

# Appendix 6

## SUMMARY REPORT OF THE MAY 2002 ADVISORY PANEL MEETING

**Advisory Meeting on the Special  
Statutory Funding Program for Type 1  
Diabetes Research**

National Institutes of Health

May 16, 2002

An external advisory panel of scientific and lay experts with respect to type 1 diabetes research (*see Acknowledgements*) convened at the National Institutes of Health (NIH) on May 16, 2002, to discuss the special statutory funding program for research on the prevention and cure of type 1 diabetes. The advisors were charged with evaluating the research efforts supported by the special funds, identifying scientific gaps and opportunities for future research, and advising the NIH and the Centers for Disease Control and Prevention (CDC) on the use of remaining funds for FY 2002 and FY 2003. This meeting constitutes a major source of input for a mandated report to the Congress evaluating the special funding program.

The panel expressed great enthusiasm for research coordination mechanisms—consortia, clinical trial networks, repositories, databases, and registries—that have been established, in whole or in part, with the special funds and urged the development of additional programs of this nature. The importance of continuity of support for these valuable research resources and infrastructure was strongly emphasized. Several strategies for facilitating the maximal use of these resources were proposed. Significant ideas included the addition of ancillary studies to large clinical trials, an increase in coordination among the various research groups, and expansion of the core missions of some research consortia to encompass emerging issues of high scientific priority. In addition, the advisors were pleased with the support of innovative, high-impact research through funding of pilot and feasibility grants to individual investigators. They appreciated the success of solicitations issued with these funds in attracting new investigators and established investigators who were new to diabetes research. The initiatives undertaken were felt to maintain an appropriate balance between large-scale research

programs and investigator-initiated research. Moreover, these requests for applications (RFAs) have been issued periodically throughout the duration of the special funding program to ensure that they attracted the best, most cutting-edge science. The advisory panel emphasized that it is not yet possible to fully assess the outcome of the special funding program in that many projects are recently or newly initiated, not all of the FY 2002 funds have been deployed, and funding plans for FY 2003 have not yet been finalized.

### Research Coordination and Connections

The advisory panel made several recommendations for extending and capitalizing on existing research coordination efforts, maximizing connections among research groups with related interests, and developing new resources to enhance cross-disciplinary research in complex scientific fields.

#### The panel identified the following elements as important to coordination:

- ▶ bioinformatics initiatives to integrate data from multiple consortia and trial networks;
- ▶ a multi-institutional review board (IRB) to review multi-site clinical research;
- ▶ common informed consent documents;
- ▶ improved assay standardization;
- ▶ ancillary studies and other mechanisms to ensure that maximal value is obtained from research data and samples from clinical research study participants;

- ▶ partnerships between industry and academia to spur drug development and testing, including fast track mechanisms to facilitate clinical trials;
- ▶ mechanisms to bring discoveries with therapeutic applications that originate in academic laboratories through preclinical development—the National Cancer Institute’s (NCI) Rapid Access to Intervention Development (RAID) program was discussed as a possible model.

**The panel identified additional opportunities for coordination of efforts in several research areas:**

- ▶ enhancement of research on diabetic complications by:
  - ▶ creating a central knowledge base to coordinate information on NIH-wide initiatives related to diabetic complications;
  - ▶ improving dissemination of information about existing animal models;
  - ▶ facilitating animal model research projects that address multiple complications and evaluate multiple tissues in the same animal(s);
  - ▶ stimulating the development of new animal models for complications research;
- ▶ systematic evaluation of approaches to islet transplantation including:
  - ▶ pancreas harvesting;
  - ▶ islet isolation, evaluation, and preservation;
  - ▶ site and method of islet transplantation;
  - ▶ immunosuppression, tolerance, and other aspects of immunomodulation;

- ▶ expansion of the islet cell resource centers’ mission to include the procurement of pancreata for basic research on insulinitis;
- ▶ application of insights from angiogenesis research to the study of islet graft vascularization;
- ▶ investigating hypoglycemia unawareness in new islet transplant recipients;
- ▶ recruitment of neuroscientists and brain-imaging specialists to study similarities in the glucose-sensing mechanisms of the pancreatic beta cells, the brain, and other glucose-sensitive tissues;
- ▶ establishment of type 1 diabetes as a reportable illness throughout the U.S.;
- ▶ the use of type 1 diabetes as a model for understanding immunology and autoimmunity.

**Major Research Opportunities**

Based on recent research progress in type 1 diabetes as well as in broader areas relevant to diabetes research, the advisors recognized several critical areas of opportunity.

**Pursuing initiatives in these areas would expand on recent scientific advances to enhance progress on the understanding, treatment, or prevention of type 1 diabetes:**

- ▶ understanding the autoimmune basis of type 1 diabetes:
  - ▶ the role of HLA molecules in the development of autoimmunity;
  - ▶ central tolerance and reprogramming of T cells;
  - ▶ the effect of parental type 1 diabetes on possible immune tolerization of offspring during pregnancy;
  - ▶ beta cell antigen identity;
  - ▶ developing assays for pathogenic T cells;
  - ▶ applying new methodologies, such as proteomics approaches, to studying insulinitis and identifying circulating beta cell markers;
  - ▶ designing beta cell imaging technology for use in assessing progression of autoimmune destruction of beta cells;
  - ▶ identifying genes conferring susceptibility to or protection from development of type 1 diabetes;
  
- ▶ pursuing stem cells or stimulators of stem cells as a source of beta cells that could overcome the short supply of islets available for transplantation by current protocols;
  
- ▶ improving islet transplantation procedures and documenting their risks and benefits, including issues of cost-effectiveness, quality-of-life, and the development of complications;
  
- ▶ understanding the mechanisms of hypoglycemia unawareness and nocturnal hypoglycemia;
  
- ▶ uncovering the role of inflammation in vascular complications of diabetes, particularly functional interactions between monocytes and endothelial cells.

## Conclusions

Recent progress in type 1 diabetes research has allowed great strides in our understanding of this disease, but much work remains to be done. Studies to identify how genetic propensities and environmental triggers initiate the disease process in humans are now critical. Continued research on animal and cell models will be needed to understand mechanisms and develop novel preventive agents for type 1 diabetes and its devastating complications. Ongoing investment in clinical trials and research will help scientists translate research advances into real improvements in patients' health. The research initiatives and resource development undertaken with the special funding program to date have sparked exciting new opportunities for future, cutting-edge research on understanding, preventing, and treating type 1 diabetes.

## Special Funds for Type 1 Diabetes Research

Special funding for type 1 diabetes research, in the total amount of \$390 million for FY 1998 through FY 2003, was provided to the Secretary of Health and Human Services by the Congress through Section 330B of the Public Health Service Act. The original enabling legislation was the Balanced Budget Act of 1997 (Public Law 105-33), which was later amended by the FY 2001 Consolidated Appropriations Act (Public Law 106-554) to extend the special funding program in time and amount. This funding program supplements regularly appropriated funds that the Department of Health and Human Services (HHS) receives for diabetes research through the Labor-HHS-Education Appropriations Committees.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), through authority granted by the Secretary, has a leadership role in planning, implementing, and evaluating the allocation of these funds. To ensure the most scientifically productive use of the funds, the NIDDK initiated a collaborative planning process that involves the participation of the relevant institutes and centers of the NIH, the Centers for Disease Control and Prevention (CDC), the Agency for Health Care Research and Quality (AHRQ), the Food and Drug Administration (FDA), and the two major diabetes voluntary organizations: the Juvenile Diabetes Research Foundation International (JDRF) and the American Diabetes Association (ADA). Critical to this process is scientific advice the NIH has garnered from a

variety of scientific workshops and conferences, the recommendations in the 5-year plan of the congressionally-established Diabetes Research Working Group, and the advice of a group of distinguished scientists from research institutions across the country who convened in April 2000 to consider opportunities for allocation of the special funds.

**The pursuit of six major research goals that offer exceptional promise for the treatment and prevention of type 1 diabetes underlies the planning process:**

---

### Goal I

Identify the Genetic and Environmental Causes of Type 1 Diabetes

---

### Goal II

Prevent or Reverse Type 1 Diabetes

---

### Goal III

Develop Cell Replacement Therapy

---

### Goal IV

Prevent or Reduce Hypoglycemia in Type 1 Diabetes

---

### Goal V

Prevent or Reduce the Complications of Type 1 Diabetes

---

### Goal VI

Attract New Talent to Research on Type 1 Diabetes

---

---

### **Evaluation of the Special Funding Program**

The laws providing the special funds for research on the prevention and cure of type 1 diabetes also mandated interim and final evaluation reports on the use of the funds. Initiatives pursued with the P.L. 105-33 funds are described in a 2000 interim report to the Congress, which is posted on the NIDDK website (<http://www.niddk.nih.gov/federal/initiative.htm>).

A final evaluation of research efforts under the special funding program is due on January 1, 2003.

A critically important aspect of the final evaluation is input received from an external panel of 15 leading scientists and lay persons with expertise on type 1 diabetes research, which was convened by the NIDDK in May 2002. The panel was provided with details on the goals and accomplishments to date, or expected outcomes, of more than 65 major initiatives supported by or planned for the special funding program for type 1 diabetes research. The advisory group was not charged with performing a project-by-project analysis, especially for many of the smaller initiatives and for those funded in the early years of the program. Rather, the panel was asked to discuss research opportunities and initiatives made possible by the special funding program, as well as newly emerging areas of promise. Panel members were urged to identify the most innovative research ideas—both within and beyond the traditional diabetes field—that the NIH should emphasize as future efforts in type 1 diabetes research are developed. To the extent that flexibility exists in allocating the remainder of the special funds through FY 2003, the panel was invited to comment on current or planned initiatives.

## Meeting Agenda

The advisory meeting was designed to serve as a free-flowing scientific exchange about progress, challenges, and opportunities in type 1 diabetes research and the broad scientific directions that the NIH, CDC, and/or other components of HHS should pursue. The meeting began with introductory remarks and an overview of the special type 1 diabetes funding program by Dr. Allen Spiegel, NIDDK Director, and Dr. Judith Fradkin, Director of the NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases. Mr. Charles Queenan, JDRF Chair of Research, and Dr. Robert Sherwin, immediate past president of the ADA, presented the perspectives of these voluntary organizations, which each commit significant funds to research. The remainder of the meeting was devoted to individual sessions on each of the six major research goals. For each goal, program staff from the NIH or CDC made brief presentations on key initiatives and one or two panel members served as moderators for the subsequent group discussion. These presentations augmented more detailed information about each initiative undertaken or in progress utilizing the special type 1 diabetes funds, descriptions of which were provided in briefing books distributed in advance of the meeting. Panel members were also invited to submit their personal views on advances and opportunities in type 1 diabetes research either before or following the meeting.

## Overview of the Special Type 1 Diabetes Funding Program

In allocating the special funds for type 1 diabetes research, the NIDDK has relied on the help and advice of scientific experts and its funding partners throughout the NIH, HHS, and the diabetes voluntary community to make productive use of these special resources. The basic structure for using the special funds has evolved as the amount of funding has increased. In the early years of the program, most of the funding was expended through Requests for Applications (RFAs) targeted at traditional investigator-initiated research projects and pilot and feasibility grants, which covered a wide range of research areas relevant to type 1 diabetes. An increase in the special funding in FY 2001 permitted the NIH and CDC to expand the scope of the program by launching multiple long-term initiatives, including new clinical trials networks, epidemiologic studies, research consortia, and research resources. In addition, the NIH issued additional solicitations for support of investigator-initiated research. Importantly, NIH and CDC commitments to many of these initiatives will extend beyond FY 2003, when the special type 1 diabetes funding program expires.

The initiatives begun after expansion of the special type 1 diabetes research funds in FY 2001 derived in large part from the recommendations of a special type 1 diabetes research advisory panel that was convened in April 2000. The input of the May 2002 panel is especially crucial for modulating ongoing projects and identifying critical opportunities to ensure that the overall funding strategy continues to meet the needs of the type 1 diabetes research community as it progresses towards the goal of the prevention and cure of type 1 diabetes.

---

### **Perspective of the JDRF**

The primary mission of the JDRF is to find a cure for diabetes and its complications through the support of research. JDRF funds research with the goals of achieving normal blood glucose levels, preventing type 1 diabetes, and treating diabetic complications. In FY 2001, the JDRF committed \$115 million to diabetes research and expects to devote more than \$100 million in FY 2002. Thirty-five percent of JDRF funds support research outside of the U.S. This commitment to international research enables JDRF to partner with other funding organizations and research groups, including the NIH, in scientific ways that transcend national boundaries.

The JDRF seeks to maximize the impact of its funding by complementing, not duplicating, the research efforts of the NIH, and other private and public sources of type 1 diabetes research funding. To this end, the JDRF is developing an ongoing, goal-oriented “roadmap” of type 1 diabetes research funding. The foundation is characterizing its own funding as well as that of the NIH and other government agencies, non-profit groups, and industry to identify what research areas are currently supported and what gaps and opportunities might exist. This process facilitates the assessment of progress by the diabetes community at large and measurement of that progress against milestones along the path to a cure. An example of a gap in funding that the JDRF is currently moving to fill is in the field of stem cell biology, which holds promise as a source for replacement beta cells. The JDRF has been a committed partner with the NIH and CDC in planning and implementing the new initiatives in type 1 diabetes research that have been made possible through the special funding program.

### **Perspective of the ADA**

The ADA has worked in recent years to make the general public aware of the growing problem of diabetes and its health implications in the U.S. and to generate interest in supporting diabetes research by the Congress as well as HHS. A major focus of the ADA’s efforts is the support of research, often in cooperation with the NIH and JDRF. The ADA sponsored \$31 million in research this year, representing an increase of more than 100 percent over the last 3-4 years. An estimated 15 percent of the ADA portfolio represents research specifically related to type 1 diabetes and an additional 60 percent constitutes studies on therapy and complications, which have implications for all forms of diabetes.

An example of the type of research that the ADA supports is a project to identify risk factors for type 1 diabetes in newborns in the state of Florida. In addition, the ADA is in the process of formulating a new initiative on beta cell biology research. The ADA expressed strong support for the special type 1 diabetes funding initiative and has been pleased to partner with the NIH and CDC in developing the goals and initiatives of this program.



# GOAL I Identify the Genetic and Environmental Causes of Type 1 Diabetes

MODERATOR: Åke Lernmark, MD

## Genetics of Type 1 Diabetes

Dr. Catherine McKeon, NIDDK Senior Advisor for Genetic Research, explained the goals and progress of three major initiatives undertaken to find genes responsible for type 1 diabetes and to develop resources for the genetics research community. The International Type 1 Diabetes Genetics Consortium (T1DGC), a joint initiative between the NIH and JDRF, will generate a large, standardized family collection of genetic and phenotypic data that will aid in the search for non-HLA genes involved in type 1 diabetes susceptibility. Similarly, the EDIC genetics study will collect genetic data and DNA samples on the type 1 diabetes patients and their families from the Diabetes Control and Complications Trial (DCCT), who have been followed for over 15 years. DNA and cell lines from the participants in both the T1DGC and EDIC will be stored in repositories for access by the research community, following peer-review of proposals. Finally, the International Histocompatibility Working Group (IHWG) has been formed to examine HLA, a major genetic influence in type 1 diabetes, and its relationship to disease. A single nucleotide polymorphism (SNP) discovery project will identify SNPs in the HLA region and other autoimmune modulating genes that might be candidate genes for type 1 diabetes. The SNPs will be deposited in a database that can be used by investigators to conduct gene association studies for type 1 diabetes and other autoimmune diseases.

The growth of the type 1 diabetes genetics research field that has been gained by establishment of the T1DGC and other genetics initiatives made possible by the special funding program was considered very important by the advisory panel. By greatly expanding the size of the genetic sample collections, these projects will add much-needed power to the search for non-HLA susceptibility genes and shorten the time needed

for analysis. The panel discussed significant gaps and opportunities in current research plans that have recently emerged.

**Research topics that could be fostered through the genetics research consortia, or by complementary initiatives, include:**

**T cells:** Monocytic infiltration of the human pancreas is observed in about 60 percent of newly diagnosed type 1 diabetes patients. Understanding the mechanism of T cell mediated disease is a critical research topic that could be pursued.

**Autoantibodies:** Robust autoantibody markers can predict the development of type 1 diabetes; opportunities now exist to identify the role of autoantibodies in disease pathogenesis. This is an extremely important research avenue that could be addressed by epidemiology studies and the genetics consortium.

**HLA:** It is clear that certain HLA molecules are the major genetic component of type 1 diabetes susceptibility. Opportunities exist to build on this knowledge to determine why these specific molecules are so crucial to the development of disease.

**Synten mapping:** A powerful approach to finding disease susceptibility genes in humans is synten mapping. This technique compares related DNA sequences in the genomes of different species, such as human, mouse, and rat, to find genes implicated in disease. Indeed, a recent advance was made by using this approach to find a gene that causes lymphopenia in the BB rat. This gene is from a novel family of immune-associated nucleotide binding genes and represents the first description of a non-HLA or non-MHC gene involved in disease pathogenesis in an animal model of type 1 diabetes.

---

**The advisory panel identified several opportunities to leverage and optimize the research resources of the new genetics groups made possible with the special funding program for type 1 diabetes research:**

**Database cross-talk:** Many of the consortia will be developing databases for storage of and access to genetic data. The panel underscored that these databases need to be compatible with each other and to those associated with related projects such as the Beta Cell Biology Consortium (*see Goal III*) and the Type 1 Diabetes Genetics Consortium. The importance of developing bioinformatics initiatives was emphasized. The Bioinformatics Integration Support Contract (BISC) program, which is partially supported by the special funds, was recognized as one means to address this issue; although, BISC is not primarily focused on genomics.

**Resource sharing:** Critical issues that arise through the establishment of multiple research consortia include the need to build commonality in the structure of repositories, the use of common informed consent materials that will facilitate the transfer of data and resources between research groups, and mutual standards for the collection and preservation of samples.

**Industry collaboration:** Collaboration should be encouraged with the private sector to expedite scientific discovery and translation in the field of type 1 diabetes genetics. The panel underscored the importance of enhancing small business grants as a means of fostering increased type 1 diabetes research in the biotechnology industry. It was noted that private industry partners are welcome to participate in the current research consortia, under the appropriate rules of common access to all data developed by the consortia.

## **Epidemiology of Type 1 Diabetes**

Dr. Judith Fradkin presented two initiatives that are under development to study environmental causes of type 1 diabetes. The TrialNet epidemiology study will prospectively study relatives of type 1 diabetes patients screened for eligibility for the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) or for future prevention studies through TrialNet. The Triggers and Environmental Determinants of Diabetes in Youth (TEDDY) consortium will identify newborns at high genetic risk and follow those children for the development of type 1 diabetes. The ongoing collection of samples from these high-risk children over time will assist in the search for environmental triggers of this disease.

The advisory panel strongly supported the planned use of a consortium structure to promote data sharing and assist investigators in powering their large-scale epidemiological studies.

**Several opportunities for further research on the environmental causes of type 1 diabetes were identified, some of which stem directly from recent scientific advances made possible with the special funding program.**

**Identification of risk:** A remarkable finding from initial studies of HLA-typed relatives of patients with type 1 diabetes followed from birth is that a subgroup with a genetic risk of 50 percent of activating autoimmunity can be identified at birth. Importantly, from the parenteral insulin arm of DPT-1, researchers now know they can identify autoimmune individuals with a 50 percent risk of developing type 1 diabetes within 5 years. These findings and other data on the quantitation of risk for diabetes provide an unprecedented opportunity to look for environmental factors that trigger initiation and progression of disease in the highest risk group from birth.

**Infectious agents:** Some patients are known to be infected with Coxsackie virus at the time of type 1 diabetes clinical onset, yet a cause-effect relationship has not been established. An opportunity exists to look at Coxsackie virus and other infectious agents, which might trigger an autoimmune reaction in susceptible individuals, using state-of-the-science PCR-based RNA and DNA analyses.

**Biology of HLA proteins:** Type 1 diabetes research has contributed greatly to the understanding of HLA protein function and antigen presentation. This knowledge base provides an outstanding opportunity to use the type 1 diabetes model as a platform for understanding the human immune system and to develop novel drugs to treat the underlying cause of type 1 diabetes.

**Pregnancy and type 1 diabetes:** The offspring of diabetic mothers have approximately one-half the risk of developing diabetes as the offspring of diabetic fathers. This disparity might, in part, be related to the environment of pregnancy. This observation provides an opportunity to identify environmental factors during gestation that modulate future susceptibility and might yield new approaches to mitigate risk in offspring of people with type 1 diabetes.

**The advisors saw a critical opportunity for additional resources that would help to define the full scope of the type 1 diabetes problem in the U.S.**

**Screening for insulinitis:** Very little is known about the state of the human pancreas prior to or at the onset of diabetes. An opportunity to gain new knowledge can be seized through the establishment of a mechanism by which pancreata could be collected from young individuals who die for unknown reasons, or from patients who die shortly after onset of type 1 diabetes. Screening such tissues for insulinitis would enable molecular studies of the human pancreas at disease onset, research on infectious agents that might be related to disease pathogenesis, or cloning of T cells that might be involved in the autoimmune response. Such a bank of human tissue would be an extremely important resource, which would provide researchers with enormous opportunities for investigating how type 1 diabetes in humans differs from the disease in animal models.

- ▶ **Screening of organ donors:** A related opportunity exists to screen organ donors for autoantibodies of relevance to type 1 diabetes. This screening would help to identify individuals with likely insulinitis whose pancreata could be harvested for study.
- ▶ **Islet morphology:** The islet cell resource centers (*see Goal III*) could receive support to examine a small portion of islets from each pancreas handled. Such a project could lead to valuable information on the normal spectrum of islet morphology across a heterogeneous donor population and uncover new opportunities for research progress. Laser capture microdissection and nanotechnologies would provide novel interdisciplinary approaches to analyze small islet samples.

**Public health reporting:** Type 1 diabetes in children could be made a reportable disease throughout the country, as it now is in Oregon. Together with SEARCH, a CDC-led population-based registry for type 1 diabetes in children that is supported in part by the special funding program, such a public health effort could shed light on the magnitude of the type 1 diabetes epidemic and reveal clues about the disease that would open up additional research opportunities.

### **Animal Models for the Study of the Genetics and the Immune Mechanisms of Type 1 Diabetes**

Dr. Kristin Abraham, NIDDK Cell Signaling Program Director, described the Type 1 Diabetes Mouse Repository. This repository, located at the Jackson Laboratory, will acquire, preserve, and disseminate 150 mouse strains that are used for type 1 diabetes research. In addition to providing a centralized location for breeding and distribution of important mouse strains, this repository will promote genetic quality control and uniform health status of the animals, as well as ensure strain survival.

The advisors recognized the importance of the animal repository initiative established with the special funding program. They supported the continued expansion of available models to include non-NOD mouse backgrounds, such as C57BL/6 or BALB/c. Other relevant strains that might be considered include molecular mouse models, which have beta cells that express viral antigens, or “humanized” mice that carry human HLA genes.

### **Opportunities for future research that could be facilitated by the repository include:**

**Environmental causes:** Inbred mouse strains will be very useful for studying the genetic control of response to pathogens that may be involved in triggering diabetes.

**Drug testing:** The available mouse models of type 1 diabetes, along with the BB rat, present an opportunity to be used as preclinical testing platforms for new drugs that might eventually lead to phase 1/phase 2 clinical trials in humans.

## GOAL II Prevent or Reverse Type 1 Diabetes

MODERATOR: George Eisenbarth, MD, PhD

Dr. Catherine Cowie, NIDDK Type 1 Diabetes Clinical Trials Program Director, reported on TrialNet, a national network of clinical sites whose major goal is to perform intervention studies to preserve beta cell function in new-onset diabetics and, ultimately, prevent type 1 diabetes in at-risk individuals. The network will also support clinical studies on the natural history and genetics of type 1 diabetes to better understand the immunopathogenesis of this disease. In the short term, TrialNet is completing the ongoing oral insulin arm of the DPT-1. Trials of new potential agents for immunoprevention, immunosuppression, or combinations of therapies are under consideration by the TrialNet steering committee. TrialNet is one of the major new initiatives made possible by the special funding program for type 1 diabetes research.

Dr. Daniel Rotrosen, Director of the National Institute of Allergy and Infectious Diseases (NIAID) Division of Allergy, Immunology, and Transplantation, described two complementary initiatives, the Immune Tolerance Network (ITN) and the Autoimmune Disease Prevention Centers—key initiatives that have received substantial support from the special funding program. The ITN focuses on autoimmune diseases, transplantation, and allergy. Research on type 1 diabetes accounts for about one-third of the autoimmune disease proposals. An extensive network of core facilities is being developed by the ITN to provide support for genomic analysis, tetramer assays, research and development support services, and reagent production. Importantly, the ITN core facilities will be made available to TrialNet investigators to maximize the utility of these resources. The Prevention Centers were launched at the end of 2001 with support from the special type 1 diabetes research funds. Researchers at these Centers will investigate immune-based approaches to all autoimmune diseases, with a significant focus on type 1 diabetes.

The advisory panel agreed that the results of the parenteral insulin arm of the DPT-1 represented a significant advance by validating the biomarkers that were used to predict

individual risk of type 1 diabetes. Though the trial showed that injecting insulin in high-risk patients was not an effective prevention strategy, the study provided information that will be invaluable to the design of future research through TrialNet. Moreover, the panel was optimistic about the potential for successful immunoprevention of type 1 diabetes, including the ongoing oral insulin trial that has been subsumed within TrialNet and other agents to be studied through the newly created networks.

**The creation of large-scale consortia to study the prevention and treatment of type 1 diabetes—from basic studies through clinical trials—highlights the need and opportunity for further research in several areas identified by the scientific advisory panel.**

**T cells:** Assays to identify and quantitate disease-associated T cells in both animal models and humans are critical to the design of future prevention trials. Major efforts to speed up research on T cell assays could be productively pursued through the ITN core facilities.

**Animal models:** Humanized animal models could be used to study the trafficking of human T cells to the islet and the recognition of islet antigens. Rodent model systems could lead to the development of more specifically targeted therapies for prevention trials. Such systems are being approached through the Autoimmune Disease Prevention Centers. Additional, complementary efforts to develop a non-human primate model of autoimmune beta cell destruction would greatly facilitate the testing of potential treatments.

**C-peptide:** Clinical trials of type 1 diabetes prevention and immunological treatment approaches have been hampered to date by lack of a beta cell function test accepted as a clinical endpoint sufficient for drug approval. Measurement of C-peptide may provide a suitable endpoint. A joint NIH-CDC project to standardize C-peptide assays is being supported by the special type 1 diabetes funding

program. This project was regarded by the advisors as an extremely important and positive use of the special funds and an example of the type of standardization efforts that should be pursued in other areas of diabetes research for the attainment of more rapid clinical progress.

**The panel identified multiple infrastructure opportunities that would capitalize on resources of the already-established consortia and further expand the capacity of the research community to translate findings from academic laboratories into potential human therapies.**

**Drug development resources:** The advisors emphasized the benefits that could be derived from a trans-NIH mechanism that would facilitate the ability of investigators to efficiently move compounds with high potential for use in human studies through the requisite studies for efficacy and safety in preclinical in vitro and animal models.

- ▶ **Efficacy studies:** The panel envisioned a diabetes research center that could house relevant mouse and rat models of type 1 diabetes and accrue the expertise to apply these models to preclinical efficacy testing. Academic investigators could send potential therapeutic compounds to such a center for blinded animal trials before proceeding to human trials through the TrialNet and/or ITN. A center of this type would produce significant cost-savings and would be a very important resource for ongoing and future clinical trial initiatives.
- ▶ **Safety studies:** Acquisition of the safety and toxicity data that is required by the FDA for compounds that may be used in human trials may be needed for studies to be conducted through the TrialNet and the ITN. Such studies do not require animal models of diseases, but must be performed in GLP (good laboratory practice)-approved labs. NIAID has a contract resource for this purpose and TrialNet may subcontract for these services through its coordinating center.

- ▶ The National Cancer Institute (NCI) has mounted a significant effort in this area through the RAID program (Rapid Access to Intervention Development). RAID gives investigators access to contracted drug development resources, such as GMP (good manufacturing practice) synthesized material, formulation research, pharmacological methods, or toxicology studies, for the preclinical development of drugs and biologics. The advisors recommended that the NIH look at this model program as one that might prove useful in diabetes-related clinical research.

- ▶ **Biostatistics:** Many investigators could benefit from biostatistical support services for the statistical design and analysis of studies on drug development and clinical trials.

**Centralized IRB:** The creation of a centralized Institutional Review Board (IRB) for diabetes studies, along the lines of an initiative being piloted by the NCI, would provide considerable assistance to TrialNet, ITN, and similar clinical trial consortia. Such a mechanism could reduce the enormous amount of duplicative work that is currently required for large-scale, national trials. For example, the protocols of the DPT-1 and TrialNet involved consideration by 160 IRBs. At the same time, a centralized IRB would not require local institutions to abdicate all responsibility for trial oversight.

**Consortia interactions:** The panel reinforced the benefits of developing and maintaining close interactions among the various research consortia to maximize their complementary expertise. For example, appropriate consultation between the ITN and TrialNet should occur when selecting potential interventional agents for further study. Mechanisms are ongoing for joint review and development of trial protocols by these groups. In addition, each consortium will partner with the Non-Human Primate Cooperative Study Group, which receives partial support from the special funding program, when proposed trials require additional data from animal studies.

## GOAL III Develop Cell Replacement Therapy

MODERATOR: Bernhard Hering, MD

Dr. Sheryl Sato, NIDDK Program Director for the Cellular Basis of Metabolic Diseases, provided an overview of NIH's work to foster collaboration among investigators who study pancreatic beta cell biology. The recently established Beta Cell Biology Consortium (BCBC) is an international collaboration of more than 30 laboratories in the U.S. and Europe. The Consortium facilitates interdisciplinary approaches to the study of pancreatic islet development and function. A related initiative, the Comprehensive Programs in Beta Cell Biology, is being established to promote collaborative research to understand signaling pathways in the beta cell and among all cell types of the pancreatic islet. This program supports cooperation between beta cell or diabetes researchers and investigators in other fields who can bring needed expertise to the study of the beta cell.

Dr. Thomas Eggerman, NIDDK Islet Transplantation Program Director, reported on initiatives that address clinical islet transplantation research. Infrastructure critical to the support of clinical trials in islet transplantation has been developed through the Islet Cell Resource Centers, which isolate cadaveric islets for transplantation and research purposes, and the Islet/Beta Cell Transplant Registry, which plans to track progress and promote safety in all islet/beta cell transplants performed in the U.S. or Canada. The ITN supports a multi-site study to replicate the Edmonton protocol of islet transplantation. An islet transplantation protocol is also ongoing at the NIH. The Non-Human Primate Immune Tolerance Cooperative Study Group and the ITN will investigate new immunosuppressive regimens in animal models and humans, respectively. Finally, investigator-initiated projects are being solicited to develop gene therapy approaches for enhancing islet viability and function after transplantation.

The advisors supported the NIH's efforts to implement collaborative, "big science" programs in beta cell biology. They emphasized the dramatic advances in this field that have been made possible by the infusion of the special funds for type 1 diabetes research and support from the NIH. The panel observed that the substantial infrastructure established in recent years by the NIH and the JDRF has positioned the field to capitalize on new developments in basic research, especially from cell biology and immunobiology. The pancreatic beta cells and their biology need to be fully explored to understand the targeted immune response in type 1 diabetes that destroys the beta cells yet leaves neighboring endocrine cells intact. They stressed the importance of sustaining momentum and support in this area, so that this infrastructure can be maintained and so that real gains can be made in reversing type 1 diabetes in patients.

A major breakthrough in the treatment of type 1 diabetes has been the "Edmonton protocol" of islet transplantation. This procedure has permitted patients with poorly controlled diabetes to achieve insulin independence. Despite encouraging early results from this experimental technique, the paucity of available donor organs to secure islets for transplantation severely limits the number of patients who can be treated. The advisors advocated continued investment in basic beta cell biology research to support the development of surrogate beta cells and research to optimize transplantation techniques.

---

**The panel identified many opportunities to advance islet transplantation research:**

**Benefits and outcomes:** As clinical trials are beginning to deliver positive results, it is vital to clearly document the risks and benefits of islet transplantation and to perform meaningful outcomes research. Areas of study should include issues of secondary complications, quality-of-life following transplantation, and cost-effectiveness. Such information will be necessary for acceptance of this procedure by physicians and patients and for eventual approval by the FDA and third party payers.

**Pancreas availability:** At current levels of organ donation and islet isolation efficiency, approximately 250 transplant procedures could be performed each year in the U.S. This number is inadequate to address the needs of the estimated one million persons with type 1 diabetes in the U.S. who might benefit from this procedure if additional research demonstrates long-term safety and efficacy. Research should address ways to increase the number of suitable donors. Research is also needed to improve islet transplantation to the point that it is safe, cost-effective, and reimbursable by insurance companies. Increased transplantation efficacy could also positively affect pancreas allocation policies so that more organs can be made available for islet transplantation purposes.

**Islet isolation:** An investment in understanding the cell biology of stressed or injured cells could help to optimize islet isolation techniques and, thereby, extend the number of suitable donor organs and/or the number of people who could benefit from each organ.

**Islet vascularization:** Research should be intensified to discover ways to improve the vascularization of grafted islets as a route to increasing transplantation efficacy. Insights from the field of angiogenesis research could be applied to this issue.

**Islet delivery:** Intrahepatic portal vein injection, which is the preferred route for islet transplantation under the Edmonton protocol, carries a significant risk of portal vein thrombosis. More extensive research into islet delivery techniques and sites was endorsed by the advisors.

**Immune tolerance:** A significant drawback to islet transplantation in type 1 diabetes patients is the need for lifelong immunosuppression to prevent both rejection of the transplant by the recipient's immune system and autoimmune attack on the donor islets. Additional research on therapies that would induce immune tolerance after transplantation is crucial to the long-term success of islet transplantation in the patient population.

**Loss of insulin independence:** For reasons that are not well understood, some islet transplantation patients begin to lose insulin independence over time. Performing transplant protocols on diabetic patients without underlying autoimmune disease would provide an opportunity to study the mechanisms of reduced insulin independence. Efforts to extend this line of research in non-human primates, as are under way in the NIDDK intramural program, are also critical to addressing this problem.

**Stem and progenitor cells:** The panel members were encouraged by significant progress in the production of functional islet cells from both adult and embryonic stem cells and they emphasized continued investment in cellular therapy as a high priority. This line of research could overcome the limitations of cadaveric islet transplantation by increasing the supply of transplantable beta cells. Support was advocated for preclinical testing of stem cells and stem cell stimulators in diabetic animal models. Discussion also focused on further research on the immune components of stem cells as they differentiate as a means to determine whether stem cell-derived replacement beta cells can resist autoimmunity.



**Beta cell antigens:** Discovery of novel beta cell antigens that might be involved in initiating the disease process was identified as an important research avenue deserving of further pursuit. Pilot projects on this topic are under way within the auspices of the BCBC, but stepped-up efforts could foster beneficial interdisciplinary communication between cell biologists and immunologists.

**Proteomics:** Proteomic approaches could be developed to measure beta cell specific proteins in plasma. Such research could provide a means of monitoring insulinitis and lead to better understanding of the mechanisms of autoimmunity recurrence after islet transplantation.

**Maximizing the impact of research infrastructure and ensuring access to the resources made possible by the special funding program were identified as high priorities by the advisory panel.**

**Consortia interactions:** The panel was impressed with the breadth of cooperative programs and resource development that has been made possible through the special funding program. However, the group reiterated the need to strengthen mechanisms for cross-talk and data sharing among the various research consortia and networks, as well as with the general research community.

▣ **International cooperation:** The intellectual capital of the research consortia or other groups could be maximized by including more international components. For example, the islet transplantation registry, which currently monitors procedures performed only in the U.S. or Canada, could benefit from expanding its data collection to include NIH- or JDRF-funded transplantation procedures in additional countries.

**Coordination of transplantation trials:** The islet transplantation field would benefit enormously from the development of a “cell replacement trial network” analogous to the clinical consortia that have been instrumental in pursuing other goals. The proposed network could help to coordinate research in this field by prioritizing clinical trials in cell replacement therapies, expediting evaluation of promising new technologies, developing standard procedures for immune and metabolic monitoring and for outcomes research, and providing biostatistical support.

▣ **Industry collaboration:** Collaboration between academic partners and cell-based biotechnology companies for the development of stem cell-derived therapies could be fostered through small business grants.

**Coordination of immunologic monitoring:** Unlike islet transplantation trials supported by the ITN, a significant number of trials performed outside the network structure do not have a coordinated mechanism for immunologic monitoring of patients after transplantation. An opportunity exists to maximize existing funding by ensuring that all investigators have access to established core facilities.

## GOAL IV Prevent or Reduce Hypoglycemia in Type 1 Diabetes

MODERATOR: Robert S. Sherwin, MD

Dr. Barbara Linder, NIDDK Clinical Endocrinology and Diabetes Complications Program Director, discussed three initiatives that support investigator-driven research on the problem of episodes of dangerously low blood sugar—hypoglycemia—in patients with type 1 diabetes. These programs, which are co-sponsored by the NIH and JDRF, solicited grant applications for research on hypoglycemia unawareness, clinical approaches to prevention of hypoglycemia, and the effects of hypoglycemia on the central nervous system. A fourth NIH initiative supports studies on glucose sensor development and validation.

Dr. Karen Winer, Medical Officer at the National Institute of Child Health and Human Development (NICHD) Endocrinology, Nutrition, and Growth Branch, presented information on DirecNet, a newly-established clinical trial network to test glucose sensors in children. The network will validate the accuracy of available glucose monitors, characterize the frequency and severity of hypo- and hyperglycemia in children, examine whether repeated use of a monitoring system improves diabetes control, and determine glucose levels in non-diabetic children.

The advisory panel was pleased with the NIH's responsiveness to a meeting held in 2000 that identified a need for scientific investigation at the interface of neuroscience and diabetes. Such research is critical to understanding hypoglycemia and its impact on diabetic patient care. The panel applauded NIH for stimulating basic neuroscience research related to hypoglycemia as well as for initiating trials to develop and validate glucose sensors as a way of detecting and preventing hypoglycemia.

**The advisors identified several opportunities for future research on hypoglycemia that could expand upon the current portfolio.**

**Neuronal cell lines:** The development of neuronal cell lines that can be used for biochemical or molecular biology studies of glucose sensing mechanisms could be fostered.

**Transporters:** Increased efforts are warranted to study transporters, including glucose and monocarboxylic acid transporters, that might play significant roles in hypoglycemia.

**Sleep and hypoglycemia:** Half the episodes of severe hypoglycemia in the Diabetes Control and Complications Trial (DCCT) occurred during sleep. Nocturnal hypoglycemia presents significant risks to patients. Greater efforts are needed to investigate how sleep promotes hypoglycemia and to understand the molecular mechanisms involved in this phenomenon.

**Long-term consequences of treatment:** The long-term consequences of current treatments for diabetes, in terms of their impact on neurological functions, could be studied through animal models or with continuing clinical research over an extended period of time. In particular, the effect of recurrent hypoglycemia in very young children should be studied. Advanced imaging technology, such as MRI spectroscopy and brain volume measurement, could be applied to identify brain changes that occur in patients who experience severe hypoglycemia over extended periods of time.

**Brain sensors:** The adverse consequences of hypoglycemia are mediated via alterations in brain neurochemistry. Sensors that measure neurotransmitters and substrates in the brain are being developed; this research should be fostered and applied to diabetes.

**Brain glucose metabolism:** There is evidence that recurrent hypoglycemia in diabetes alters the efficiency of brain glucose (fuel) metabolism so that cognitive function may be better preserved when glucose levels fall. This might contribute to “hypoglycemia unawareness.” Efforts are needed to study the effect of diabetes, and particularly iatrogenic hypoglycemia, on the metabolism of glucose by the brain (or specific brain regions) in the resting state and during activation.

**Counter-regulation:** The mechanism underlying the occurrence of hypoglycemia unawareness and defective counter-regulation after recurrent episodes of hypoglycemia is poorly understood, but it is clearly reversible by treatment of diabetes that does not produce hypoglycemia. Uncovering the mechanism of this phenomenon of reversal of defective counter-regulation could foster the development of pharmaceutical agents that produce the same effect.

**Effect of transplantation:** Hypoglycemia is eliminated after islet transplantation and this reversal provides an opportunity to understand mechanisms involved in hypoglycemia unawareness and defective counter-regulation and to develop strategies by which hypoglycemia can be ameliorated.

**Glucose sensing technology:** The panel commended the NIH for its support of research validating the utility of glucose sensing devices that have received FDA approval. Continued efforts were strongly urged towards development of a closed-loop artificial pancreas system.

▣ **Interstitial glucose sampling:** The relationship between interstitial glucose levels and glucose concentrations in the blood or brain should be further investigated. Factors that may alter accuracy of devices that measure interstitial glucose, such as changes in oxygen concentration at night, should be evaluated.

▣ **Sensor development for animals:** A need was identified for non-invasive glucose sensing or metabolic screening technology that can be used with research animals.

▣ **Behavioral research:** Studies of glucose sensors could be extended to encompass behavioral research, particularly with respect to the effect of this technology on quality-of-life issues.

**Cross-disciplinary approaches:** Exploring questions such as how the brain senses glucose, how it activates counter-regulation, and how counter-regulation is suppressed during treatment will require NIH to find ways to encourage collaboration between neuroscientists and diabetologists. In addition, because similar mechanisms for sensing and responding to glucose may exist in brain and beta cells, collaboration is needed between neuroscientists and beta cell biologists. To this end, a consortium, similar to that for beta cell biology (*see Goal III*), could be established to bring together investigators from multiple disciplines and foster new approaches to the problem of hypoglycemia. In addition, the use of existing partnership initiatives, such as those supported by the special funding program (*see Goal VI*), should be fully exploited for the purpose of recruiting neuroscientists to diabetes research.

▣ **Other glucose-sensitive tissues:** Glucose sensing is also being studied in tissues other than the brain and pancreatic beta cell. Indeed, the hypothesis that glucose sensing in response to both hyper- and hypoglycemia can be mediated by malonyl CoA and AMP-activated protein kinase has in great measure been derived from research in skeletal muscle. It is possible that glucose-sensing mechanisms may be similar in all tissues with glucokinase (e.g., beta cells, liver, some brain cells) or insulin-sensitive glucose transport (e.g., muscle, adipose tissue, some brain cells). Collaborative interactions between researchers studying a range of glucose-sensitive cells should be encouraged.

## GOAL V Prevent or Reduce the Complications of Type 1 Diabetes

MODERATOR: Neil B. Ruderman, MD, DPhil and Ann Marie Schmidt, MD

Dr. Robert Star, Senior Scientific Advisor of the NIDDK Division of Kidney, Urologic, and Hematologic Diseases, reported on the recent establishment of an Animal Models of Diabetic Complications Consortium (AMDCC). The consortium plans a coordinated effort to develop and validate animal models that closely mimic human complications of diabetes. These animal models will be used to study the genetic causes and underlying mechanisms of diabetic complications. These models will also spur the development of translational products such as diagnostic, imaging, prevention, and treatment strategies. Importantly, the consortium will share all protocols, research tools, and animal models with the larger research community.

Dr. Patricia Mueller, Chief of the CDC Diabetes and Molecular Risk Assessment Laboratory, updated the panel on progress in the Genetics of Kidneys in Diabetes Study (GoKinD) that investigates genetic risk factors for diabetic kidney disease. GoKinD is part of an international effort to assemble a collection of biological samples that will enable research on genetic susceptibility to both type 1 diabetes and kidney disease complications.

Dr. Peter Dudley, Director, Retinal Diseases Program at NEI, discussed the formation of a clinical trial network for diabetic macular edema. The network will plan, implement, and conduct human clinical trials and clinical research on the problem of diabetic macular edema.

The advisory panel identified the Diabetes Control and Complications Trial (DCCT), which showed that close glycemic control can ameliorate microvascular complications in type 1 diabetes, as a tremendous advance in the clinical management of this disease. Nonetheless, the panel also recognized that complications account for the vast majority of diabetes-associated medical costs.

**Research on diabetic complications spans a complex and diverse array of investigators and the panel members proposed many ways to focus the field on common goals and to maximize the research resources available to the community.**

**Research opportunities:** Several opportunities were identified for future research that could build on and extend past successes.

- ▶ **Cardiovascular risk:** Individuals with type 1 diabetes experience an increased risk of cardiovascular complications. However, few mechanistic or outcome studies on this significant health problem are available. An opportunity exists to promote research on cardiovascular risk and outcomes in the type 1 diabetes population.
- ▶ **Inflammation:** An emerging area of research interest is the study of inflammation as a contributing pathway to macrovascular disease. In particular, monocytes are readily accessible for study and could be very useful in assessing the effects of interventions that affect inflammatory pathways in relation to complications. Endothelial-monocyte interactions may be important for microvascular as well as macrovascular disease.

- ▶ **Collaboration:** Bringing together endothelial cell biologists, immunologists, and investigators interested in inflammation is a high priority for collaborative research in the complications field.
- ▶ **Surrogate markers:** The panel emphasized the need for development of surrogate markers for diabetes complications. The endothelial cell might provide a common focus for the field, but more work is needed to validate particular aspects of the biology of this cell as an appropriate surrogate marker for multiple complications.
- ▶ **Drug therapy:** Studies of patients with type 2 diabetes have shown that drugs such as aspirin and statins diminish the incidence of coronary artery disease. Such research could be extended to study the potential benefits of these therapies in individuals with type 1 diabetes. Studies of the role of insulin sensitizers in preventing cardiovascular disease in type 2 diabetes are now under way and these agents could also be considered for type 1 diabetes.
- ▶ **Translational research:** Efforts could be fostered to move the most successful advances from basic research into clinical trials. An initiative similar the NCI RAID program (*see Goal II*) would provide a very focused mechanism to help investigators develop potential clinical applications of their research.
- ▶ **Collaboration:** Investigators who normally study a single type of diabetic complication could be encouraged to collaborate on assessing the impact of new therapeutic agents or targets on multiple tissues or organs to maximize the impact of new treatments.

- ▶ **Advanced technology:** The complications field could benefit tremendously from the development of microarrays or chips that are targeted to both human and rodent genes relevant to the various complications. Facilitating the availability and use of microarrays and other advanced methodologies could help identify similarities between tissues and organs involved in diabetes complications.

**Animal model resources:** The panel was very enthusiastic about the availability and sharing of animal models that will be a key feature of the AMDCC. The group identified several opportunities for leveraging the infrastructure created by the consortium and for optimizing the use of animal models in the study of complications affecting multiple organs.

- ▶ **Retinopathy:** The development of mouse models of retinopathy was identified as an important goal for the AMDCC to pursue. Also, in studies of other complications using rodent models, eyes should be harvested for use by interested investigators to get the most out of these models.
- ▶ **Models of long-term diabetes:** The panel members, many of whom serve on NIH study sections, noted a recurring problem with grant applications of investigators from different disciplines who propose to study diabetes complications in animals that have been made diabetic for very short periods of time. The research community could benefit greatly from a resource structure that could induce diabetes in animals (e.g., the streptozotocin rat model), maintain those animals with insulin for several months, and distribute such long-term models of diabetic complications to investigators.

▶ **Large animal models:** Researchers would benefit from the development of large animal models of long-term diabetic complications that could serve as pre-clinical models for testing new therapeutic agents.

▶ **Tissue sharing:** Investigators who develop animal models of diabetes often study only one organ system or complication. Mechanisms to facilitate sharing of available cells or tissues among investigators could maximize resource utilization and propel research forward.

▶ **Rat models:** The BB diabetic rat is a useful research model because the physiology of a rat is often more accessible than that of a mouse; however, the BB rat does not develop any complications other than neuropathy. An opportunity exists, through congenic technology, to develop novel lines that combine diabetic susceptibility with genetically determined complications seen in other rat models.

**Collaborative interactions:** The field of diabetic complications research is very diverse, yet has many potential commonalities. The panel was concerned with the lack of cohesion among investigators in the field and, thus, encouraged the development of mechanisms to facilitate productive interactions.

▶ **Consortium:** The field could benefit significantly from the establishment of a research consortium similar to the BCBC (*see Goal III*). A complications consortium, which would complement, not replace, the AMDCC, would serve to unify the field and expedite the sharing of expertise and knowledge among investigators who tend to focus on a single complication.

▶ **Information resource:** Because diabetic complications affect so many organ systems, initiatives in this field are sponsored by several NIH institutes and centers. Extramural investigators would benefit from a central knowledge base that would provide information on complications-related initiatives that are currently available across the NIH.

▶ **Priority setting:** An organized forum would be beneficial for bringing together investigators with diverse expertise in complications for discussions of key research issues. Such a forum could address high priorities for future research, scientific areas that need development, availability of resources, and other topics that could help to focus the field on common approaches and metabolic themes.

▶ **Interdisciplinary research:** An example of the type of interactions needed is collaboration among transplant surgeons, immunologists, and vascular disease specialists to evaluate the effect of immunomodulatory agents on vascular complications. As established agents are more widely used in islet transplant protocols or new agents are developed, it will be important to study the effects of these immunomodulators on the progression of diabetic complications.

## GOAL VI Attract New Talent to Research on Type 1 Diabetes

MODERATOR: Margaret Grey, DrPH, FAAN

Dr. James Hyde, Training Grant Program Director of the NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases, spoke about three initiatives designed to attract new scientific talent to research on type 1 diabetes. Bench-to-bedside and innovative partnerships will promote, respectively, collaborative research between basic and clinical scientists, and between diabetes researchers and scientific experts from other fields who have not previously studied diabetes or its complications. Pediatric endocrinologists will be encouraged to pursue career paths in type 1 diabetes research through a program that combines research training and research career development awards.

The efforts to recruit new investigators to type 1 diabetes research were considered by the advisory panel to be among the most important initiatives undertaken through the special funding program. The panel was greatly impressed by the number of applications received in response to these RFAs. Moreover, the panel supported the use of the R21 (pilot and feasibility) mechanism in the short term as a way to generate new ideas in diabetes research. In addition, the NIH was commended for its development and support of the pediatric endocrinology research training and career development program, which was deemed a creative means of bolstering entry into this under-represented, but vital, clinical specialty.

**Though they were pleased with the overall program, the advisors raised several issues regarding the scope and long-term support for the partnership and training initiatives.**

**Long-term partnership initiatives:** To ensure the ongoing recruitment of new scientific talent, consideration should be given to developing ways to sustain the type 1 diabetes research training opportunities beyond the life span of an RFA initiative that has a single receipt date.

**Research solicitation mechanisms:** Because the RFA mechanism is generally limited to one receipt date, many investigators may not have sufficient time to obtain preliminary data and position themselves to take advantage of the funding opportunity. Strengthening and expanding use of the Program Announcement (PA) mechanism may alleviate this issue. In addition, many of the newly-formed consortia provide opportunities for expanded funding through support of pilot and feasibility projects or through accrual of additional research or satellite centers. The careful consideration of research solicitation mechanisms is an issue that applies equally to all goals of the funding program.

---

**Investigator-initiated research:** Though RFAs are an important means of focusing research efforts on a specific topic, the panel urged continued commitment to traditional investigator-initiated R01 grants for diabetes research that might not fit neatly into an RFA category, and to R01 applications for research that follows up on successful R21 projects. It was noted that several RFAs within the special type 1 diabetes program—such as the partnership and training solicitations—support research on type 1 diabetes and its complications that is not limited to a specific topic. These RFAs allow investigators to identify promising projects from a breadth of research areas.

**Research talent needs:** Attention should be given to ensuring that these initiatives promote the most productive type of partnerships and attract new investigators who can fill gaps in the diabetes research field. High priority specialties for recruitment include research on neuroscience, inflammation, behavior and quality-of-life issues, imaging technology and its application to metabolism, and associated autoimmune diseases such as celiac disease, Graves' disease, hypothyroidism, and Addison's disease. Partnerships with AHRQ could be developed to perform health services and outcomes research on clinical innovations in type 1 diabetes treatment.

**Basic research talent:** Programs to attract basic science graduate students and postdoctoral fellows to type 1 diabetes research would complement the initiative for clinical researchers. Loan alleviation programs and targeted training grants could be considered as additional means of attracting new talent to research on type 1 diabetes.