

GOAL VI

**ATTRACT NEW TALENT AND
APPLY NEW TECHNOLOGIES TO
RESEARCH ON TYPE 1 DIABETES**

The *Special Statutory Funding Program for Type 1 Diabetes Research* has expanded the research opportunities in type 1 diabetes and its complications by harnessing cutting edge tools and technologies in addition to attracting creative and skilled scientists with diverse backgrounds.

New and emerging technologies, coupled with a cadre of talented scientists, have the potential to generate breakthroughs in the understanding, prevention, treatment, and cure of type 1 diabetes. The *Special Funding Program* has facilitated the creation of multiple research consortia to tackle specific challenges that will impact the health of people with type 1 diabetes. These efforts have brought together clinical and basic researchers—linking scientists investigating the pathogenesis and therapy of type 1 diabetes and its complications with new technologies needed to pursue evolving areas of opportunity. In addition, the strategies used to study type 1 diabetes have expanded through interdisciplinary research approaches. This increased collaboration will be essential as type 1 diabetes research evolves.

The tools of biomedical research have changed rapidly due to the biotechnology revolution. Many technologies that were used 20 years ago have been replaced by technologies that permit scientists to conduct research more efficiently and to ask and answer new research questions. Imaging advances now afford researchers the ability to track cells in the body by means never before possible. Advances in genetics and molecular biology provide researchers with new insights into cellular processes. New animal models provide more realistic test systems in which to study disease onset and progression. These new and emerging technologies hold promise for advancing the type 1 diabetes research field.

The pace of discovery is accelerating, and, as in the past, future research advances should directly translate into improvements in the health and quality of life of patients. The *Special Funding Program* has enabled scientists to study biologic processes in ways that were once not possible. The *Special Funding Program* has allowed researchers to harness new technologies and information that have emerged in order to optimize progress. A talented workforce of researchers is being mobilized to apply their expertise to overcome current barriers. Pursuing novel research directions and attracting new research talent are key elements in conquering type 1 diabetes.

HIGHLIGHTS OF SCIENTIFIC PROGRESS

While numerous significant advances have emerged since the beginning of the Special Funding Program, many of the research efforts to attract new talent and apply new technologies to research on type 1 diabetes are still in progress, and the full impact of these projects will not be realized for several years. The advances made possible by the Special Funding Program thus far are therefore only the beginning of the scientific gains that can be expected in the future.

Novel Imaging Technologies To Monitor Type 1 Diabetes Disease Progression and Islet Transplantation:

Type 1 diabetes is typically diagnosed very late in disease progression, when most of the insulin-producing beta cells of the pancreas have already been destroyed. Imaging technologies are needed that can detect the first signs of beta cell destruction, monitor therapy against immune attack, or look for possible regeneration of beta cells. Scientists have recently developed a new, noninvasive imaging technology to monitor infiltration of inflammatory cells into the pancreas in an animal model of type 1 diabetes. This project was initiated with a small pilot and feasibility award supported by the *Special Funding Program*, which helped unite imaging and immunology experts. Under another pilot award from the *Special Funding Program*, scientists are exploring the use of positron emission tomography (PET) imaging to see radiolabeled ligands targeted to the insulin-producing beta cells within the pancreas. If such an approach proves successful, it would permit physicians to estimate the number or mass of a patient's own endogenous beta cells, as well as to monitor the fate of transplanted islets. These approaches are now being tested in people. If successful, they could dramatically improve the ability of researchers to perform type 1 diabetes clinical trials. They could also permit physicians to detect beta cell loss in people prior to onset of symptoms, facilitating earlier attempts to intervene in the disease process.

Another important advance is the successful labeling of isolated human and mouse islets, and mouse T cells, with non-toxic imaging probes that can be detected with magnetic resonance imaging (MRI), fluorescence, or nuclear imaging. The islets have been imaged quantitatively over time after implantation in the liver or under the kidney capsule in mice. T cells have been seen as they infiltrate the pancreas of a non-obese diabetic (NOD) mouse. Although such molecular imaging approaches are still very new, trials are beginning to test them in human patients, and it is hoped that these will soon include studies in type 1 diabetes.

Reducing Gut Permeability To Block Triggers of

Autoimmune Diseases: Researchers funded by the *Special Funding Program* determined that a protein, called zonulin, is expressed at very high levels in the intestines of diabetic rats. Zonulin is involved in regulating intestinal tight junctions, which are gates through which molecules may cross into the intestine. When the tight junctions are not working properly, it becomes easier for foreign molecules to enter and possibly trigger the immune system. Increased intestinal permeability has been observed in numerous autoimmune diseases, including type 1 diabetes. Researchers have found that the increased level of zonulin correlates with an increase in intestinal permeability and the progression toward development of type 1 diabetes. When the rats were treated with an agent

that blocks zonulin from binding to its cellular receptor, the incidence of progression to type 1 diabetes was decreased by 70 percent. These findings suggest that zonulin is involved in the development of type 1 diabetes, and inhibition of zonulin may be a possible therapeutic approach to prevent or treat the disease. Based on these exciting discoveries and a Small Business Innovation Research (SBIR) grant, pharmaceuticals that target zonulin are being developed by academic and industry researchers.

Generation of a Pipeline for Novel Therapeutic Agents:

The *Special Funding Program* has created the infrastructure for investigators to translate research discoveries through the drug development process, ultimately resulting in therapeutic agents. For example, researchers have recently demonstrated that, in a mouse model of type 1 diabetes, treatment with an

anti-inflammatory drug, called lisofylline (LSF), after islet transplantation protected against recurrent autoimmunity (destruction of the transplanted cells by the autoimmune process that initially led to type 1 diabetes). Because recurrent autoimmunity is a major clinical barrier in human islet transplantation (CIT), LSF is a promising therapeutic agent to test in humans. Building upon these results, the Clinical Islet Transplantation (CIT) Consortium (see Goal III) will be testing LSF in humans. The LSF that will be used in the trial is being manufactured through the Type 1 Diabetes Rapid Access to Intervention Development (T1D-RAID) program. This example demonstrates how the *Special Funding Program* is supporting the discovery, manufacture, and testing of promising therapeutic agents, thereby creating a pipeline of agents that can potentially improve the health of patients.

EVALUATION OF MAJOR EFFORTS TO BRIDGE DISCIPLINES, ATTRACT NEW TALENT, AND APPLY NEW TECHNOLOGIES TO RESEARCH ON TYPE 1 DIABETES

With the increase in Special Funds that became available in FY 2001, unique, innovative, and collaborative research consortia, clinical trials networks, and resources for the diabetes research community were launched. This section evaluates the progress of these ongoing efforts thus far and describes the impact that the efforts have already had—and have the potential to have—on type 1 diabetes patients.

Bench to Bedside Research on Type 1 Diabetes and Its Complications

The “bench to bedside” research initiatives have stimulated translational diabetes research by fostering interactions between basic and clinical scientists to move discoveries from a laboratory setting to pre-clinical or clinical testing of new therapies that could improve the health of people with type 1 diabetes. The goal of the program is for the basic and clinical scientists to use their combined expertise to foster the development of a basic research finding to the point where the underlying hypothesis can be tested in a clinical trial or an animal model to assess its value in the treatment and/or prevention of type 1 diabetes or its complications. Applicants are encouraged to propose pilot studies to evaluate a potential therapeutic approach with pre-specified milestones to determine feasibility of the approach. If the milestones are met, the novel R21/R33 grant mechanism allows for rapid transition from the first pilot phase (R21) to a possible second extended phase (R33) with more substantial support. Five of eight R21/R33 grants from the 2002 and 2003 “bench to bedside” initiative awards achieved their milestones and transitioned directly to the second phase R33. Those with evidence of feasibility could apply directly for the R33 exploratory/developmental awards. Two grants awarded as R21 alone successfully applied for 3-year R33 grants from a subsequent “bench to bedside” solicitation. R21 awards from the third solicitation in 2004 are still in progress.

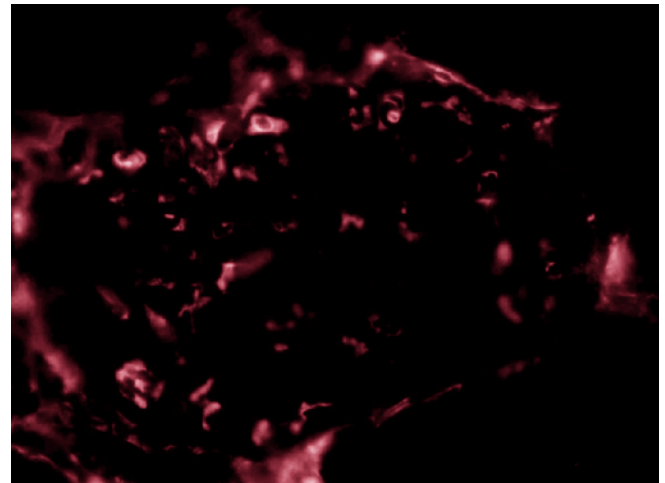
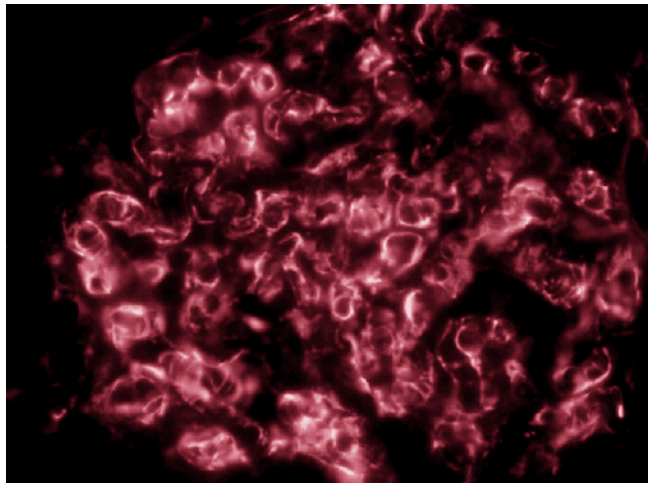
Highlights of Progress

Highlights of progress made by researchers supported through the “bench to bedside” initiative as of March 1, 2006, include:

- Demonstrated that the incidence of diabetes could be significantly delayed in a mouse model of type 1 diabetes. Researchers treated NOD dendritic cells (DCs) *ex vivo* with a mixture of antisense oligonucleotides and injected these engineered DCs one time into NOD mouse recipients. This single injection was sufficient to significantly delay the incidence of diabetes in the animal model. The protection was due to an increase in regulatory T cells. Previously, the investigators had tried this approach with DCs treated with NF-kappaB-specific oligodeoxyribonucleotide (ODN) *in vitro* and demonstrated that administration of these treated DCs into NOD mice aged 6-7 weeks effectively prevented the onset of diabetes. Thus, genetically engineering DCs to express “designer” immunosuppressive molecules suggest that gene therapy may be a viable method for preventing the onset of type 1 diabetes in genetically at-risk people.
- Demonstrated that, in a mouse model of type 1 diabetes, treatment with an anti-inflammatory drug, called lisofylline (LSF), after islet transplantation protected against recurrent autoimmunity. Because recurrent autoimmunity is a major clinical barrier in human islet transplantation, LSF is a promising therapeutic agent to test in humans. Building upon these results, the CIT Consortium (see Goal III) will be testing LSF in humans. The LSF that will be used in the trial is being manufactured through the T1D-RAID program (see additional information later in this chapter).
- Demonstrated that kidneys of diabetic mice have reduced levels of a protein that blocks blood vessel formation, called pigment epithelium-derived factor (PEDF). Furthermore, the researchers found evidence, in studies of cultured kidney cells, that increased glucose levels significantly decreased PEDF secretion. Subsequent studies showed that

increasing PEDF expression in diabetic mice using gene therapy reduced several factors associated with the development or progression of diabetic kidney disease including urine albumin, a marker of diabetic kidney disease. PEDF is therefore a potential therapeutic target for preventing or treating this devastating disease complication.

- Determined that a protein, called “zonulin,” is expressed at very high levels in the intestines of diabetic rats. Zonulin is involved in regulating intestinal tight junctions, which are gates through which molecules may cross into the intestine. When the tight junctions are not working properly, which can lead to increased intestinal permeability, it may be easier for molecules to enter into the intestine. Increased intestinal permeability has been observed in numerous autoimmune diseases, including type 1 diabetes. Researchers have found that the increased level of zonulin correlates with an increase in intestinal permeability and the progression toward development of type 1 diabetes. When the rats were treated with an agent that blocks zonulin from binding to its cellular receptor, the incidence of progression to type 1 diabetes was decreased by 70 percent. These findings suggest that zonulin may be involved in the development of type 1 diabetes, and inhibition of zonulin may be a possible therapeutic approach to prevent or treat the disease.



Analysis of the protein expression of pigment epithelium-derived factor (PEDF) in the kidneys of wild-type rats (left image) and diabetic rats (right image), is depicted by the red color. Less PEDF protein is expressed in the kidneys of diabetic rats. This study suggests that PEDF is a possible therapeutic target for diabetic kidney disease. (Images courtesy of Dr. Jian-xing Ma. Copyright © 2005 American Diabetes Association. From *Diabetes*, Vol. 54, 2005; 243-250. Reprinted with permission from *The American Diabetes Association*.)

Anticipated Outcomes

The “bench to bedside” initiatives were developed to address a major barrier in clinical research—moving promising therapeutic agents from a laboratory setting to testing in actual type 1 diabetes patients. Although the full benefits of the program may not be realized for several years, the program has

already facilitated the conduct of clinical trials. For example, through research supported by this initiative, a therapeutic agent was found to prevent recurrent autoimmunity after islet transplantation in an animal model of type 1 diabetes. The agent will be tested to see if it has the same beneficial effects in a clinical trial of islet transplantation in humans. The

translation of a potentially beneficial therapeutic agent from bench to bedside is a key example of how the continuum of research supported by the *Special Funding Program* is making a significant impact on the lives of type 1 diabetes patients. Other potential therapeutic targets have also been identified through research supported by the *Special Program*—and additional targets and therapeutic agents are expected to be identified in the future—which can pave the way to more clinical trials to test promising agents. Another major strength of the program is the research partnerships that it has fostered. Partnerships between basic and clinical scientists enable both types of researchers to use their expertise to accelerate the movement of agents from bench to bedside. It is critically important to continue these types of translational research efforts so that there is a constant pipeline of therapeutic agents to test in future clinical trials. Such trials will propel the pace by which real improvements are made in the prevention and treatment of type 1 diabetes and its complications.

External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of the “bench to bedside” initiatives at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ This type of program is important and should continue. It is an excellent way to stimulate investigators to propel their laboratory research into a clinical or pre-clinical phase.
- ▶ One strength of this program is that it creates synergies between basic scientists and physicians at the same or different institutions.
- ▶ The critical juncture of research supported under this initiative is the transition from the R21 phase (the “bench”) to the R33 phase (the “bedside”).
- ▶ It is premature to judge success of this program; its impact will be realized in the next several years.

Actions Taken in Response to Expert Panel Recommendations

The NIDDK took the following action in response to a recommendation of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

Recommendation: Continue To Support Bench to Bedside Research on Type 1 Diabetes and Its Complications

- ▶ R33 phase support continues through conversions from the R21 phase.

Ongoing Evaluation

A trans-NIH committee, consisting of representatives from the NIDDK, NIAID, NHLBI, NINDS, and NEI, was established to oversee the transition from the R21 phase to the R33 phase for grants supported through this initiative. In some cases, external reviewers are convened to review the formal application requesting transition to the R33 phase; the reviewers make recommendations to the trans-NIH committee regarding whether the transition should occur.

Bench to Bedside Research Administrative History

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NEI, NHLBI, NINDS, ODS

In September 2002, 11 awards were made (5 R21 grants and 6 R21/R33 awards). In September 2003, 10 awards were made (7 R21 grants; 1 R33 grant; and 2 R21/R33 awards). In September 2004, 11 awards were made (6 R21 grants; 2 R33 grants; and 3 R21/R33 awards).

Innovative Partnerships in Type 1 Diabetes Research

The overall objective of this research program is to support collaborations between investigators who focus their research efforts on type 1 diabetes or its complications and researchers from other research areas with relevant expertise. The intent is to attract new talent to type 1 diabetes research; strengthen the ongoing efforts of type 1 diabetes researchers by providing access to specialized expertise or technologies relevant to their research; and facilitate the formation of interdisciplinary research partnerships to investigate significant biological and medical problems associated with type 1 diabetes. Through this program, type 1 diabetes researchers are encouraged to act as “talent scouts” by identifying and recruiting leading scientists with expertise relevant to the field of type 1 diabetes research. Using this mechanism, researchers with expertise in areas such as cell-based screening, imaging, genomics, and systems engineering are now pursuing research on type 1 diabetes. While awards issued under the program in 2002 provided only limited pilot support to initiate collaborations, it is noteworthy that 6 of 12 of those who applied for continued support to pursue these projects through regular research grants (R01s) were successful; this is substantially higher than the general R01 success rate.

Highlights of Progress

The progress that has been accomplished through the Innovative Partners initiative as of March 1, 2006, includes:

- After analyzing pancreatic sections from persons with and without type 1 diabetes, researchers demonstrated that 88 percent of type 1 diabetes patients still had insulin-producing beta cells. Furthermore, the number of remaining beta cells was unrelated to duration of disease or age at death. The data suggest that most patients with the disease continue to make new beta cells throughout their lives, and these cells continue to be destroyed by the immune system. The source of these beta cells is unknown. Further research is needed to uncover the mechanism by which the body continues to make beta cells throughout the lifespan (such as research that is being pursued by the Beta Cell Biology Consortium [BCBC] [see Goal III]), so that new therapies could be developed to “coax” beta cell formation, together with halting the destruction of existing beta cells.
- Scientists have demonstrated that a cytokine, called stromal cell derived factor-1 (SDF-1), plays a key role in the development of diabetic retinopathy (eye disease). SDF-1 levels were found to be increased in eyes of patients with severe diabetic retinopathy. SDF-1 is thought to attract cells derived from bone marrow that are involved in response to injury, a process that goes awry in diabetic eye disease with excessive formation of leaky new blood vessels. Importantly, blocking SDF-1 function in the eyes of a rodent model of diabetic retinopathy prevented the formation of abnormal blood vessel growth—a hallmark of this disease complication. Therefore, SDF-1 is a promising target for preventing diabetic retinopathy, which is a serious and debilitating complication of type 1 diabetes.
- Lack of appropriate recognition of all partners is a serious deterrent to collaboration. Through this initiative, the NIDDK pioneered a novel solicitation mechanism so that all partners funded under this initiative were named as co-equal “Principal Investigators.” Previously, the standard policy at the NIH was to award an actual grant to only one principal investigator, while the partner was listed as a co-investigator. The new mechanism provided an important incentive to collaboration and attracted experts from diverse fields. The new awards benefited both partners, who receive equal recognition

for their contributions to the research study. This recognition can be beneficial to investigators, who may be evaluated by their home institution in terms of the number of grant awards they have received. The “co-principal investigator” mechanism—first employed by the NIDDK with this initiative—has now been implemented by the NIH as a whole.

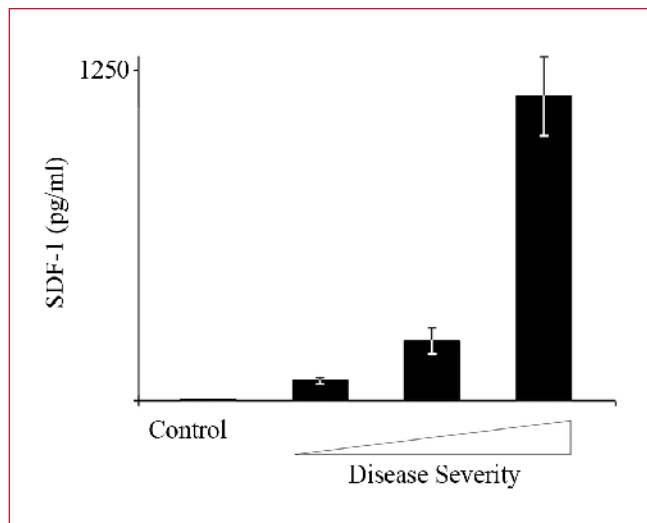
Anticipated Outcomes

Because type 1 diabetes affects so many different organ systems (e.g., pancreas, eyes, kidneys, heart, nervous system), and involves such diverse areas of science (e.g., immunology, stem cell and developmental biology, bioengineering) and medicine (e.g., pediatrics, transplant surgery), it is imperative to attract new talent to pursue research in this complex disease field.

Type 1 diabetes will also benefit from the application of new and emerging technologies, such as imaging, proteomics, and metabolomics. As these types of new technologies are revolutionizing the biomedical research field, it has become increasingly important to build “teams” of researchers with diverse expertise. For example, researchers who study islet transplantation most likely do not have expertise in the specialized field of imaging. However, imaging techniques can greatly enhance the islet transplant field by allowing researchers to “see” the transplanted islets. This ability would permit them to determine if the islets are being rejected by the immune system and possibly intervene earlier to prevent graft rejection and the need for patients to resume insulin administration. Researchers with expertise in these two areas must partner to make real advances in this field, and the Innovative Partners program has supported just this type of partnership. The *Special Funding Program* has enabled the NIH to facilitate these and other types of important research partnerships that are necessary for attracting new talent to type 1 diabetes research, as well as taking advantage of new technologies to accelerate research progress.

External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of the Innovative Partnerships program at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:



Researchers supported by the *Special Funding Program* measured the levels of a cytokine, SDF-1, in samples from the eyes of human patients with differing severity of diabetic eye disease, compared to non-diabetic control patients. They found that levels of SDF-1 increased with increasing severity of disease. The results of the study suggest that inhibiting SDF-1 could be a therapeutic approach for preventing diabetic eye disease. (Figure courtesy of Dr. Edward Scott [*J Clin Invest.* 115: 86-93, 2005]. Adapted from the *Journal of Clinical Investigation* by Butler, JM. Copyright 2005 by American Society for Clinical Investigation. Reproduced with permission of American Society for Clinical Investigation in the format Other Book via Copyright Clearance Center.)

- ▶ The program is an important way to attract new research talent and it should be continued. It is difficult for researchers in fields outside of diabetes to successfully apply for grant support if this partnership mechanism is not employed.
- ▶ The program's progress has been very good.
- ▶ A possible way of funding this program is by supporting competitive supplements to existing NIH type 1 diabetes research grants in order to enhance and broaden the roles of non-diabetes collaborators.
- ▶ A strength of the program is defining both partners as co-Principal Investigators (PI) rather than having a single PI and a collaborator. This co-equal distribution of leadership helps to incentivize the investigators.
- ▶ The program may be strengthened by increasing the award duration, which is currently 2 years. This increase would permit more time for researchers to build productive partnerships and perform collaborative research.

Ongoing Evaluation

The NIH continually seeks input from the external scientific community regarding future research directions and emerging

research opportunities. The Innovative Partnership initiatives have been informed and enhanced by external input. For example, the repeat issuance of this initiative was recommended in 2002 by an *ad hoc* expert panel convened by the NIDDK to evaluate progress of the *Special Funding Program*. In addition, external experts encouraged the NIDDK to recognize both research partners as PIs. This mechanism was employed when the initiative was reissued. These are just a few examples of how the NIH solicits broad external input to evaluate ongoing programs and inform future research directions.

Innovative Partnerships Administrative History

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, NIAID, NEI, NHLBI, NINDS, NINR, ODS

The solicitation for investigator-initiated research grants was issued twice. In September 2002, 16 awards were made using the R21 grant mechanism for 2 years of support. The second initiative was issued in July 2004, using the R01 grant mechanism such that both of the research partners would receive recognition as the Principal Investigator on an NIH grant. In 2004, 23 R01 grants (supporting 11 research projects) were awarded.

Research Training and Career Development in Pediatric Diabetes

Management of diabetes in children is particularly arduous and requires an exceptional level of effort from the children, their families, and their health care providers. These extraordinary clinical care demands make it challenging for pediatric endocrinologists involved in diabetes care to also pursue research careers. The purpose of this research program is to support research training and career development in pediatric diabetes at institutions with environments, mentors, and programs that will make them particularly effective in enhancing the number of independent investigators contributing to research in pediatric diabetes. The training program uses the T32 (Institutional National Research Service Awards) and the K12 (Mentored Clinical Scientist Development grants) mechanisms of support. In combination, the T32 and K12 programs provide an opportunity for continuous training from the clinical fellowship years to emergence as a fully trained independent investigator.

Highlights of Progress

Highlights of progress made by trainees supported through the Pediatric Diabetes Research Training Program as of March 1, 2006, include:

- Fifty-nine pediatric endocrinologists have received training and career development to foster careers in pediatric diabetes research through this program.
- Eighteen of the trainees have attained faculty positions at universities (e.g., Stanford University, University of Iowa, Children's Hospital of Buffalo, Children's Hospital of South Carolina, The Ohio State University, University of Alabama, and University of Pennsylvania).
- Trainees have published over 200 peer-reviewed papers, editorials, book chapters, and reviews (published or in press) and over 200 scientific abstracts.
- The T32/K12 trainees have obtained numerous other prestigious grants to support their research and training (e.g., Lawson-Wilkens Pediatric Endocrine Fellowships and Clinical Scholar Awards, Juvenile Diabetes Research Foundation (JDRF) regular research grants, Centers for Disease Control and Prevention (CDC) grants, awards through the NIH Loan Repayment Program, pilot and feasibility awards through NIH/NIDDK Center grants, and private foundation awards).
- The T32/K12 trainees have been involved in numerous significant scientific activities, such as: mentoring summer research students; giving invited scientific lectures; preparing invited reviews of publications for scientific journals; and completing Certificates in Clinical Science or Public Health.

Anticipated Outcomes

Several of the trainees who have been supported by this program have already moved forward in their career path to secure their own research funding and/or begin their own independent research program studying pediatric diabetes (for example, see "Investigator Profile" in this chapter). This program provides critical support to incentivize persons to enter the pediatric diabetes research field—and, importantly,

to continue to pursue research in this area after their training ends. For example, the K12 award could provide "bridge" funding between a fellowship and finding an independent faculty position; the award permits recipients to continue their research endeavors while securing independent funding. Because pediatric endocrinologists have such specialized knowledge about diabetes in children, applying their expertise



The *Special Funding Program* supports research training and career development in pediatric diabetes. Training a workforce of talented individuals to pursue diabetes research is essential to accelerating and maintaining research progress. (Photo credit: Getty Images.)

to research is truly critical to advancing research progress on type 1 diabetes. Furthermore, their combination of research and clinical experience is extremely beneficial to translational research efforts. The *Special Funding Program* has spurred the expansion of a workforce of these specialists to tackle research on type 1 diabetes in children. As more of the trainees leave their training institutions and begin their own independent research programs, the beneficial effects of this program will be realized for many years to come.

External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of the pediatric endocrinology training program at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ This program is extremely important to attracting new investigators to research on pediatric diabetes, and it should be continued.

- ▶ It is important to continue to follow the trainees after they receive their awards to determine if they remain in the pediatric diabetes research field.

Actions Taken in Response to Expert Panel Recommendations

The NIDDK took the following actions in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

Recommendation: Follow Trainees After They Receive Their Awards to Determine if They Remain in the Pediatric Diabetes Research Field

- ▶ NIDDK program staff track the career path of T32 and K12 trainees.

Recommendation: Maintain Communication with Trainees in Order To Hear their Concerns To Help Retain New Investigators

- ▶ K12 trainees are invited to NIDDK K awardees meetings. In this setting, the trainees have an opportunity to meet the NIH staff members who will most likely be the program directors for their independent R01 grants. The goal of the meetings is to assist the researchers in their transition from being trainees to independent investigators. In addition, the meetings provide an opportunity for the NIH to receive feedback from the trainees.
- ▶ T32 trainees are invited to JDRF-sponsored fellows meetings. This venue also allows trainees to give feedback on their training experiences.

Ongoing Evaluation

The T32/K12 program directors from each institution and NIDDK staff meet at least annually to discuss the overall progress of the training programs. Plans to collaborate in the training of the T32/K12 trainees have been discussed. The institutions also submit annual progress reports, which are

reviewed by NIDDK staff to ensure that sufficient progress is being made. Nearly all of the K12 trainees attended the NIDDK New Investigators' Workshop held in September 2004. In 2005, the JDRF hosted a forum that included the T32 trainees. Another NIDDK New Investigators' Workshop was held in April 2006, and new K12 trainees were invited to participate.

**Research Training and Career Development in Pediatric Diabetes
Research Administrative History**

Date Initiative Started	2002
Date <i>Special Program</i> Funding Started	2002
Participating Components	NIDDK, ADA, JDRF

Five combined research training/career development programs were established in FY 2002 for periods up to 5 years. Two additional programs were launched in FY 2003. Each program supports up to 5 pediatric endocrinologists (fellows or junior faculty) on either the T32 training grant or the K12 Mentored Clinical Scientist Development grant. In addition, each program was offered the opportunity to support the training of medical students during a summer research experience each year.

Type 1 Diabetes—Rapid Access to Intervention Development (T1D-RAID)

Promising ideas for novel therapeutic interventions can encounter roadblocks in movement from bench to bedside testing. Many investigators who have discovered a promising therapeutic agent in the laboratory do not have the resources or the background knowledge, for example, to “scale up” production of the agent for use in clinical trials. The T1D-RAID program was established to help overcome this major barrier to development of potential new therapeutics for type 1 diabetes and its complications. The program provides resources for pre-clinical development of drugs, natural products, and biologics that will be tested in clinical trials. The goal of T1D-RAID is to facilitate translation from the lab to the clinic of novel, scientifically meritorious therapeutic interventions for type 1 diabetes and its complications. T1D-RAID is not a grant mechanism and it does not sponsor clinical trials. Rather, it sponsors the work needed to get ready to do clinical trials. The program will assist investigators by providing pre-clinical development steps, the absence of which may impede clinical translation.

Highlights of Progress

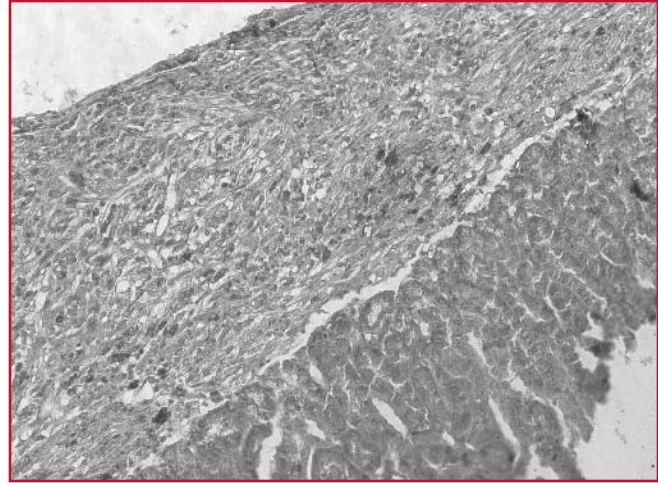
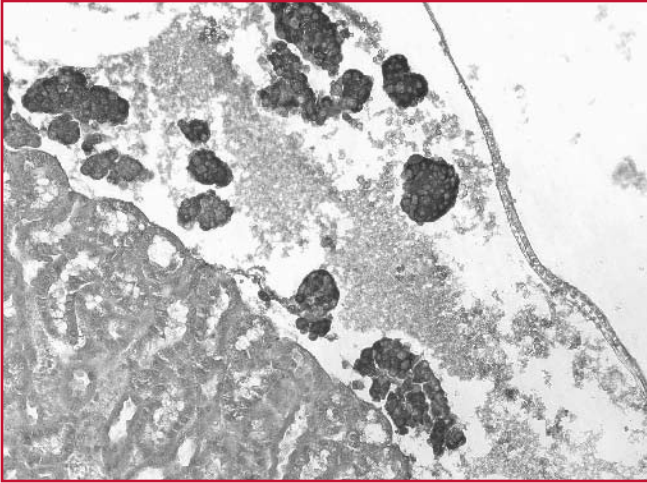
The progress that T1D-RAID has made as of March 1, 2006, includes:

- Approved five requests for use of pre-clinical drug development resources: (1) lisofylline, which is an anti-inflammatory compound that has a unique spectrum of activity to improve beta cell function and viability; (2) Starch-Deferoxamine, which is an iron-binding drug that will be tested in the treatment of diabetic neuropathy; (3) hOKT3-Gamma-1 (Ala-Ala) monoclonal antibody, which is a molecule that prevents the progression of type 1 diabetes in newly-diagnosed patients and may be useful in slowing onset of disease and in islet transplantation; (4) IL-2/Fc and mutant IL-15/Fc to be used in combination with rapamycin for treatment of new onset type 1 diabetes and for islet protection after islet transplantation; and (5) recombinant site-inactivated Factor VIIa (ASIS) to protect islets after islet transplantation.
- hOKT3-Gamma-1 (Ala-Ala) monoclonal antibody is being tested in a clinical trial in the Immune Tolerance Network (ITN) (see Goal II) to determine if it can halt the progression of type 1 diabetes in new onset patients and may also be studied for its ability to prevent type 1 diabetes in the Type 1 Diabetes TrialNet (TrialNet) (see Goal II);
- Lisofylline will be tested in a clinical trial supported by the CIT (see Goal III) to determine if it can help to prevent recurrent autoimmunity after islet transplantation.
- Recombinant site-inactivated Factor VIIa will be tested in a clinical trial supported by the JDRF to determine if it can help to prevent recurrent autoimmunity after islet transplantation.

Anticipated Outcomes

Because clinical trials of agents to prevent, reverse, or treat type 1 diabetes and its complications are so important to realizing real improvements in the health and quality of life of patients, it is crucial to have a research continuum from the laboratory, where therapeutic agents are identified and initially tested, to the clinic, where agents are tested in patients. T1D-RAID provides a necessary resource that permits

researchers to overcome the major barrier to moving promising agents from bench to bedside. This type of resource has also been identified as critically important for propelling translational research efforts through the NIH Roadmap for Medical Research, and an initiative supporting an NIH-RAID pilot project has been released. T1D-RAID is already manufacturing agents for testing in type 1 diabetes clinical trials and



Scientists supported by the *Special Funding Program* demonstrated that an agent, lisofylline, prevented the recurrence of type 1 diabetes after islet transplantation in a mouse model. The islets were engrafted into the mouse's kidney capsule. To assess islet survival and insulin production, the kidneys were stained with an antibody to detect insulin. The grafts of mice treated with lisofylline (left panel) made insulin (depicted by the dark circles), while insulin could not be detected in untreated mice (right panel). Overall, the study suggested that lisofylline protected transplanted islets from autoimmune rejection. The Type 1 Diabetes—Rapid Access to Intervention Development program supported the manufacture of lisofylline for human studies that will be undertaken through the Clinical Islet Transplantation Consortium. (Images courtesy of Dr. Jerry Nadler and reprinted with permission from Yang Z, et al. *The novel anti-inflammatory agent lisofylline prevents autoimmune diabetic recurrence after islet transplantation*. *Transplantation*. 77 (1): 55-60, 2004.)

is expected to produce several more. As more knowledge is gained about the underlying mechanisms of disease development, including genes and environmental factors that cause disease (see Goal I), as well as key immune system players (see Goal II), researchers could use this information to develop additional targets for disease prevention and treatment. Therefore, having the T1D-RAID resource in place will help to translate these new discoveries from the laboratory to the clinic, thereby accelerating the pace at which therapeutic agents can be used to prevent or treat type 1 diabetes.

External Evaluation by Expert Panel

Leading scientific and lay experts were asked to evaluate the progress of T1D-RAID at an *ad hoc* planning and evaluation meeting convened by the NIH in January 2005 (see Appendix 3). Comments from the panel review included:

- ▶ T1D-RAID is extremely important and should be continued.

- ▶ Although the program is relatively new, investigators have already begun to submit requests to use T1D-RAID resources, suggesting that there is a need for this type of program.
- ▶ The program should support pre-clinical development of therapeutic agents that span the type 1 diabetes research field, including complications.
- ▶ The monetary resources that support T1D-RAID must be sufficient to support the breadth of necessary research and resource development.

Actions Taken in Response to Expert Panel Recommendations

The following actions were taken in response to recommendations of the expert panel at the *ad hoc* planning and evaluation meeting convened by the NIH in January 2005:

Recommendation: Continue To Support the T1D-RAID Program

- ▶ Funding for T1D-RAID is being continued.

Recommendation: Create Initiatives Which Support Pre-Clinical Studies of New Therapeutic Agents To Prevent or Treat Type 1 Diabetes or Its Complications in Animal Models

- ▶ Two RFPs were issued in March 2005 to support performance of pre-clinical studies in animal models of potential new therapeutics for the prevention or treatment of type 1 diabetes or its complications.

Recommendation: The Program Should Support Pre-clinical Development of Therapeutic Agents That Span the Type 1 Diabetes Research Field, Including Complications

- ▶ The T1D-RAID program is supporting the production of Starch-Deferoxamine, which is an agent that will be tested for treating diabetic neuropathy—a devastating complication of type 1 diabetes.

Ongoing Evaluation

To determine which submitted requests are scientifically meritorious, the NIDDK convenes qualified external reviewers who make recommendations to the Institute regarding whether a project should receive support. Investigators whose projects are supported are invited to present their project to a joint NIDDK/NCI T1D-RAID team, at which time questions can be asked and decisions made regarding the exact next steps. Milestones for progression of the project are then set by the NIDDK, NCI, and the PI. Monthly meetings of the NIDDK/NCI T1D-RAID team review the progress and roadblocks on each project to ensure that projects are progressing and that information is widely disseminated.

Coordination with Other Research Efforts

T1D-RAID is supporting the pre-clinical development of therapeutic agents that will be tested in clinical trials supported by the *Special Funding Program*. Therefore, this resource has been critically important in facilitating the translation of agents from bench to bedside, where they will be tested in type 1 diabetes patients.

Facilitating Type 1 Diabetes Clinical Trials:

- ▶ T1D-RAID is supporting the manufacture of lisofylline, which will be tested in the CIT Consortium to determine if it can help reduce islet autoimmune destruction after islet transplantation.
- ▶ T1D-RAID is assisting in the manufacture of the hOKT3-Gamma-1 (Ala-Ala) monoclonal antibody, which will be tested in a clinical trial conducted by the Immune Tolerance Network to determine if it can halt further destruction of beta cells in new-onset type 1 diabetes patients.

T1D-RAID Administrative History

Date Initiative Started	2003
Date <i>Special Program</i> Funding Started	2004
Participating Components	NIDDK, NCI
Website	www.T1Diabetes.nih.gov/T1D-RAID/index.shtml

The T1D-RAID program was modeled after the NCI's RAID program and is a collaboration between the NIDDK and NCI. The sponsors of approved requests to T1D-RAID gain access to the pre-clinical drug development contract resources of NCI's Developmental Therapeutics Program.

EVALUATION OF INVESTIGATOR-INITIATED RESEARCH

The Special Funding Program has supported pediatric diabetes research training and career development, as well as investigator-initiated research projects addressing particular challenges and opportunities identified by the NIH with the aid of scientific experts at workshops and advisory meetings. Often these recommendations were disseminated to the research community in a Request for Applications (RFA) or Request for Proposals (RFP). (For a list of initiatives supported by the Special Funding Program, please see Appendix 1.) The NIDDK conducted a Grantee Survey (see Appendix 5) to evaluate the impact of the Special Funding Program on investigators with research project grants principally supported by the Special Funds. The survey was used as a tool to assess the research accomplishments (e.g., publications, resulting patents, impact on patients' health), research collaborations, and impact that the Special Program had on careers of investigators supported by it. Data from this survey are found in the "Assessment" chapter.

Impact of Special Funding Program on Extramural Grantees

Principal investigators who received grants related to attracting new talent and applying new technologies to research on type 1 diabetes responded to the survey that asked, in part, about the value of their grant or funding source. Representative remarks include:

- ▶ "The T32 diabetes training program has been extremely helpful in increasing the number of fellow trainees we have been able to accommodate. The K12 mentor-based program has, likewise, allowed us to train young pediatric endocrinologists in diabetes research producing excellent clinical investigators. An added bonus has been an increased clinical research productivity of our faculty as a byproduct of training our fellows and junior faculty in clinical research techniques."
- ▶ "The fellowship has produced exactly the type of candidate [highly ranked University Pediatric Endocrine programs are] looking for: a well-trained clinician with skills in clinical investigation who will be capable of collaborating in and initiating clinical research in their institution. Parenthetically, the availability of many excellent job opportunities for a well-trained pediatric endocrinologist attests to the continued significant shortage of pediatric endocrinologists across the United States."
- ▶ "The R21 was an invaluable way for me to establish independence as a clinician-scientist. I was the recipient of a K08 award as a junior faculty member. I received a small R03 grant, as a supplement to my K08, prior to my R21. The R21 began the day my K08 ended—enabling me to stay in diabetes-related research. As a pulmonologist doing cross-disciplinary research, it would have been nearly impossible to continue doing diabetes-related research without this support."
- ▶ "This program was a creative solution to increase the number of investigators in the area of type 1 diabetes, and to bring new ideas to bear on the problem. The people who developed the program should be complimented for that. I believe that collaborative research and generation of global resources will accelerate our ability to translate findings into new strategies for prevention and clinical cures."
- ▶ "This has been a very valuable source of funding for me and has allowed me, an active clinician-scientist, to remain in biomedical research. We have made some exciting discoveries, which I believe will have an immediate and positive impact on the field of human islet transplantation."

- ▶ “This grant has had a tremendous impact on my career. Because this was my first grant as a Principal Investigator, it greatly contributed in establishing my independent research project. In addition, it played an important part in my ability to keep focusing on type 1 diabetes and its complications in my research program.”
- ▶ “Before this grant I had never worked on diabetes. This grant gave me the opportunity to apply tools and concepts from tissue engineering and gene therapy to engineer potential solutions for this devastating disease. In this respect, this was a highly valuable grant that resulted in development of a project that would not have been pursued otherwise.”

Research in Pediatric Endocrinology: Road to Independence

A Lifelong Ambition

Dr. Andrew Norris always knew that he wanted to be a researcher. “Going into research was a lifelong ambition,” recalls Dr. Norris, an Assistant Professor at the University of Iowa. “Beginning in second grade, I read every science book in the library of my elementary school.”

Dr. Norris also developed an interest in medicine, so in order to pursue both medicine and research, he enrolled in a combined M.D. and Ph.D. training program at the Washington University School of Medicine in St. Louis. He entered the program intending to pursue medical research, with a particular interest in nutrition and the role that carbohydrates and lipids play in the development of human disease. He also enjoyed working with children. After receiving his degrees, he completed a pediatrics residency program. During that time, more and more children were being diagnosed with type 2 diabetes, and this sparked his interest in studying diabetes, an endocrine disease, in the pediatric population.

For further training as a sub-specialist in pediatric endocrinology, Dr. Norris applied to and was accepted into a combined fellowship program at the Children’s Hospital Boston and the Joslin Diabetes Center. “The fellowship program was an extremely wonderful experience for me,” recalls Dr. Norris, “and I went there with the intention of doing diabetes research.” During the first year of his fellowship, he worked directly with children with diabetes.

“I found that I really enjoyed working with children with diabetes and their families. This positive experience also synergized with my interest in research,” states Dr. Norris. During the next 2 years of his fellowship, he pursued research in the laboratory of Dr. C. Ronald Kahn, a prominent diabetes researcher. Dr. Norris recalls, “While working in Dr. Kahn’s lab, my goal was always to become an independent



Dr. Andrew Norris

investigator studying pediatric diabetes.” However, making the transition from being a research trainee to an independent investigator can be a daunting task.

Transition to Independence

At the end of his fellowship, Dr. Norris would transition from being a “fellow” to a faculty member, at which time he would be expected to find his own source of funding to support his research program. In preparation for this transition, approximately 1 year before his fellowship ended, he applied for an NIH “Mentored Clinical Scientist Development Award” (K08) to support his research. Two months before becoming a faculty member, he found out that his application was, as he states, “good, but not good enough” to receive funding. Therefore, he was facing the prospect of having to put research on hold until he could find funding support.

Fortunately for Dr. Norris, the Children’s Hospital Boston/Joslin Diabetes Center was one of seven sites participating in the *Special Funding Program*-supported “Pediatric Diabetes Research Training and Career Development Program.”

Dr. Norris was familiar with this program because, earlier in his fellowship, he was supported by an institutional research training grant (T32) under this umbrella program. In addition to T32 training grants, the program also awards K12 grants (Clinical Scientist Career Development Program), which provide funding for investigators as they transition to independent faculty positions. "Fortunately," says Dr. Norris, "a K12 slot was available when I needed funding to bridge time between completing my fellowship and receiving my own grant. Without the K12 award, I would not have had professional time to pursue diabetes research, and might have instead had no choice but to spend the majority of my time in the clinic. This award mechanism allowed me to have 'protected time' so that I could resubmit my K08 grant application and still focus on diabetes research and building my own research program." While receiving support from the K12 training grant for 1 year, Dr. Norris resubmitted his K08 application and was awarded funding. Importantly, there was no disruption to his diabetes research endeavors.

Dr. Norris recently joined the faculty at the University of Iowa, where he directs his own independent research program. His research focuses on how the events early in life affect later risk of diabetes and diabetic complications. As an example, a person's blood sugar level today has a strong effect on his or her risk of complications years down the line, even if the individual feels healthy in the interim. In other words, as Dr. Norris states, "The immediate effect is subtle and unnoticed, but over time can lead to significant problems." To this end, he is developing new mathematical models to better identify the early subtle effects of diabetes on gene expression. These tools will help determine how these barely noticeable effects eventually lead to such devastating complications. The hope is to develop improved strategies enabling doctors to better prevent or delay the development of complications, which affect patients with both type 1 and type 2 diabetes. Dr. Norris is also studying the ways that abnormal buildup of fat contributes to the complications of diabetes as well as the development of insulin resistance. This research could provide insights

into additional means to prevent or delay certain diabetic complications.

Dr. Norris stresses that, "Because of the shortage of pediatric endocrinologists throughout the country, the pediatric endocrinology research training program is of incredible importance to attracting talented individuals to pursue research in this area." Furthermore, he notes, "It is difficult to secure funding for independent research by the end of a fellowship. The K12 grant mechanism is a necessary tool to bridge the gap between completing research training and pursuing independent research."

Pediatric Diabetes Training Program

To enlarge the pool of pediatric endocrinologists conducting diabetes research, the NIH, in partnership with the ADA and the JDRF and with support by the *Special Funding Program*, awarded institution-wide research training and career development grants to seven medical centers with strong research programs in childhood diabetes: Children's Hospital Boston/Joslin Diabetes Center, where Dr. Norris received his training; Baylor College of Medicine; University of Colorado; University of Pennsylvania; University of Pittsburgh; Washington University; and Yale University. More information on the program can be found at: www.niddk.nih.gov/fund/diabetesspecialfunds/train_peddiab.htm.

The awards, through the T32 (institutional research training) and K12 (Clinical Scientist Career Development Program) grant mechanisms of the NIH, provide for 2-3 years of fellowship training, as well as 2-3 additional years of support for junior clinical investigators, for a total of 5-6 years of continuous, uninterrupted research training in diabetes. The funding supports up to five positions at each medical center; each center was free to decide how many of the five slots were to be reserved for pediatric endocrinology fellows or investigators who were transitioning from fellow to independent scientist.

INNOVATIVE PARTNERSHIPS IN TYPE 1 DIABETES RESEARCH: A NOVEL CO-PRINCIPAL INVESTIGATOR MECHANISM

Because research on type 1 diabetes spans a broad range of scientific disciplines, propelling research progress requires a cadre of scientists with diverse research training and expertise. To attract new research talent to study type 1 diabetes and its complications, the NIH has supported an initiative on “Innovative Partnerships in Type 1 Diabetes Research.” The overall objective of the initiative was to support collaborations between investigators who focus their research efforts on type 1 diabetes or its complications and investigators from other research areas with expertise relevant to type 1 diabetes. Type 1 diabetes researchers therefore acted as “talent scouts” by identifying and recruiting leading scientists with expertise relevant to the field of type 1 diabetes research. Using this mechanism, researchers with expertise in areas such as cell-based screening, imaging, genomics, and systems engineering are now pursuing research on type 1 diabetes.

The intent of the initiative was to encourage true partnerships in which two or more investigators with complementary expertise tackled a common problem. However, the standard policy at the NIH was to award a grant to only one principal investigator, while the partner was listed as a co-investigator—an

arrangement that did not recognize both partners as being equal and thus posed a barrier to collaboration. Based on feedback received from the external scientific community, the NIH pioneered a novel solicitation so that both partners were named as co-equal principal investigators. This arrangement was first used under the *Special Statutory Funding Program for Type 1 Diabetes Research*. It provided an important incentive to collaboration and attracted expertise from diverse fields. For example, one project brought together diabetes complications investigators with experts in angiogenesis (small blood vessel formation), thereby helping to move therapeutics currently used for cancer toward applications for diabetes complications. The new awards benefited both partners, who have now received equal recognition for their contributions to the research study. This recognition can be beneficial to investigators, who may be evaluated by their home institution in terms of the number of grant awards they have received. The “co-principal investigator” mechanism—first employed by the NIDDK with this initiative—is now being considered for broader implementation by the NIH as a whole, under the NIH Roadmap for Medical Research.

EMERGING RESEARCH OPPORTUNITIES RESULTING FROM THE SPECIAL STATUTORY FUNDING PROGRAM FOR TYPE 1 DIABETES RESEARCH

The Special Funding Program has fueled the emergence of a wide range of research opportunities. Opportunities that have largely been made possible by the Special Funding Program have been excerpted below from the Type 1 Diabetes Research Strategic Plan (see Appendix 6).

Engaging Talented Scientists

Recruit Expertise from Diverse Fields:

- ▶ Encourage interdisciplinary collaborations.

Design Incentives That Reward Research Innovation:

- ▶ Promote high-risk, high-impact research.
- ▶ Create an environment conducive to innovation and collaboration.

Train New Scientists in Clinical Type 1 Diabetes Research:

- ▶ Attract and train new diabetes investigators.

Development and Application of New Technologies

Develop Noninvasive Imaging Technologies To Monitor Type 1 Diabetes:

- ▶ Develop imaging for pancreatic beta cell mass, function, and inflammation.
- ▶ Develop brain imaging techniques to use in understanding hypoglycemia.

Promote Application of Advances in Bioengineering to Type 1 Diabetes:

- ▶ Develop novel drug delivery methods.
- ▶ Develop noninvasive glucose monitoring technologies.
- ▶ Integrate tissue engineering and regenerative medicine to develop tissues and organs to replace those destroyed by diabetes and its complications.
- ▶ Apply nanomedicine to drug delivery, islet encapsulation, noninvasive imaging, and glucose-sensing technologies.

Foster Application of Gene Delivery and Gene Silencing Technology To Develop New Therapies for Type 1 Diabetes and Its Complications:

- ▶ Develop technology for gene delivery to cells and tissues that are therapeutic targets for type 1 diabetes.
- ▶ Create siRNA vectors for gene silencing in target tissues.

Apply New and Emerging Technologies in Functional Genomics, Proteomics, and Metabolomics to Type 1 Diabetes Research:

- ▶ Use “omics” technologies to identify interactions among genes, proteins, and metabolites in type 1 diabetes and its complications.
- ▶ Utilize proteomic and metabolomic technologies to identify and validate surrogate markers that predict risk, rate of progression, or response to therapy for type 1 diabetes and its complications.

Improve the Power of Diabetes Research by Utilizing Computational Biology and Bioinformatics:

- ▶ Enhance type 1 diabetes research efforts by incorporating bioinformatics at the inception of the research effort.
- ▶ Apply computational biology to the complex systems in type 1 diabetes.
- ▶ Integrate information technology into type 1 diabetes self-care and medical management.

Apply New Technology to the Development of Improved Animal Models for the Study of Type 1 Diabetes:

- ▶ Develop models needed to identify cellular and molecular pathways influencing beta cell formation and function.
- ▶ Develop animal systems with greater fidelity to human disease to enhance pre-clinical testing and biomarker development.