ability of embryonic and multipotential adult stem cell sources to make pancreatic beta cells. A parallel strategy to be pursued is the possible genetic reprogramming of extra-pancreatic tissue, such as liver hepatocytes or gut K cells, to produce insulin. Researchers are currently using mouse models to explore the use of these surrogate beta cells and their efficacy in replacing impaired islet cell function. This is a highly promising, new avenue of future exploration.

## ▶ FACTORS CONTROLLING PANCREATIC CELL PROLIFERATION AND DIFFERENTIATION

Genetic manipulations in mice have enabled a dissection of the roles that specific signaling molecules or transcription factors play in the growth and differentiation of the endocrine pancreas. Through technological advances in mouse genetics, investigators have gained the capability of altering gene expression in beta cells and their precursors during pancreatic development, thus making the mouse an attractive model system. Other vertebrate animal model systems—such as chickens, frogs, and zebrafish—have contributed to overall understanding of the embryological pathways that lead to pancreatic islet formation. Factors released from tissues adjacent to the developing pancreas that regulate the development of insulin-producing cells of the pancreas have been identified in multiple model systems. This finding suggests that there is strong conservation among vertebrates in the process of islet formation. Determining the hierarchy of events that lead from the earliest steps of tissue specification to the production of differentiated islet cell types will provide the basis for the future development of cell-based therapies.

## GAINING INSIGHTS INTO BETA CELL BIOLOGY THROUGH NEW CONSORTIA

Based on recommendations of the DRWG and two international workshops, the NIH has established consortia to facilitate progress in beta cell biology. The Functional Genomics of the Developing Endocrine Pancreas Consortium is generating important genomic and bioinformatics tools from studies of developing mouse and human pancreatic tissue. These tools are being made rapidly and freely available to the diabetes research community ([www.cbil.upenn.edu/EPConDB/index.php4](http://www.cbil.upenn.edu/EPConDB/index.php4)). The Beta Cell Biology Consortium is developing new mouse models and research tools to investigate beta cell development and regeneration, and is exploring new ways of producing differentiated islet cell types from multiple mouse and human stem cell sources ([www.betacell.org](http://www.betacell.org)). These consortia are jointly assembling a public database that will permit rapid dissemination of data, which should greatly stimulate research in this area. Another multi-disciplinary initiative is under development to understand the signaling pathways in the mature beta cell.

## IMPROVING TRANSPLANTATION RESULTS THROUGH BIOENGINEERING

Studies are under way to identify factors that confer enhanced viability in islets. Researchers have found one type of mouse (ALR/Lt) that is resistant to beta cell damage. These mice are able to maintain insulin production after exposure to chemicals known to promote inflammation and destroy insulin-producing capacity in other mice. When ALR/Lt mice are mated with NOD mice, their offspring are also resistant to type 1 diabetes. Though the gene (or genes) that confers resistance is not yet known, once such factors that enhance viability of islets are identified, gene therapy techniques might be used to deliver them to islets to enhance their engraftment and survival after transplantation. Gene therapy could also target immune cells involved in rejection or autoimmunity to impede these processes. Pilot studies have been solicited to explore the potential utility of gene therapy approaches to improve outcomes with islet transplantation. Islet encapsulation has been proposed as another means to protect islets from rejection and potentially eliminate the need for immunosuppressive drugs. Researchers are also trying to identify the signaling molecules that are essential for glucose-regulated insulin secretion. With this information, bioengineering techniques might be used to develop cell lines that faithfully mimic the properties of beta cells and could be used to replace islets that have been destroyed by the autoimmune process in type 1 diabetes.



# Opportunities to Apply New Technologies to Autoimmunity and the Beta Cell

Many of the recommendations of the DRWG require a comprehensive approach involving multi-disciplinary teams of investigators in innovative, high impact studies.

In response to the recommendations of the DRWG and utilizing the special type 1 diabetes funding provided by statute through 2003, a number of such projects have been newly initiated. Many of these efforts, described previously, will require long-term commitments for completion. These efforts cover the full spectrum from “bench”—basic research geared toward development of new approaches to therapy—to “bedside”—clinical trials to test promising approaches as they emerge from laboratory and animal studies.

At the basic level, use of emerging genomic and proteomic methods will elucidate beta cell specific developmental and signaling pathways and novel components of the islet and its microenvironment that are required for proper beta cell function. State of the art bioimaging techniques will be applied to develop measures of beta cell mass and function and immune cell infiltration of the pancreas. Such measures will be useful as surrogate markers in clinical trials of therapies to prevent diabetes or preserve beta cell function in new onset diabetes. Novel immunologic techniques will be used to analyze disease-related immune cells. New molecular tools

will help to identify potential causative environmental agents that trigger autoimmunity leading to type 1 diabetes. At the molecular level, the steps in immune activation and in tolerance induction will be probed. Tools to enhance the viability of islets or to impede immune-mediated beta cell destruction will include state of the art techniques of cell and tissue engineering. The challenges are large but the potential rewards are exponentially greater.

Mechanisms are now in place to move new basic understandings forward—to test potential therapies in animal models of diabetes and then to apply them clinically, in individuals with or at risk of diabetes. Agents that prevent or delay development of diabetes in mouse models can now be swiftly evaluated in a nationwide TrialNet. There is a new impetus to develop unlimited supplies of islets for transplantation, improved immunosuppression, and methods of tolerance induction—as successes are now reported with islet transplantation at multiple centers. Enthusiasm is high but much remains to be learned about therapies to prevent diabetes and about the development of islet transplantation to treat it.

# PATIENT PROFILE: Mollie Singer

## LIVING WITH TYPE 1 DIABETES

### *13-Year-Old Mollie Singer's Story*

It happened the day before ten-year-old Mollie Singer was to testify before Congress on behalf of the 1999 Children's Congress of the Juvenile Diabetes Research Foundation International. Mollie was a guest in the Senate gallery absorbing the legislative process. She was seated next to her mother and a senator's wife when her mother happened to clasp Mollie's hand and felt it cold and clammy to the touch. "I took one look at Mollie, tested her right there in the gallery and realized she was going into a low blood sugar emergency," says Mrs. Singer. "I literally had to pick her up, rush her out into the hallway and immediately give her glucose to raise her blood sugar." All this, while the sympathetic senator's wife looked on with great concern. Had Mrs. Singer not acted as she did, Mollie, who was already beginning to feel groggy and disoriented due to the sudden drop in her blood sugar, ran the very real risk of passing out, going into convulsions, and slipping into a diabetic coma. The very next day, Mollie testified before Congress, asking representatives to "promise to remember me" when they provide resources for biomedical research.

This is the story of a very courageous little girl and her equally courageous family who battle with type 1 diabetes every minute of their lives. The family lives in constant fear, walking a tightrope between the potentially deadly complications that can steal vision, limbs, and years of productive life from their loved one on the one hand and the immediate danger of swings in blood sugar levels on the other. And they are doing everything in their power to help each other, and the 17 million other Americans with



*Since Mollie Singer was diagnosed with type 1 diabetes when she was four and a half years old, she has been struggling to manage the disease every day of her life. Mollie at right, Jackie at left.*

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type 1 and type 2 diabetes, live better, fuller, and more hopeful lives.

"My DREAM is that the doctors find the cure for diabetes," Mollie Singer wrote at age 11, six and one-half years after she was diagnosed with type 1 diabetes. "When that happens...I'll be so happy, I'll cry!!...NO MORE SHOTS!... I would like to know what it feels like not to have this horrible disease and just be a regular kid."

"Diabetes is something I have to live with," says Mollie, now 13 years old. "And," she adds in her upbeat, giggly adolescent voice that belies the strength and dedication behind it, "I'm going to do everything I need to do to stay alive and live a good life until they find a cure for me and other children with this disease." The fact is, she and her fraternal twin sister, Jackie, are true profiles in courage, commitment, and love when it comes to fighting the good fight against diabetes.

## “DIABETIC (GUARDIAN) ANGELS”

“I hate that my sister has this disease,” says Jackie, who does not have diabetes. Nor is there a history of the disease in the adopted twins’ biological family. “It’s hard to watch Mollie go through all the pain. I don’t sleep nights because I’m afraid that something will happen to her.” Jackie’s fears are not unfounded. Over the past several years, Jackie has had to rouse her parents in the middle of the night on several occasions when she realized that Mollie’s blood sugar had dropped to dangerously low levels. While mother and father tended to Mollie’s urgent health needs, Jackie called 911. When paramedics arrived at the door, Jackie described to them what her twin sister was going through. “Jackie is my guardian angel,” says Mollie, with deep affection. “She’s always watching over me. She’s totally cool.”

S-o-o-o cool, that when the twins were in fourth grade they started a club they called Mollie’s and Jackie’s Diabetic Angels to educate other kids about diabetes, and to get them to become guardian angels for Mollie and others with the disease. In class, for example, if the teacher forgot, the kids would yell, “It’s time for Mollie to test her blood sugar.” The 40 or so classmates who joined the club also wrote to their congressional representatives in support of research dollars to find a cure for diabetes. Never ones to miss out on an opportunity to educate others about diabetes, Mollie and Jackie wrote up a plan and mission statement for their club and used the Internet to promote it. Today, according to Mrs. Singer, who gave up her profession as a film production consultant after Mollie was diagnosed with type 1 diabetes in 1993, there are more than 20 Diabetic Angels clubs around the country, as well as in Australia and Israel.

“My twin sister Jackie wonders how many more birthdays we will celebrate, before someone finds the cure (for diabetes),” says Mollie. It makes me so sad that Jackie can’t be a regular kid either, because she is always worrying about me.”

The rules and mission statement Mollie and Jackie established for their club speak volumes about their love and dedication to one another, and their commitment to seeking a cure for diabetes for others. The original club rules read as follows:

- ◆ Know what it means when Mollie says her blood sugar is high or low and also know what to do to help her.
- ◆ You have to know how to test her in case she’s having trouble testing herself and I’m (Jackie) not around.
- ◆ You have to agree to write a short letter to our representatives when it’s necessary and ask them to please give more money for diabetes research.
- ◆ Help raise funds for research by walking... in the Juvenile Diabetes “Walk to Cure Diabetes” if your parents say it’s O.K.
- ◆ And the last rule is, represent the Diabetic Angels with honor. This means accepting the differences in all people and be a kind and understanding person.

# PATIENT PROFILE: Mollie Singer

Starting the club was just the first salvo in the twins' never-ending war against diabetes. To raise awareness about the disease and its deadly complications, these two adolescent dynamos have met with President George W. Bush and appeared on TV's Good Morning America, and they routinely take part in the annual Juvenile Diabetes "Walk to Cure Diabetes," appear in documentaries, do interviews, stay current on research and political issues related to diabetes — writing letters to members of Congress whenever they feel it's necessary — and more. "At night, Jackie and I pray for everyone who is sick," says Mollie, "and we ask God to help the doctors find the cure for diabetes and other terrible diseases."

## **MOLLIE'S AND JACKIE'S DIABETIC ANGEL'S MISSION STATEMENT**

The goal of a "Diabetic Angel" is to support his or her diabetic friend...be prepared to help in an emergency... bring about awareness by educating classmates, friends, and parents...and help raise funds for diabetes research until diabetes is cured!

## **LIVING WITH THE DISEASE**

Mollie's and Jackie's activism is a direct result of the lack of understanding and insensitivity Mollie encountered shortly after she was diagnosed with type 1 diabetes — sometimes referred to as juvenile diabetes — at age four. When the twins were five, Mollie was in the hospital for open-heart surgery, which was unrelated to her diabetes. "I had a real bad time," Mollie recalls. "No one knew how to handle a child with diabetes, so I got the wrong amount of insulin and the wrong food." In school, she's been embarrassed when her high blood sugar has made her vision blurry, making it hard for her to read, and people have told her point-blank that "diabetic kids are a hassle."

If the misunderstandings and insensitivities aren't enough, consider the fact that, from the time she was diagnosed until the day she received an insulin pump in January 2000, Mollie had been injected with 12,889 shots of insulin and had her little fingers poked more than 25,000 times in order to take her blood sugar readings. "Everything I do is planned around my diabetes," says Mollie, including eating, sleeping, playing, and even homework. "If things are not planned exactly, my blood sugar levels can go out of control." Just ask her parents. "In the past, when we would go to restaurants," says Mollie's father, Dr. Singer, an anesthesiologist, "I'd always worry about how long it would take for us to get our food. Sometimes I'd see Mollie crashing right in front of me." Mrs. Singer quickly adds that ladies' rooms, airplanes and cars are horrible places to give insulin shots.

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**NIH-supported clinical research studies have demonstrated that intense control of blood sugar levels for even a few years can significantly mitigate the complications of diabetes—including nerve, eye, and kidney disease—later in life. The recent development of the insulin pump, also with NIH support, has made it easier for insulin-dependent diabetics to manage their blood sugar levels throughout the day, reducing the risk for developing complications.**

**The NIH is supporting efforts aimed at not only improving treatment for those who already have type 1 diabetes, but also preventing type 1 diabetes through the identification of the genetic and environmental factors that interact to predispose persons to developing type 1 diabetes (see “Genetics,” “Clinical Trials,” and “Special Needs for Special Problems: Diabetes in Women, Children, the Elderly, and Minority Populations”). Through research both identifying those at risk and developing means to prevent the autoimmune destruction of the insulin-producing islet cells, the onset of type 1 diabetes might be significantly delayed or prevented altogether.**

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For years after she was first diagnosed, the only item on Mollie’s Christmas gift wish list was a cure for diabetes. “Finding a cure for diabetes is all I think about every hour of every day,” says Mollie. “I try to be brave but sometimes I get very sad and cry myself to sleep.”

All that has been mitigated somewhat since Mollie began using an insulin pump nearly three years ago. Proper use of the device takes a relatively high degree of awareness and responsibility, including the ability to count carbohydrate intake. However, the pump has changed Mollie’s life. She no longer needs to take insulin shots four to six times a day, nor carry around the syringes, alcohol pads and other supplies necessary for injections. She’s also able to eat foods she wasn’t able to eat before. In short, although she still needs to test her blood sugar levels regularly, the pump has introduced lots of freedom into Mollie’s and her family’s lives. “My pump looks like a beeper, it’s so cool,”

says Mollie. To make it even cooler, Jackie, of course, adorns Mollie’s pump cases using silver pens, colorful materials and little patches. “The pump makes having the disease a little less painful for Mollie,” says the ever-loyal Jackie.

Always in the vanguard, Mollie and Jackie are eagerly awaiting the day Mollie can use an implantable insulin pump, which is still in clinical trials. They are also excited about the many scientific advances being made in diabetes research, including promising studies of islet transplantation, better ways to monitor blood sugar levels at home, medicines that can prevent or delay complications in people with diabetes, and more. “Every night, night after night, I have the same routine,” says Mollie. “I pray for the cure and dream about what that day will be like. The cure is all I dream about, because my future depends on whether or not my dream comes true.”