Meeting Summary and
Panel Recommendations

Special Statutory Funding Program for Type 1 Diabetes Research

Convened by the
National Institute of Diabetes and
Digestive and Kidney Diseases

For Administrative Use

January 18–19, 2005
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EXECUTIVE SUMMARY

An external panel of 16 scientific and lay experts with expertise relevant to type 1 diabetes and its complications convened at the Holiday Inn in Bethesda, Maryland, January 18–19, 2005, to discuss the *Special Statutory Funding Program for Type 1 Diabetes Research*. The goals of the two-day meeting were to perform a mid-course assessment of current efforts supported by the program, to identify new and emerging opportunities, and to solicit recommendations for future type 1 diabetes research. The meeting focused largely on the program's research consortia and networks. The meeting constitutes a major source of input for a congressionally-mandated program evaluation report, which is due to the Congress by January 2007.

Type 1 Diabetes Research Goals

The meeting was framed around six major research goals that offer exceptional promise for the treatment and prevention of type 1 diabetes:

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 and Apply New Technologies to Research on Type 1 Diabetes

Cross-Cutting Recommendations

The panel was charged with reviewing specific on-going projects supported by the program and making recommendations for future research opportunities. Throughout the meeting, many common themes emerged that cut across research efforts supported by the program.

The panel identified several cross-cutting opportunities to enhance and synergize type 1 diabetes research efforts:

Extend and capitalize on existing research efforts by maximizing connections among research groups with both related and distinct interests: The panel recommended that strong existing coordination across consortia be further enhanced to synergize research efforts. These interactions should not be limited to consortia with overlapping interests. Collaboration between researchers with distinct interests can facilitate the pursuit of novel research directions. Increased coordination can prevent duplicative work by promoting the sharing of resources and methodology as well as by facilitating cross-disciplinary research approaches.

Develop new modes of interaction to foster diabetes research: The panel encouraged interactions between biologists and chemists to identify small molecules that could be used as therapeutics for disease. The panel strongly endorsed the use of novel mechanisms such as innovative partnership awards to foster collaboration and interaction between diabetes researchers and researchers outside of the diabetes field, such as neuroscientists and bioengineers. These types of partnerships can accelerate research progress by fostering the application of novel technologies and expertise to the type 1 diabetes research field.

Enhance opportunities for data sharing and integrated analysis: The panel recommended that bioinformatics approaches to data creation and maintenance be coordinated and integrated across the multiple research consortia to enhance communication and data sharing/analysis.

Foster translational research to enhance the timely transfer of important advances in the laboratory to a clinical research setting: The panel endorsed on-going efforts and encouraged continued support of the Special Funding Program regarding translational research, such as through the Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program. The panel stressed the importance of promoting interaction between basic and clinical scientists to facilitate translational research. Additionally, the National Institutes of Health (NIH) commitment to research clinicians, particularly at the junior faculty level, was seen as critical for attracting and retaining research talent.

Capitalize on research investments with patient follow-up: The panel recognized the opportunity to maximize data collection in longitudinal studies, particularly those involving children and newly diagnosed cases of type 1 diabetes, by maintaining contact with the patients and their families to track their medical progression.

Promote partnerships with industry to advance research: The panel encouraged interactions between type 1 diabetes clinical trials consortia and industry to promote testing of potential

therapeutic agents. The panel favored utilizing the Small Business Innovation Research (SBIR) program to produce reagents that would facilitate basic science and the translation of laboratory discoveries to the clinic.

Maintain strong oversight mechanisms for ongoing efforts: The panel strongly endorsed the contributions of external advisory boards (EABs) that have been created to guide and monitor the progress of consortia and resources supported with the Special Funding Program. The panel encouraged the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to ensure that all consortia receive regular oversight from such panels.

Develop a strategic plan for future type 1 diabetes research: To build upon the new and emerging opportunities identified at the meeting, the panel strongly endorsed a broad state-of-the-science review and development of a long-range plan for type 1 diabetes research.

Major Research Opportunities

The expert panel recognized several critical areas of research opportunity that will accelerate research progress in type 1 diabetes.

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

- Identifying novel biomarkers and surrogate end points that would enhance the development of therapeutics and the conduct of type 1 diabetes clinical trials;
- Understanding the autoimmune basis of type 1 diabetes by enhancing research in the field of human type 1 diabetes and regulatory T cells;
- Exploring the role of the gastrointestinal mucosal barrier in the pathogenesis and possible prevention of type 1 diabetes;
- Creating a renewable source of human beta cells by developing approaches to expanding functional islets and to creating conditions to differentiate embryonic and adult stem cells to islet/beta cells;
- Defining normal glucose profiles in children;
- Improving animal models to study type 1 diabetes and its complications;
- Alleviating type 1 diabetes and its complications by understanding regenerative pathways;
- Promoting collaborative research by supporting multi-disciplinary "self-assembled" research consortia to tackle current barriers that limit progress in type 1 diabetes research;
- Providing support to investigators to pursue high-risk, high-payoff projects without requiring extensive preliminary data; and

- Supporting focused "innovative partnership" programs that facilitate collaborative interactions and attract new research talent.

Conclusions

The Special Funding Program has supported research that has greatly increased our understanding of type 1 diabetes. Because many of the programs are newly established, the future potential for directly impacting patients' health is extremely high. However, there is still much work to be done. It is critical to coordinate efforts of these consortia and networks to provide an integrated understanding of the disease. Continued support of basic research will help to provide insights on the molecular underpinnings of disease development as well as to identify novel therapeutic targets and agents. On-going investment in basic and clinical research will help investigators translate positive results from the laboratory to the clinic to improvements in patients' health. The projects supported by the program and the future research opportunities endorsed by the panel are critical to the understanding, prevention, and treatment of type 1 diabetes.

BACKGROUND

Special Funds for Type 1 Diabetes Research

Special funding for type 1 diabetes research, in the total amount of $1.14 billion for Fiscal Year (FY) 1998 through FY 2008 (Table 1), 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 (P.L.) 105-33. This funding was later extended and augmented by Section 931 of the 2001 Consolidated Appropriations Act, P.L. 106-554, and by the Public Health Service Act Amendment for Diabetes, P.L. 107-360. 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 other federal agencies represented on the Diabetes Mellitus Interagency Coordinating Committee (DMICC), such as the Agency for Healthcare Research and Quality (AHRQ) and 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

Table 1: Special Statutory Funds for Type 1 Diabetes Research–in Millions of Dollars

FY:	98	99	00	01	02	03	04	05	06	07	08	Total
P.L. 105-33	30	30	30	30	30	----	----	----	----	----	----	150
P.L. 106-554	----	----	----	70	70	100	----	----	----	----	----	240
P.L. 107-360	----	----	----	----	----	----	150	150	150	150	150	750
TOTAL:	30	30	30	100	100	100	150	150	150	150	150	1,140

process is scientific advice the NIH has garnered from a variety of scientific meetings, workshops, and conferences, including the following two key planning meetings:

- In April 2000, the NIDDK brought together a group of distinguished scientists from research institutions across the country to advise on the remaining funds provided by P.L. 105-33.
- In May 2002, the NIH convened an advisory panel composed of 15 scientific and lay experts on type 1 diabetes. The panel members were asked to identify the most innovative research ideas—both within and beyond the traditional diabetes field—that the NIH and CDC should emphasize as future efforts in type 1 diabetes are developed.

Distribution of Funds Over the Course of the Special Program

Most of the initial Special Funds (FY 1998–2000) supported investigator-initiated research projects. When the program was augmented in FY 2001, the additional funds allowed the creation of unique, innovative, and collaborative research consortia and clinical trials networks. The majority of the funds since 2001 have supported these collaborative research efforts, with a goal of promoting progress in type 1 diabetes research that could not be achieved by a single laboratory.

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 June 2000 interim report to the Congress, which is posted on the NIDDK website (http://www.niddk.nih.gov/federal/initiative.htm). An important interim assessment of the program by external scientific experts, grant recipients, and NIDDK staff who analyzed the associated scientific literature and other relevant data on the program was published in April 2003 and is available on the NIDDK website (http://www.niddk.nih.gov/federal/planning/type1_specialfund/). A final evaluation of research efforts supported by the Special Funding Program is due to the Congress by January 1, 2007.

In addition to external advice received throughout the program planning process, a major source of input for the final program evaluation will be that from an *ad hoc* planning and evaluation panel of 16 leading scientists and lay persons with expertise relevant to type 1 diabetes and its complications, which was convened by the NIDDK in January 2005. The focus of the meeting was on the research consortia and networks supported by the Special Funding Program. The panel was provided with details on the goals, milestones, accomplishments, and future directions of over 20

different projects supported by the program. The group was charged with performing a mid-course assessment of these projects and providing recommendations for future research opportunities. The panel was invited to comment both on on-going initiatives as well as on other areas of opportunity that should be pursued with the funds.

Solicitation of Innovative Ideas

Since the inception of the Special Funding Program, the NIH has solicited input and recommendations from scientists external to the NIH through forums such as scientific and planning/evaluation panel meetings. To solicit broader input for future research opportunities, the NIDDK issued a "Request for Information" (RFI) calling for innovative ideas to advance prevention, treatment, and cure of type 1 diabetes. The RFI was announced to the scientific community in the *NIH Guide for Grants and Contracts* (NOT-DK-04-013) and in the journal *Science*. The NIDDK's announcement made clear that ideas submitted would not be treated as confidential or proprietary and that there was no research funding associated with this process. Ideas were collected for seven weeks, and the NIDDK received more than 80 submissions. The submitted innovative ideas were presented to the panelists for their review and comment at the January 2005 meeting and were used as a springboard for discussion of emerging opportunities in type 1 diabetes research.

INTRODUCTION

Meeting Agenda

The planning and evaluation meeting convened January 18 and 19, 2005, was designed to serve as a free-flowing scientific exchange about the on-going initiatives supported by the program and the emerging opportunities in type 1 diabetes research that the NIH, CDC, and/or other components of HHS could productively pursue. The meeting began with welcoming remarks and a program overview from Dr. Judith Fradkin, Director of the NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases. Ms. Margery Perry, JDRF Chair of Research, and Dr. Scott Campbell, ADA National Vice President of Research, presented the perspectives of these voluntary organizations, each of which commits significant funds to research. The remainder of the meeting was devoted to sessions on each of the six major research goals. For each goal, two panelists were asked to be either primary or secondary discussants for each project or the discussion of the innovative ideas. Each primary discussant gave an overview summary of the project or the submitted innovative ideas based on background information that he or she received prior to the meeting. The discussant also provided feedback on the current status of the project and made recommendations for future opportunities. The secondary discussant followed with comments and recommendations. After opening remarks by the discussants, the entire panel was invited to make comments on the project or innovative ideas and to suggest methods to enhance research efforts supported by the program. From discussion of specific projects under each goal, cross-cutting themes emerged regarding current projects or other novel research directions that should be pursued—within or outside of on-going efforts—to help realize the research goal.

Overview of the *Special Statutory Funding Program for Type 1 Diabetes Research*

To ensure the most scientifically productive use of the Special Funds, the NIDDK has solicited the help and advice of scientific and lay experts, its collaborators in the NIH and HHS, and the diabetes voluntary community. 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 broad range of research areas relevant to type 1 diabetes. Investigator-initiated research that has been pursued with the Special Funds has sought to capitalize on new technology and emerging opportunities. In addition, the funds have supported high-risk, high-impact research, with a focus on promoting multi-disciplinary collaborations and recruitment of "new-to-diabetes" researchers.

When the Special Funding Program was extended and augmented in FY 2001, the additional funds enabled the creation of unique, innovative, and collaborative research consortia and clinical trials networks. The majority of the funds since 2001 have supported these collaborative research projects, with a goal of promoting progress in type 1 diabetes research that could not be achieved by a single laboratory.

To integrate and coordinate scientific themes that are common to all or most of the large research consortia, the NIDDK has established a Type 1 Diabetes Consortia Coordinating Committee. This Committee is charged with coordinating issues of recruitment and enrollment; standardizing assays, phenotyping, and patient consents; using clinical populations for development and validation of assays for immune and metabolic monitoring; and coordinating bioinformatics. This Committee assisted in the development of an NIDDK website with information for patients interested in participating in clinical research studies supported by the Special Funding Program (accessible at http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D_CTCR/studies.asp).

Through a broadly consultative planning process, the NIH seeks advice from experts external to the NIH on emerging opportunities in type 1 diabetes research. Program-wide planning and evaluation meetings were convened in April 2000 and May 2002 and many of the recommendations from these meetings have been implemented. The January 2005 meeting provided an opportunity for external experts to evaluate on-going activities supported by the program and to make recommendations for future type 1 diabetes research.

Perspective of the JDRF

An overview of the JDRF was provided by Ms. Margery Perry, JDRF Chair of Research. The JDRF is a volunteer organization led by individuals who either have type 1 diabetes or have children with the disease. The primary mission of the JDRF is to find a cure for type 1 diabetes and its complications through the support of research. The organization is pleased to be a part of the planning, implementation, and evaluation of the Special Funding Program. The JDRF partners with the NIH on many research projects sup-

ported through the program. For example, JDRF funds international sites that are part of NIH-supported clinical trials.

The JDRF was enthusiastic that the Special Funds have promoted bench-to-bedside translation and have enabled the establishment of clinical infrastructure. The Special Funds have made possible the creation of a new pathway of opportunity for basic research and preclinical studies to be translated to clinical studies. In addition, implementing a "consortium" approach to advance research progress has been an important success of the Special Funding Program. Consortia have united the research community to focus on common goals, and they have the potential to accelerate research programs by linking investigators from multiple institutions.

Because the Special Statutory Funding Program for Type 1 Diabetes Research represents only a portion of the type 1 diabetes research supported by the NIH, the JDRF recommends that the NIH initiate a much broader review of the entire state-of-the-science with respect to type 1 diabetes. This review would be critical to informing future planning and evaluation efforts of the Special Funding Program. In addition, the organization believes that the program could be enhanced by developing specific, measurable, and clinically relevant milestones for the supported projects. The JDRF also encourages budgetary flexibility for rapid response to new and emerging opportunities.

Perspective of the ADA

An overview of the ADA was presented by Dr. Scott Campbell, ADA National Vice President of Research. He emphasized that the Special Funding Program has supported research that has resulted in major advances in the understanding of the pathophysiology of type 1 diabetes and its complications. Furthermore, the six research goals under which the Special Funding Program is framed are essential to research progress in this field.

The mission of the ADA is to prevent and cure diabetes and to improve the lives of all people affected by diabetes. Research supported by the Special Funding Program is directly contributing to achieving this mission. For example, the goals relevant to preventing hypoglycemia and disease complications contribute to the portion of the mission that will "improve the lives" of people with type 1 diabetes. Importantly, the clinical trials being conducted by Type 1 Diabetes TrialNet and the Immune Tolerance Network have real potential to identify new disease prevention strategies.

GOAL I:
IDENTIFY THE GENETIC AND ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

Session Chair:
Jørn Nerup, M.D., DMSc, ERCP, EDIN

Type 1 diabetes has a strong genetic basis that is modified by environmental risk factors. Epidemiological research to adequately investigate the underlying genetic and environmental factors that trigger type 1 diabetes requires a large-scale, well-coordinated research effort. The panel discussed some of the larger research efforts that address Goal I.

Type 1 Diabetes Genetics Consortium (T1DGC)

http://www.t1dgc.org/

The T1DGC organizes an international effort to identify genes that determine an individual's risk of developing type 1 diabetes. To this end, the T1DGC collects genetic samples from families that have multiple members with type 1 diabetes. Four networks based in North America, Asia-Pacific, UK, and Europe are funded by the NIDDK, the National Institute of Allergy and Infectious Diseases (NIAID), the National Human Genome Research Institute (NHGRI), JDRF, and Diabetes UK.

Discussant Comments

- Genes that participate in diabetes susceptibility are apparently very common in the population, yet only certain gene combinations confer disease susceptibility. The way to study these interactions is with extremely large databases; hence, the T1DGC provides the best strategy to identify genetic factors and their interactions.
- The consortium is committed to making its resources available to the research community and has developed the necessary infrastructure to achieve this objective. The EAB has developed policies that weigh the interests of funded consortium members who have invested years in collecting material with the interests of the research community at large.
- Genetic analysis technology is undergoing transition. The consortium has rapidly and adroitly converted to the more advanced and cost-effective Single Nucleotide Polymorphism (SNP) genotyping approach, and

the resulting samples will be available in the NIDDK repository for future technological applications.

Highlights of Panel Discussion

Building an International Database Through Patient Recruitment: The consortium's goal is to collect data and samples from 4,300 affected sibling pairs (2,800 new families)—the largest proposed collection for any autoimmune disease. However, recruiting participation from such a large number of families is very difficult, and the rate of enrollment has been slow to date. There was an initial delay in the collection of data due to initial institutional review board (IRB) concerns, and it is expected that the rate of data collection will increase with time. The panel expressed concern about whether the project is sufficiently supported, considering the high costs of recruiting, and questioned whether recruiting goals would be met.

Maximizing Data Collection With Patient Follow-up: The panel recommended maintaining contact with the families to track the medical progression of patients as they develop complications and to identify currently unaffected siblings who may later develop diabetes. This follow-up would require a major investment; however, the genetic samples are already in hand, and accrual of additional information on the clinical status of participants will allow samples to be mined to the fullest extent in the quest for new genetic knowledge. Additional emphasis should be placed on coordinating mouse work and human work, much as it has been done in the type 2 diabetes genetics group.

The Environmental Determinants of Diabetes in the Young (TEDDY)

http://www.teddystudy.org/

TEDDY is an international consortium to recruit genetically-susceptible newborns for studies that test the role of infectious agents, dietary factors, and other environmental conditions that may trigger type 1 diabetes. Funded by the NIDDK, NIAID, National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), CDC, and JDRF, this long-term project will follow participating individuals through adolescence to ascertain the onset of autoimmunity and/or type 1 diabetes.

Discussant Comments

- TEDDY is a major project with an important goal. The design and implementation of TEDDY represent the best research approach to that goal.
- The rigorous design of the TEDDY consortium redresses weaknesses in previous newborn diabetes environmental studies with regard to

methodological standardization, sample sizes, research biases, study designs, and follow-up.

- As the consortium came on board, TEDDY successfully cooperated with on-going newborn studies.
- The consortium has made significant progress forming reference laboratories, establishing proficiency tests, and developing a protocol manual.
- Recruitment has been understandably slow because the centers have only been recruiting subjects for a few months.

Highlights of Panel Discussion

Improving the Study Design by Increasing Flexibility: Considerable thought has gone into the assays and materials to be collected; however, the panel suggested bolstering the design by publishing the protocols on the website and soliciting broad community input. The design could also be further strengthened by developing a mechanism for grafting on new technologies as they become available, such as non-invasive imaging, or for culturing populations of cells. Furthermore, conducting hypothesis-driven analyses might expedite translating laboratory discoveries into the clinic.

Strategic Use of Funds in Terms of Opportunity Costs: The project represents a major research investment, particularly because patients are tracked for 15 years. However, the panel agreed that the collections were valuable and that this consortium is a strategic investment given that similar NIH studies on the role of environmental impacts in childhood diseases would not have the statistical power to evaluate type 1 diabetes. The active oversight from TEDDY's EAB ensures that resources are used most effectively and that the study is designed appropriately.

SEARCH for Diabetes in Youth Study

http://www.searchfordiabetes.org/

This epidemiological study is investigating the incidence and prevalence of diabetes in children in six geographically-dispersed populations that encompass the ethnic diversity of the United States. SEARCH is a joint initiative of the CDC and the NIDDK.

Discussant Comments

- The strength of the SEARCH study is the collection of careful epidemiological data representative of the U.S. population. The preliminary findings have shown a higher incidence of childhood diabetes than was previously believed; however, it will be easier to assess actual progress once the data are published.
- Coordinating the genetics of SEARCH with the other genetics consortia supported by the Special Funds and linking their repositories

would greatly benefit the research community. Samples and data should be available for ancillary studies.

- SEARCH could be restructured by more clearly developing its secondary aims (in addition to its primary aim of prevalence calculations) and by tightening the management structure through reorganization. Clearer definitions of protocol extensions and establishment of an EAB would strengthen the future of the project.

Highlights of Panel Discussion

Mechanisms to Improve Coordination: SEARCH already benefits to a large degree from trans-agency collaboration. Management is supervised by the CDC with monthly calls and with meetings, but the regional operations are managed by each of the six centers. An EAB for program oversight could benefit protocol design. Benefits could also emerge from coordination with the other genetics consortia and the linking of databases.

Opportunity to Study Patient Care and Health Disparities: The panel recognized an opportunity to move into the public health arena and study patient care in the second phase of SEARCH. The six regional sites are in a position to assess the standard of care and the access to treatment. In the new research solicitation (Request for Applications), SEARCH will also be reconfigured to address the challenge of follow-up rate in adolescents.

Broaden the Scope of SEARCH: The panel saw an opportunity to expand SEARCH to look at the long-term outcomes of type 1 diabetes that cause premature death. By including research clinicians who understand complications and by looking at surrogate markers of disease progression, SEARCH can lay the groundwork for better epidemiologic knowledge about the development of debilitating and life-threatening complications, particularly cardiovascular disease.

Submitted Innovative Ideas

Discussant Comments

The four general themes of the submitted innovative ideas were:

- Environmental antigens triggering secretory immune system: Inflammation caused by increased intestinal permeability or airborne contaminants may render the mucosal immune system vulnerable to an autoimmune chain reaction.
- Pancreatic stress contributing to autoimmune attack: Stresses such as obesity or metabolic stress on the endoplasmic reticulum in the target organ may augment the immune system attack on insulin-producing cells.

- Proteomics and gene expression signatures: New technologies will allow identification of factors contributing to the disease.
- High-throughput population genetic sequencing to identify rare alleles:
  - A proposed new cost-effective technology (Pyrosequencing™) to simultaneously sequence hundreds of thousands of DNA fragments.
  - An opportunity to probe the genetic and environmental factors underlying the high prevalence of type 1 diabetes on the island of Sardinia. The panel recognized the promising opportunity to explore genetic and environmental triggers of type 1 diabetes in bottleneck populations such as Tasmania and Sardinia.

Discussion of Opportunities

Protecting or Triggering Autoimmunity via the Gut Barrier

Recent experiments on breeches in the intestinal wall (induced by genetic mutation, chemical treatment, or diet) yielded not only immune effector cells that cause inflammation and autoimmune disease, but also regulatory cells that prevent disease. The panel discussed the opportunities to explore the complex interactions between the environment and the immune system. It is possible that microflora (bacteria in the gut) could induce cross-reactive responses from the pancreatic islet cells affected in type 1 diabetes because homing receptors on the T lymphocyte immune cells that invade the pancreas are shared with the gut. The panel recommended that this opportunity would best be pursued through a high-risk, high-payoff funding mechanism.

Resolving Complex Processes Through Mouse Genetics

The panel discussed the difficulties of teasing out the nature of gene-gene interactions in humans. At the same time, they recognized the power of mouse models to discover the genes and pathways that lead to diabetes. For example, at a fraction of the cost of human genetics, mouse models for type 2 diabetes successfully narrowed several genetic loci for disease susceptibility to within a megabase. The panel encouraged more interaction between human and mouse geneticists; understanding disease pathophysiology in the mouse will lead more rapidly to therapeutic interventions.

Harnessing Systems Biology Approaches

Peripheral blood lymphocytes collected from individuals with type 1 diabetes and their unaffected siblings or from at-risk individuals followed in natural history studies at various stages of progression to autoimmunity and type 1 diabetes could

constitute a valuable scientific resource. Collection of such cells and distribution for large-scale analysis using proteomic and genomic approaches was encouraged. A cautionary note was sounded regarding the difficulty of distinguishing primary alternations involved in the pathogenesis of disease from those secondary to the development of disease.

Opening New Avenues of Research by Exploring Innate Immunity

The panel encouraged examining the influence of the innate immune system genetics on type 1 diabetes. There are 12–14 "toll-like" molecular receptors, and each of these has common and unique cellular signaling pathways. These pathways could be probed with the known ligands (agents that stimulate the molecular receptors). The search for innate immune abnormalities could begin in families with rare recessive genetic defects, particularly "high load" families with susceptibility to multiple autoimmune diseases.

Campaigns to Aid Patient Recruitment

The panel recognized an opportunity to partner with the JDRF and ADA to address the cross-cutting challenge of patient recruitment. The campaign would identify and recruit potential study participants via referring physicians, academic institutions, families, and patient groups. Type 1 diabetes might serve as a model disease for small business partnerships to develop recruitment strategies.

Coordination of Consortia

The panel strongly recommended a meeting between the heads of research consortia to coordinate common efforts. In particular, research efforts would benefit from interoperable databases that provide investigators with access to data and materials from other projects.

GOAL II:
PREVENT OR REVERSE TYPE 1 DIABETES

Session Chair:

Mark Atkinson, Ph.D.

Major objectives of research supported under this goal are to advance knowledge regarding the molecular and cellular causes of autoimmunity and to explore novel therapies to prevent or reverse the fundamental immune system defects that lead to type 1 diabetes.

Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers)

The mission of the Prevention Centers, which are led by the NIAID, is to engage in scientific discovery to significantly advance knowledge for the prevention and regulation of autoimmune disease. The Prevention Centers support a multidisciplinary collaborative network of investigators focused on understanding the immune mechanisms that underlie autoimmunity and autoimmune diseases; approaches to immunomodulation in autoimmunity; and the application of this knowledge to the prevention of these chronic, debilitating diseases.

Discussant Comments

- This research effort is important to pursue because autoimmunity is a cornerstone of type 1 diabetes research.
- Research supported through this network is carried out through two major arms: (1) the five members of the consortium; and (2) pilot and feasibility projects.
- This research group has made progress toward all of its major goals.
- An interesting project is the "NOD Roadmap," which aims to study the life history of the NOD mouse from 1–20 weeks of age. The group has made progress in this research endeavor.
- Expansion of regulatory T cells is a promising area for future investigation through this network.

- The program could be enhanced by: (1) additional external oversight; and (2) increased sharing of data and information with the scientific community.
- Future research opportunities include: (1) increasing synergy by tackling large scientific projects; and (2) identifying ways to propel research studies from mice to humans.

Highlights of Panel Discussion

Accelerating Research Progress by Increasing Interactions Among Consortium Members: The panel stressed that the existence of a cooperative study group is crucial to advance the autoimmunity research field. Increased interaction among individual researchers in this study group would help to achieve synergistic scientific progress "over and above" what could be supported through regular investigator-initiated research projects. In addition, it is important for group members to coordinate efforts to translate research results from the bench to the bedside.

Attracting New Research Talent Through Pilot and Feasibility Awards: The panel endorsed the consortium's pilot and feasibility award mechanism as a venue to attract new research talent. Funds are awarded to participants in the consortium and investigators not previously associated with the consortium. The NIH should identify new ways to widely advertise the pilot and feasibility program and make it available to the broader research community. For example, the consortium could develop a website, and funding opportunities could be announced in the *NIH Guide for Grants and Contracts* and the NIDDK's website dedicated to the Special Funding Program (accessible at http://www.niddk.nih.gov/fund/diabetesspecialfunds/funding.htm).

Standardization Programs

http://www.idsoc.org/committees/antibody/dasphome.html

http://web.missouri.edu/~diabetes/ngsp/

The CDC-led standardization programs discussed were: (1) Diabetes Autoantibody Standardization Program (DASP); (2) C-peptide standardization; and (3) National Glycohemoglobin A1c Standardization Program (NGSP). The purpose of these standardization programs is to improve the measurement of: (1) the autoantibodies predictive of type 1 diabetes; (2) C-peptide as an indicator of insulin production; and (3) hemoglobin A1c (HbA1c) as an indicator of glycemic control, respectively.

Discussant Comments

- These programs are key for advancing research on predicting susceptibility to type 1 diabetes and preventing the disease. For example, autoantibodies are used to predict whether a person may develop type 1 diabetes, and C-peptide measurements are used

to determine whether strategies to prevent or reverse the disease are successful.

- The programs have had many accomplishments, have been managed well, and can be considered a "success story."
- An important component of the programs is the training that is provided to other laboratories and researchers.
- These studies would not be successfully funded through an NIH R01 grant mechanism, so these programs are an appropriate mechanism for conducting this type of research.
- This investment of type 1 diabetes Special Funds could have a large payoff in terms of the importance of these assays to future clinical research efforts.

Highlights of Panel Discussion

Identifying New Surrogate Markers: The panel emphasized the importance of pursuing research to identify new surrogate markers, for example, to predict disease onset or monitor disease progression. Currently, an individual researcher could obtain the serum samples collected through DASP if he or she registers for the program. However, the research conducted on those samples is not supported by DASP. Therefore, the panel suggested finding a mechanism to provide funding for investigators to utilize samples distributed through DASP to identify and test new surrogate markers, such as a pilot and feasibility program.

Improving Clinical Trials by Increasing Emphasis on C-peptide: Because standardized measurements of C-peptide are critical to achieving statistically significant results in prevention and new onset type 1 diabetes clinical trials, the panel encouraged the bolstering of research efforts on C-peptide measurement and standardization.

Increasing Involvement of the International Community: The panel encouraged the participation of international research laboratories in these standardization programs.

Type 1 Diabetes TrialNet

http://www.diabetestrialnet.org

TrialNet is an international network of investigators, clinical centers, and core support facilities. It supports the development and implementation of clinical trials of agents to slow the progression of type 1 diabetes in new onset patients and to prevent the disease in at-risk patients. The network also supports "natural history studies" that will provide information on the risk factors associated with the development of type 1 diabetes and will help in the formulation of future trials. TrialNet is supported by the NIDDK, NIAID, NICHD, and JDRF.

Discussant Comments

- The concept of a standing infrastructure to test promising therapeutic agents to prevent or slow the onset of type 1 diabetes is of critical importance.
- TrialNet's completion of the Diabetes Prevention Trial—Type 1 (DPT-1) was a significant achievement.
- TrialNet could be strengthened by: (1) increasing the number of protocols; (2) identifying highly innovative projects; and (3) decreasing time required for protocol implementation.
- When TrialNet researchers are considering proposed projects, it would be beneficial to have more rigorous mechanisms in place to critically assess the scientific rationale and aid in prioritization among agents proposed for study.
- It is important to conduct studies that will add scientific knowledge to the field of type 1 diabetes research, even if results are negative.

Highlights of Panel Discussion

Rate-Limiting Factors in TrialNet Protocol Implementation: The panel discussed several factors that have limited the rapidity with which TrialNet implements new protocols, including: (1) expansion from the U.S. to international sites; (2) de-centralized leadership making management complex; (3) revised screening procedures; (4) large number of required patients; and (5) current limited availability of therapeutic agents to test. Panel members commended TrialNet for critically analyzing protocols before they are approved and implemented; it is not appropriate to test proposed agents solely because the TrialNet infrastructure exists. However, the panel stressed that this caution must be balanced with promoting the testing of agents that potentially may be a "breakthrough" in the prevention or treatment of type 1 diabetes.

Enhancing Prioritization and Decision-making by Increasing External Oversight: The panel encouraged TrialNet to institute an advisory group consisting of external scientists with expertise in both basic and clinical research. This group would provide insights regarding the proposed protocols and assist in prioritization and decision-making.

Synergizing Research Efforts Through Increased Collaboration With the Immune Tolerance Network (ITN): TrialNet and ITN already collaborate in a number of different and efficient ways. For example, ITN and TrialNet work together so that samples for mechanistic studies are collected and processed using common standardized procedures. In addition, proposed protocols are submitted to both networks using the same format, and both networks use a common Data and Safety Monitoring Board (DSMB). The panel encouraged TrialNet and ITN to enhance collaborations in order to further research efforts. While some panel members felt ITN may be a venue to do

smaller studies to identify a promising therapeutic agent that could then be tested in TrialNet, other members cautioned that until valid biomarkers of efficacy are available, the "small" studies should be powered to observe statistically significant differences in C-peptide levels.

Immune Tolerance Network (ITN)

http://www.immunetolerance.org/

The ITN is an international consortium dedicated to the clinical evaluation of tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and the prevention of graft rejection following kidney, liver, and pancreatic islet transplantation. ITN clinical trials include mechanistic studies designed to uncover the basic biological features of clinical tolerance. The network is supported by the NIAID, NIDDK, and JDRF.

Discussant Comments

- The goal of creating immune tolerance is critical to combating type 1 diabetes.
- Significant accomplishments and progress have been made.
- The ITN conducts studies that have the potential for long-term benefit to type 1 diabetes patients.
- Major strengths include the network's productive interactions with the transplant community and the emphasis on investigator-initiated studies.
- The ITN could be strengthened by: (1) having external oversight by investigators outside of the network; and (2) increasing the diversity of projects.

Highlights of Panel Discussion

Filling the Clinical Trial Pipeline by Identifying Promising Therapeutic Agents: The ITN researchers were encouraged to act as "scouts" to proactively identify promising therapeutic agents (i.e., identify agents by using mouse models). The NIH participants noted that ITN resources are restricted to clinical studies. Nonetheless, both ITN investigators and NIH staff continue to proactively identify promising therapeutic agents.

Synergizing Research Efforts by Enhancing Collaborations: The panel encouraged the ITN to increase collaborations with TrialNet and the Autoimmunity Centers of Excellence (ACE), as well as share resources with researchers in other consortia, such as TEDDY. NIH staff noted that there was significant collaboration among ITN, TrialNet, ACE, TEDDY, and the Non-Human Primate Transplantation Tolerance Cooperative Study Group. For example, the ITN provides technical advice to investigators in TrialNet and TEDDY regarding the repositing of biological samples.

Trial to Reduce IDDM in the Genetically at Risk (TRIGR)

http://www.trigr.org/

TRIGR is a randomized controlled clinical trial with centers in Europe, Canada, and the U.S. The trial seeks to determine whether weaning infants at increased risk for type 1 diabetes (also referred to as insulin-dependent diabetes mellitus [IDDM]) to an extensively hydrolyzed formula versus standard cow's milk formula will decrease the initiation of and/or progression of islet autoimmunity to diabetes. The trial is supported by NICHD, the Canadian Institutes of Health Research, JDRF, the European Foundation for the Study of Diabetes, Novo Nordisk, the Netherlands Diabetes Foundation, and the European Union.

Discussant Comments

- This trial has made excellent progress.
- If the results of the trial are affirmative and show a decrease in autoantibodies in children first exposed to an extensively hydrolyzed formula, then the study has the potential for making a positive impact on patient care.
- The natural history aspect of the study could provide insights into disease pathogenesis, particularly if it is integrated with the TEDDY study. Therefore, TRIGR is encouraged to increase collaboration with the TEDDY consortium.
- A major strength of this study is that the participant retention rate is extremely high.

Highlights of Panel Discussion

Integrating Research Efforts Through Coordination With TEDDY: The TRIGR study is testing a specific scientific hypothesis regarding the effect of weaning infants at increased risk for type 1 diabetes to an extensively hydrolyzed formula versus standard cow's milk formula. The study population enrolled in TRIGR is similar to that of the TEDDY consortium, which is establishing a cohort of children with elevated genetic risk for type 1 diabetes by screening newborns from the general population and from families with first-degree relatives diagnosed with type 1 diabetes. Because TRIGR began before the TEDDY consortium was established, TRIGR has been conducted as a separate trial. However, both TEDDY and TRIGR share the same data coordinating center principal investigator, which provides integration. Nonetheless, the panel encouraged the NIH to explore methods to increase interaction and collaboration between investigators in TRIGR and TEDDY, in order to integrate and coordinate efforts supported by these consortia and to foster the future conduct of analyses combining data from the two consortia.

Generalizability of Results: The panel members encouraged the NIH to think about how the re-

sults of the TRIGR study, in which most sites are outside of the U.S., will be generalized to the U.S.

Submitted Innovative Ideas

Discussant Comments

The four general themes of the submitted innovative ideas were:

- Regulatory T cells: Many innovative ideas are based on the notion that there are naturally occurring regulatory T cells in the body that prevent the development of autoimmune disease. There may be deficiencies in these cells, which can lead to autoimmune disease.
  - One noteworthy innovative idea was based on the hypothesis that researchers could identify, select, and expand regulatory T cells prior to disease development or at the time of disease onset, store the cells by cryopreservation, and reintroduce them after disease onset.
  - The panel supported the idea of enhancing research in the field of regulatory T cells. For example, a consortium approach to address specific barriers (such as determining a standardized protocol to expand regulatory T cells) may help advance this research field. The panel also stressed that scientists with expertise outside of immunology may provide novel and important contributions to these research efforts.
- Blockage of antigen presentation: As its name implies, the "antigen presenting cell" presents an autoantigen to a T cell—the first step in the development of autoimmunity. The autoantigen presentation induces the T cell to become the "effector" cell, which actually causes the disease. Therefore, if the first step of this process—the antigen presentation step—could be inhibited or blocked, then the effector cell and subsequent disease development would also be blocked.
- Characterization of effector cells: As described previously, effector cells play an important role in the development of autoimmunity. Submitted innovative ideas described methods to, for example, modulate the function of effector cells or remove the effector cells by using a molecule that is uniquely expressed by that particular cell type. The panel discussed the idea of preventing the expansion of effector cells expressing CD40 to prevent development of type 1 diabetes and aid in treatment of disease complications.
- Deviation of the immune response:
  - The panel discussed the concept of developing an antigen-specific DNA vaccine for type 1 diabetes. The goal would be to downregulate the activity of the effector T cells to avoid the destruction of islet

cells. This idea is novel, although human studies may be premature.

Discussion of Opportunities

Increasing Research Synergy by Coordination of Consortia

The panel recommended that the NIH facilitate face-to-face meetings of members of the type 1 diabetes research consortia. For example, TEDDY and TRIGR investigators could be brought together to discuss issues of coordination and integration. Meetings could also facilitate the sharing of developed methodologies (such as sample collection and storage) to avoid duplicative work and increase efficiency.

Enhancing Prioritization of Clinical Trials Through the Establishment of Scientific Advisory Boards

The panel encouraged the NIH to consider establishing an overarching scientific advisory board to carefully review and prioritize proposed protocols. This would be in addition to the TrialNet/ITN DSMB. Furthermore, the panel suggested that it may be beneficial for consortia to share an overarching scientific review board, which would be involved in prioritizing protocols. These approaches would help to accelerate clinical research in the most highly promising and feasible areas.

Incentivizing Industry Participation in Type 1 Diabetes Clinical Trials

The type 1 diabetes research field would benefit from increased industry participation in clinical trials. However, there is a disincentive for industry to participate in such trials, mainly due to regulatory and intellectual property issues. The panel encouraged the NIH to find appropriate ways to incentivize industry participation.

Identifying Promising Therapeutic Agents for Type 1 Diabetes by Reviewing Clinical Trials of Other Diseases

Therapeutic agents to treat rheumatoid arthritis were identified during cancer clinical trials. It may be possible to identify agents from trials on cancer, transplantation, and/or other autoimmune diseases that may benefit type 1 diabetes.

Interrogating Molecular Libraries to Identify New Therapeutic Agents

Anti-CD3 has shown promise in preserving beta cell function in a clinical trial in new onset type 1 diabetes patients. Development of assays for steps along the CD3 signaling pathway would allow screening of compounds in existing small molecule libraries to help identify potential therapeutic agents targeting this pathway.

Understanding Autoimmunity by Studying Pancreas Transplantation Recipients

Many type 1 diabetes patients receive pancreas transplants, and they may be an informative population to study to increase understanding of the differences between recurrent autoimmunity and alloimmunity. These types of studies have been performed in animal models, but not in a clinical setting.

GOAL III:
DEVELOP CELL REPLACEMENT THERAPY

Session Chair:

Domenico Accili, M.D.

Research supported under this goal focuses on translation of discoveries from basic or preclinical research studies to clinical studies and, ultimately, to improvements in patient care. The Special Funding Program has supported several initiatives to stimulate research on the biology of the beta cell; islet encapsulation; imaging of beta cell mass and inflammation; and gene therapy approaches to enhance islet transplantation. New initiatives on xenotransplantation, beta cell regeneration, and angiogenesis are planned.

Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG)

The NHPCSG, which is supported by the NIAID and NIDDK, is a multi-institution consortium established to evaluate the safety and efficacy of novel donor-specific tolerance-induction therapies in non-human primate (NHP) models of kidney and islet transplantation. The program also supports research into the immunological mechanisms of tolerance induction and development of surrogate markers for the induction, maintenance, and loss of tolerance.

Discussant Comments

- Research supported by this program is essential to making progress in the field of cell-based therapy.
- The Group has been meeting and exceeding its goals and making tremendous progress.
- A strength of the program is the experience and strength of the participating investigators.
- An important aspect of the program is the establishment of a non-human primate breeding colony.
- A way to attract new research talent may be to provide funding for outside investigators to train with existing Group members to learn how to develop a successful research program on non-human primates.

Highlights of Panel Discussion

Accelerating Research Progress by Increasing Collaboration Among NHPCSG Investigators: The panel recommended that the individual investigators increase interaction and collaboration through venues such as retreats or additional workshops, to enhance on-going collaboration through conference calls, subcommittees, and workshops.

Beta Cell Biology Consortium (BCBC)

http://www.betacell.org/

The mission of the BCBC, which is led by the NIDDK, is to facilitate interdisciplinary approaches that will advance understanding of pancreatic islet cell development and function. The long-term scientific goal is to develop a cell-based therapy to restore normal insulin production and action to diabetic patients. To realize this goal, the BCBC is working toward the creation and distribution of important reagents that will serve the scientific community.

Discussant Comments

- This consortium works extremely well; it should be used as a model for establishing other consortia, and it should continue to be supported and, if possible, expanded.
- The consortium's progress has been very good. Successes include the development of the Mouse PancChip 5.0 and the Human PancChip 1.0.
- The consortium has many strengths: it is a solid organization; the coordinating center effectively manages the program; and the participating investigators direct their own research programs.
- Opportunities for future research include pursuing more collaborative, discovery-based research.
- The BCBC should consider "outsourcing" tool and reagent development, such as generating antibodies and transgenic mice through a contract or SBIR mechanism.
- Research could be enhanced by defining overarching goals for pursuing studies on stem cells, consistent with federal funding policies.

Highlights of Panel Discussion

Outsourcing Reagent and Tool Development: Although several members supported the suggestion to outsource this component of the BCBC, other panel members felt that reagent development, particularly generation of antibodies, was critical to the BCBC's research mission. Commercially available antibodies may not be of a sufficiently high quality to answer research questions being asked by BCBC investigators. However, the panel felt that the generation of transgenic mice

could be supported by an outside contractor. The NIH participants noted that this topic has been discussed by BCBC investigators.

Islet Cell Resource Centers (ICRs)

http://www.infosci.coh.org/icr/

The ICRs, which consist of 10 centers throughout the U.S., were established to harvest, isolate, and distribute islets for use in approved clinical transplantation protocols. The consortium also aims to optimize techniques for isolation, purification, storage, shipment, and characterization of human pancreatic islets for use in clinical protocols and to generate and distribute human pancreatic islets to investigators for use in laboratory-based research studies. The ICRs are supported by the National Center for Research Resources (NCRR) and the NIDDK.

Discussant Comments

- There are many strengths to this program, and its scientific goals are critical.
- An interesting concept being addressed by the ICRs is having certain centers in the U.S. isolate islets and then ship them to transplant programs around the country. Many details (such as shipping conditions) must be studied for this approach to be successful.
- The ICRs have helped to pair transplant and islet isolation centers.
- There is a high potential to fine-tune some of the technical goals of this program to enhance the outcomes. These types of technology-based studies may be performed by small businesses.
- Appropriate external scientific oversight is important to achieve the program's goals.

Highlights of Panel Discussion

Discussion of Using Islets for Clinical Transplantation Versus Research: The panel discussed the focus of the ICRs. The original purpose of the ICRs was to provide islets for transplantation; however, the ICRs have recently begun to meet another important scientific need by providing islets for basic research studies.

Strengthening the ICRs by Modifying Their Focus: The panel recommended that the ICRs continue to be supported, but that it may be beneficial to reconfigure the program and focus resources more efficiently. In addition, the panel suggested that the ICRs focus on: (1) research to improve quality of islets; and (2) providing high-quality islets to the scientific community. Furthermore, the panel stressed the need to undertake "systematic" approaches to increase understanding of the variables involved in islet isolation, purification, storage, shipment, and characterization.

Accelerating Research Progress by Coordination With Other Consortia: The panel suggested that the NIH organize a meeting of the ICRs, basic scientists (such as those in the BCBC), and islet transplant centers. This type of meeting could facilitate collaboration and promote novel research directions.

Clinical Islet Transplantation Consortium (CIT)

The purpose of this consortium, which is supported by the NIDDK and NIAID, is to develop and implement a program of single- and/or multicenter clinical studies, accompanied by mechanistic studies, in islet transplantation, with or without accompanying kidney transplantation, for the treatment of type 1 diabetes. The CIT will conduct a clinical trial of Medicare recipients mandated by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (P.L. 108-173).

Discussant Comments

- This newly-established group has a high potential for success.
- The mechanistic studies being performed by the consortium are important and should be supported.
- The consortium should be involved in research training to increase the number of people and institutions that could perform islet transplants. It is important that the future successes of the CIT not be limited to the five currently funded centers.

Highlights of Panel Discussion

Utilizing the Clinical Trial of Medicare Beneficiaries for Training: NIH staff noted that the five clinical centers participating in the CIT may not be able to recruit a sufficient number of patients for the mandated clinical trial involving Medicare recipients; in that case, additional sites may be involved. Therefore, this trial provides a venue for the research training of individuals at additional sites.

Synergizing Research Efforts Through Collaboration With Other Researchers: The panel encouraged the CIT to collaborate with the ICRs. In addition to the collaboration that currently exists because three institutions have both CIT centers and ICRs, the ICRs will also be providing islets for additional sites involved in the clinical trial of Medicare beneficiaries. Furthermore, the panel stressed that mechanistic studies could be enhanced if the CIT investigators collaborate with beta cell biologists.

Submitted Innovative Ideas

Discussant Comments

The three general themes of the submitted innovative ideas were:

- Applying new encapsulation technology to islet transplantation: The panel noted that the submitted ideas on this topic underscored the importance of attracting bioengineers to the type 1 diabetes field.
- Expanding insulin-producing cell lines.
- Studying regulatory T cells and molecular networks as they relate to transplantation.

Discussion of Opportunities

Exploring Multiple Approaches to Achieving an Unlimited Supply of Beta Cells

The panel encouraged the NIH to support studies of beta cell differentiation and regeneration. In particular, studies of regeneration in non-human primates and studies of approaches to expand human beta cell populations were encouraged.

Promoting Research Collaboration and Progress Through Support of Self-Aggregating Consortia

One barrier to propelling research that was identified by the panel was the lack of scientific consensus on research directions to be pursued. This barrier is evident in a consortium, where researchers who have been assembled into a large group through the NIH peer review process may have different individual research priorities or directions. One idea that the panel endorsed to help overcome this barrier is to support "self-aggregating" or "self-assembling" consortia with specific milestones, in which investigators would build their own research teams to tackle defined research barriers.

Attracting New Research Talent by Promoting Innovative Partnerships

The panel stressed the importance of engaging investigators with expertise outside of the diabetes field, such as bioengineers and imaging experts, to apply their skills to studying type 1 diabetes. However, this is a two-way street because the outside experts need input and guidance from diabetes researchers to guide research in a clinically-relevant direction. These aims could be accomplished through an "innovative partnership" mechanism.

Understanding Variability in Islet Transplantation Using Systematic Approaches

Panel members discussed the feasibility and complexity of adapting a "matrix," or systematic, approach to testing variables regarding islet

transplantation. For example, variables include islet isolation, transportation, time from procurement to transplantation, and the health of the donor and recipient. Because of these numerous complicating issues, it may be difficult to take a systematic approach to begin to understand all the variables. However, a systematic approach may be useful for a program like the ICRs to implement.

GOAL IV:
PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

Session Chair:

Robert Sherwin, M.D.

Major objectives of research supported under this goal are to identify novel technologies and therapies to ease the daily management of type 1 diabetes. These studies range from basic studies on the neuronal mechanisms that induce hypoglycemia to clinical research to improve and validate technologies that measure levels of blood glucose.

Diabetes Research in Children Network (DirecNet)

http://public.direc.net

DirecNet, which is led by the NICHD, is a multicenter clinical research group whose focus is to investigate the use of technologic advances in the management of type 1 diabetes in children and to develop a better understanding of hypoglycemia. Specific goals of the network include assessing the accuracy, efficacy, and effectiveness of continuous monitoring devices in children with type 1 diabetes and evaluating the frequency of hypoglycemia and possible related changes in neurocognitive function.

Discussant Comments

- DirecNet is an independent and scientifically rigorous program that has published and recruited well.
- An important undertaking of the network is to define a child's normal glucose profile.
- DirecNet could be enhanced by: (1) making plans for future directions if the pilot study of devices expected to be ready for testing in the near term, such as the Therasense Navigator system, does not yield results that would warrant larger-scale testing; and (2) broadening the scope of the network.
- A future research opportunity includes tackling the barrier of linking glucose monitoring with insulin delivery ("closing the loop").

Highlights of Panel Discussion

Testing Technology in Children Versus Adults: The panel suggested that DirecNet consider testing technologies in adults with type 1 diabetes. In particular, the panel noted that studies on "closing the loop" should be performed in adults; however, the NIH noted that DirecNet was created to improve therapy specifically in children.

Accelerating Research Progress by Inviting Participation of Experts in Hypoglycemia: DirecNet could benefit from the participation of external scientists with expertise in hypoglycemia. A workshop to obtain broad input on the future directions of DirecNet could be convened with experts in hypoglycemia, pediatric diabetes, and FDA regulations. The workshop participants could give insights regarding ways to broaden the research scope of DirecNet.

Utilizing DirecNet to Inform and Improve Upon Future Clinical Trials: Currently, islet transplantation studies are appropriately limited to adults. However, as the field of cell-based therapies progresses, the goal is to apply these therapies to children. When safer and more effective cell-based therapies are developed, DirecNet investigators could be crucial in designing a clinical trial to compare the efficacy of different cell-based therapies. Therefore, the panel stressed that having this network infrastructure in place could be valuable for future projects.

Cellular and Clinical Effects of Hypoglycemia for Patients With Type 1 Diabetes

Four initiatives were developed to foster basic and clinical studies to enhance understanding of how the brain and other critical tissues sense and respond to hypoglycemia; delineate the effects of hypoglycemia on brain function; and develop therapeutic approaches to prevent hypoglycemia, based on an understanding of physiological glucose sensing and counter-regulation. These initiatives have been sponsored by the NIDDK, the NICHD, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Nursing Research (NINR), and the JDRF.

Discussant Comments

- The goal of integrating cellular and clinical effects of hypoglycemia is extremely worthwhile.
- Research funded under the most recent initiative, which includes projects utilizing imaging and nuclear magnetic resonance (NMR) technologies, has high potential to provide insights into this research field.
- These types of initiatives should be supporting high-risk, high-payoff research that has the potential to identify novel research directions and approaches. The fact that a small percentage (10–20 percent) of the R21 grantees have successfully applied for and received

R01 funding is encouraging because a higher percentage would imply that the original projects were not high-risk. The NIH could use both the R21 and SBIR mechanisms to promote research progress in this field.

Highlights of Panel Discussion

Attracting New Research Talent by Building Research Partnerships: The panel encouraged the NIH to attract biomedical engineers to hypoglycemia research. One suggestion was to include the participation of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), which interacts with the biomedical engineering community. In addition, the panel encouraged the NIH to promote partnerships between neuroscientists and diabetes researchers. The NIH has previously held workshops that brought these two research disciplines together; it is important to continue to foster interactions through future workshops and/or focused research solicitations.

Submitted Innovative Ideas

Discussant Comments

- The idea of understanding alpha cell biology is important because this type of knowledge could impact treatment and prevention of hypoglycemia in both type 1 and type 2 diabetes patients. The NIH noted that investigators in the Beta Cell Biology Consortium are studying the alpha cell.
- With respect to investigations of blood glucose dynamics in normal and diabetic patients, the panel felt that it is critical to conduct studies that provide insights into the normal dynamics of blood glucose levels.

Discussion of Opportunities

Identifying Therapeutic Targets by Studying Counterregulatory Mechanisms

An area of opportunity identified by the panel is to increase the understanding of the underlying molecular mechanisms of defects in the counterregulatory response to identify promising therapeutic agents for preventing or treating hypoglycemia.

Attracting New Research Talent and Accelerating Research Progress by Promoting Partnerships Between Neuroscientists and Diabetologists

In order to promote novel translational research approaches to prevent or treat hypoglycemia, the panel encouraged the NIH to facilitate partnerships between experts in the neurosciences and in diabetes. One research opportunity that could be pursued through these partnerships is to study the long-term effects of hypoglycemic events on the brain.

Enhancing Coordination of Hypoglycemia Research Efforts

DirecNet investigators could use their expertise to assume a leadership role in coordinating hypoglycemia research efforts. In particular, they could provide guidance to researchers who do not have expertise in clinical aspects of type 1 diabetes, such as engineers, so that research directions lead to clinically-relevant results.

GOAL V:
PREVENT OR REDUCE THE COMPLICATIONS OF TYPE 1 DIABETES

Session Chair:

Ann Marie Schmidt, M.D.

Hyperglycemia in type 1 diabetes leads to accumulation of reactive oxygen species and damages the microvasculature, networks of small blood vessels embedded in tissues. These processes can lead to complications including kidney, eye, nerve, and cardiovascular diseases. Solicitations for the funding of regular research grants have been seeding a research base to address many complications of diabetes. Larger consortia have been involved in efforts such as examining the genetics of diabetic complications and establishing animal models as research tools.

Animal Models of Diabetic Complications Consortium (AMDCC)

http://www.amdcc.org

The AMDCC is an interdisciplinary consortium supported by the NIDDK, the National Heart, Lung, and Blood Institute (NHLBI), and the JDRF. It is designed to develop animal models that closely mimic the human complications of diabetes for the purpose of studying disease pathogenesis, prevention, and treatment.

Discussant Comments

- The AMDCC's major strengths include the validation criteria and standards that were developed by the very strong phenotyping cores and data coordinating center.
- The consortium fosters research progress by bringing together leaders in the animal model and diabetic complications fields.
- Constructive oversight is provided by semi-annual External Advisory Committee meetings and regular meetings with NHLBI and NIDDK program staff.
- Strong infrastructure is supported by a functional website for accessing validation criteria and technical methodologies.

- Although the focus has largely been on mouse models, new large animal models have also been developed.

Highlights of Panel Discussion

Sustain AMDCC Phenotyping Cores: The phenotyping cores of the AMDCC should be sustained and, perhaps, expanded. A major resource provided by the AMDCC has been the suggested "standardization" of measurements/end points in the various complications. It is suggested that beyond neuropathy, other key areas (nephropathy, retinopathy) be expanded as phenotyping cores that might be available to the diabetes community.

Increase Understanding of Common Pathogenic Mechanisms by Comparing Mouse Models: The panel suggested finding correlations between the best mouse models across the spectrum of different complications (cardiovascular, neuropathic, nephropathic) to determine commonalities and to shed light on the underlying mechanisms of diabetic complications. They further suggested an outreach effort to provide these animal models, or at least breeding pairs, to the complications research community.

Promote Pre-clinical Testing by Developing New Animal Model Systems: The panel encouraged expansion of non-rodent research efforts, using such animal models as pigs and non-human primates, for future use in preclinical testing of interventions. The panel identified an opportunity to recruit new talent to complications research by tapping into the zebrafish community. Zebrafish genetic and developmental models have been useful for studying cardiovascular and pulmonary systems. The potential exists for using high throughput screens for drug targets and for identifying gene products as surrogate markers for metabolic stress.

Facilitate Diagnosis of Early-Stage Complications via Novel Technologies and Surrogate Markers: Animal models provide an opportunity to identify surrogate markers for diabetic complications. Diagnosing intermediate stages of disease progression is a major challenge inhibiting clinical translation because disease progression is long-term and, at this point, the major focus of the FDA is on end points (e.g., death, cardiac events, stroke). As the AMDCC is considered for renewal, the panel suggested emphasizing novel technologies for phenotyping (e.g., proteomics, metabolomics, genomics, and signal transduction pathway assays).

Evaluate Novel Therapies With Tissue Cultures of Models: Isolation of cells (e.g., endothelial cells, smooth muscle cells, mononuclear cells, neurons) from animal models could be a springboard for studying stresses and the impact of novel therapies.

Improve Models by Incorporating Immunologists Into the AMDCC: Type 1 diabetes is an autoimmune disease, but the impact of autoimmunity on the development of complications has not been adequately investigated. The panel strongly felt a need to include an immunologist to oversee the complications models. Reproducing complications from animal models is challenging, and an autoimmune mouse model might lead to greater success. Furthermore, bringing in greater expertise in immunology might help overcome current roadblocks with respect to breeding strategies.

Epidemiology of Diabetes Interventions and Complications (EDIC): Subclinical Cardiovascular Studies and Urologic and Neuropathic Studies

http://www.bsc.gwu.edu/bsc/studies/edic.html

EDIC is the follow-up to the landmark Diabetes Control and Complications Trial (DCCT) that conclusively demonstrated that intensive diabetes therapy reduces risk and progression of microvascular diabetic complications when compared with conventional treatment. EDIC has been supported by the NIDDK since it began in 1994; the Special Funds have supported ancillary studies on cardiovascular, urologic, and neuropathic complications starting in 1998.

Discussant Comments

- EDIC has been extremely productive over the years with valuable studies, high-quality publications, and meaningful bedside applications.
- The relevant question now is to consider the value of continuing these ancillary observational studies versus designing new prospective studies with the latest technology. Despite the lack of baseline data in cardiovascular studies in the DCCT participants, there are still opportunities to capitalize on the long-term investment in resources on this select cohort of patients.
- These cardiovascular studies address a limitation in the original DCCT studies, which examined a young group of patients with few cardiac complications.
- Neurologic manifestations of type 1 diabetes have been less extensively studied than eye and kidney disease in DCCT/EDIC and plans are underway to redress this.

Highlights of Panel Discussion

Monitor Cardiovascular Events With Surrogate Markers: The study participants are just beginning to have cardiac events, so this cohort provides a good opportunity to examine subclinical cardiovascular disease markers (e.g., carotid intima-medial thickness, coronary calcification, myocardial function) as predictive of cardiovascular events. A consensus of the panel felt that these studies should

be continued at least until these surrogates can be verified; the longer-term follow-up just to monitor cardiac events will be less costly. Furthermore, cardiovascular baseline data should be considered in the design of future prospective studies.

Genetics of Diabetic Complications

The following three consortia were grouped because they all address genetic factors that predispose diabetes patients to or protect them from developing complications in various organs.

Genetics of Kidneys in Diabetes Study (GoKinD)

http://www.gokind.org/access/home.html

GoKinD collects genetic samples from cases and controls of diabetic nephropathy (kidney disease). It is supported by the CDC and the JDRF.

Family Investigation of Nephropathy and Diabetes (FIND)

The FIND consortium is largely supported by the NIDDK, the National Eye Institute (NEI), and the National Center on Minority Health and Health Disparities (NCMHD) and has been elucidating genetic susceptibility to kidney disease in diabetic patients, particularly ethnic minorities, and their families. Ten percent of FIND study participants have type 1 diabetes, and the contributions from the Special Funds have permitted expansion of FIND to study the genetic determinants of diabetic retinopathy (eye disease leading to blindness) in patients enrolled in the FIND family study.

EDIC

http://www.bsc.gwu.edu/bsc/studies/edic.html

The genetics component of the long-term familial study by the NIDDK compares diabetic complications with DNA variation in candidate genes.

Discussant Comments

- These consortia provide extraordinarily valuable collections with strengths in sample size and in heterogeneity. Despite achievement of lower-than-target recruitment numbers, there is a rich collection of material, including that from one of the largest collections of sibling-paired subjects for genetic analysis of diabetic kidney disease.
- Human genetic studies are extremely challenging because of the difficulty in recruiting a patient with type 1 diabetes who has developed complications, as well as two or more family members with the disease. These studies would be virtually impossible with an R01 grant mechanism.
- The search for genes involved in renal complications is especially promising because of the epidemiology findings: approximately 30 percent of diabetes patients develop nephropathy

within 15 years, while patients who have not developed nephropathy in 15 years rarely do so later, suggesting a genetic difference.

Highlights of Panel Discussion

Coordinate Efforts With Communication Among Consortia: The panel encouraged further communication among these three studies and with other genetic consortia, including the T1DGC and a Euro-pean research collection. Ideally, a single, coherent, accessible database combining the studies would permit observations from data in one study to be tested in another.

Expedite Recruitment and Enrollment: Enrollment is often an issue in these kinds of studies, and the genetic consortia had difficulty meeting their recruiting goals. The panel noted that the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations and IRB requirements may have contributed to slower-than-projected enrollment, and they felt that the consortia should share lessons learned about methods for effectively addressing these recruitment issues.

Distribution of Materials and Data: There was discussion on how the materials collected would be made available. The times of release for materials are different for each collection, and conventions and guidelines for release are needed. The release guidelines developed by the T1DGC could be used as a model.

Diabetic Retinopathy Clinical Research Network (DRCR.net)

http://drcr.net/

DRCR.net facilitates multi-center clinical research on diabetic retinopathy, diabetic macular edema, and associated conditions. The NEI-supported network pursues standardization of procedures across studies and promotes new technologies with an emphasis on clinical trials.

Discussant Comments:

- The DRCR network successfully met its goals in getting both private and academic based retinal practices involved in clinical trials to study epidemiology, therapies, and outcomes of diabetic retinopathy.
- Like TrialNet, DRCR.net is a very worthwhile infrastructure, but it is awaiting the emergence of additional innovative therapies to test. Currently, five protocols are being tested.
- The network incorporated technological innovations such as an electronic visual acuity tester to normalize measurements across centers and electronic clinical report forms.

- This network could serve as a model for other complications (e.g., kidney, nerve).

Highlights of Panel Discussion

Program Management: The panel was concerned that the DSMB performs both safety monitoring and protocol review. However, the panel also recognized that the Steering Committee provides oversight of protocol conduct.

Angiogenesis: In some cases, therapies to promote angiogenesis (the growth of new blood vessels) have been proposed as a remedy for many diabetic complications. However, in the eye, angiogenesis exacerbates retinopathy. The NIH participants noted that the recent research solicitation on angiogenesis in type 1 diabetes will complement on-going DRCR.net efforts in angiogenesis.

Submitted Innovative Ideas

Discussant Comments

The four general themes of the submitted innovative ideas were:

- Developing new animal models to examine a specific component of diabetes complications:
  - A particularly interesting and highly innovative suggestion is to investigate how birds protect themselves from levels of glucose high enough to kill a human (hyperglycemia). There are potential research questions to examine the effects of hyperglycemia and glycemic stress on the mitochondria and what mechanisms have evolved to dispose of the advanced glycation endproducts (AGEs).
- Developing novel surrogate markers: Proteomic and genomic approaches in animal models could contribute to this goal. Also, markers of endothelial function and cardiovascular risk factors (e.g., NT-proBNP) should be evaluated as potential surrogate outcomes. New imaging technology is also promising in this regard.
- The role of the innate and adaptive immune system in diabetic complications: The innate immunity might be altered in diabetes because mice induced to have diabetes are more susceptible to bacterial infection. Furthermore, longer-term diabetes leads to impaired wound healing. Although most attention has been focused on vascular tissue, dendritic epidermal cells or mononuclear inflammatory cells may also play a role.
- Repair and regeneration: Understanding the mechanism of hyperglycemic damage, which may involve oxidative stress in the mitochondria, has implications not only for preventing tissue damage but also for repair and regeneration.

Discussion of Opportunities

Evaluate Clinical Risks of Hyperglycemia and Glucose Fluctuations

The panel identified a major clinical challenge—that is, to determine whether stable high blood sugar (hyperglycemia) or fluctuations of high blood sugar have the same effects on complications. It is not clear if there is value in reducing excursions in glucose independent of achieving a lower mean glucose level. In the DCCT study, patients receiving intensive insulin therapy had fewer complications than those on conventional therapy for a given HbA1c or blood sugar level. Furthermore, there is evidence that greater blood sugar excursions may be associated with cardiovascular disease risk.

HbA1c is a blood protein responsive to the average blood sugar level and has been the gold-standard surrogate marker for measuring integrated blood sugar levels. However, the time course of HbA1c glycosylation (modification in response to sugar) and protein turnover may actually limit its utility for measuring fluctuations. The emergence of new proteomic technologies, such as the human serum proteome project at the University of Michigan, may provide an opportunity to find better biomarkers.

Facilitate Cross-Cutting Research With Bioinformatics Database

The panel discussed creating a bioinformatics database to unify data from studies including DCCT, EDIC, GoKinD, FIND, and T1DGC. Epidemiological data could aid in the interpretation of genetic data, which in turn would clarify proteomic data. However, a new bioinformatics database presents many challenges as well. Any new system would have to be approved by IRBs and would need to comply with HIPAA. More significantly, each study has already developed its own databases, and designing a new interoperable database would require substantial effort and expense. However, the consideration of the expense would have to be compared with the time and cost to each individual researcher who must manually search each separate database in the current system. The NIH participants pointed out that one of the goals of the NIH Roadmap is to create uniform, streamlined platforms for sharing data.

Evaluate Impact of Autoimmunity on Complications

The panel encouraged incorporating immunologists into the diabetes complications arena. Based on the increasing evidence that complications are related to inflammation and monocyte activation, autoimmunity may significantly contribute to complications, either because chronic activation of the

immune system potentiates the development of complications or because type 1 diabetes represents a genetic defect in the immune system. The same mechanisms that underlie beta cell destruction may exacerbate cardiovascular lesions, for example.

Dendritic cells in epithelial tissues such as the skin and gut confer innate immunity against pathogens and regulate inflammation. The panel suggested testing responses of dendritic cells in the skin of type 1 diabetes patients. These results could then be compared with responses from type 2 diabetes patients who share a similar glucose abnormality, but presumably do not share the underlying autoimmune abnormality.

Mediate Toxicity of Reactive Oxygen Species

Hyperglycemia leads to production of reactive oxygen species (ROS) in the mitochondria; the increased oxidative stress is considered to be one of the common pathogenic factors in diabetic complications. The panel encouraged research on factors that mediate the toxicity of ROS, including NAD^+-dependent histone deacetylase and SIR2 type enzymes. The NIH participants pointed out that the NIDDK's regularly-appropriated funds support a new translational research RFA to find a biomarker to measure ROS in patients.

Promote Clinical Trials in Industry by Developing Biomarkers and Surrogates

The panel suggested investing in efforts to identify biomarkers and surrogates to enable clinicians to easily measure the progression of complications in diabetic patients. In addition to phenotyping, the AMDCC could be charged with developing a time course profile of surrogate markers. These surrogate markers could possibly be compared with the materials already collected from GoKinD and FIND. Validation of accepted surrogate markers would likely incentivize industry to invest in translational research.

Additional Promising Opportunities

Panelists identified further areas for exploration.

- Measurements of C-reactive protein (CRP), a serum factor present in acute inflammation, may be more indicative than cholesterol LDL levels in predicting heart attacks. Preliminary evidence indicates that CRP is elevated in type 1 diabetes, as well as in type 2 diabetes, and it may serve as a biomarker for heart complications. The panel encouraged investigations into upstream steps, such as IL6 changes, that might cause CRP to increase in acute diabetes.
- Congestive heart failure incidence is higher in patients with diabetes; however, the underlying mechanisms are not understood in

type 1 diabetes. Longitudinal measurements of B-type Natriuretic Peptide (BNP) may provide insights into diastolic dysfunction (abnormal relaxation of the heart that leads to increased fluid and pressure in the ventricles).

- The panel identified a need for innovative ideas to combat neuropathy. This is a major research challenge that may require a workshop to bring together scientists from different disciplines (e.g., neurobiologists, diabetologists, clinicians). One major obstacle in this area is the lack of a surrogate marker for neuropathy.

GOAL VI:
ATTRACT NEW TALENT AND APPLY NEW TECHNOLOGIES TO RESEARCH ON TYPE 1 DIABETES

Session Chair:

Diane Mathis, Ph.D.

Understanding the molecular basis of type 1 diabetes and developing new strategies for prevention and cure will require a cadre of scientists who can bring diverse training and experience to research on this disease and its complications. In addition, it is crucial to apply novel technologies, such as proteomics and metabolomics, to provide new insights into the molecular underpinnings of the disease.

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

http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D-RAID/

The goal of the T1D-RAID program is to facilitate translation from the laboratory bench to the clinic of novel therapeutic interventions for type 1 diabetes and its complications. These potential interventions can be synthetic, biologic, or a natural product. T1D-RAID is not a grant mechanism; it does not provide any funds directly to an investigator. The sponsors of approved requests to T1D-RAID gain access to the preclinical drug development contract resources of the National Cancer Institute's Developmental Therapeutics Program (NCI DTP). TID-RAID is sponsored by the NIDDK and NCI.

Discussant Comments

- This program 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 should be sufficient to support the breadth of necessary research and resource development.

Highlights of Panel Discussion

Accelerating Translational Research Through a "Pre"-T1D-RAID Program: The panel encouraged the NIH to support "pre-T1D-RAID" resources, which would provide small molecule libraries to investigators so that they could test the molecules in their well-developed assay systems. These resources would help identify promising therapeutic agents that could be further developed through the T1D-RAID program. The NIH participants noted that the NIH Roadmap is already supporting this approach in its "Molecular Libraries" initiative. More information on this initiative can be found on the NIH website (accessible at http://nihroadmap.nih.gov/molecularlibraries/index.asp). The panel appreciated the comments of NIH staff that the NIH Roadmap may fill the gap on development of novel therapeutics for type 1 diabetes and its complications. However, the panel also recommended outreach to industry or biotechnology companies in this regard and efforts to test more limited libraries using assays validated for diabetes complications targets.

Priming the Therapeutic Agent Pipeline: The panel discussed new initiatives which support pre-clinical studies of potential new therapeutic agents to prevent or treat type 1 diabetes or its complications in animal models. The NIH participants noted that one of the goals of these studies is to help identify promising therapeutic agents to test in Type 1 Diabetes TrialNet, the ITN, or other consortia. The panel cautioned that it may take a long period of time to perform these types of pre-clinical studies in animal models.

Bench-to-Bedside Research on Type 1 Diabetes and Its Complications

The overall objective of this initiative is to stimulate translational diabetes research by encouraging the formation of collaborative research teams composed of basic and clinical scientists focused on specific projects that have the potential to develop new therapies for type 1 diabetes or its complications. The initiative involves teams of clinical and basic scientists in the hope that the combined expertise of the investigators will foster the development of a basic research finding to the point at which 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. The program is supported by the NIDDK, NIAID, NEI, NHLBI, NINDS, and Office of Dietary Supplements (ODS).

Discussant Comments

- This type of program is important and should continue. It is an excellent way to stimulate investigators to propel their laboratory re-

search into a clinical or pre-clinical phase.

- A 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 (exploratory/development phase; the "bench") to the R33 phase (the "bedside").
- It is premature to judge the success of this program; its impact will be realized in the next several years.

Highlights of Panel Discussion

Testing Promising Technologies in Uniform Animal Models: The panel noted that it is important to compare the technologies developed by different investigators in the program on uniform animal models to determine which technologies are the most promising. In addition, the technologies should be tested in the animals in the analogous time frame of human disease development. For example, if the research is aimed at slowing progression of new onset type 1 diabetes, then the animals should have recent onset diabetes. This type of uniform analysis could assist in future portfolio management decisions.

Innovative Partnerships in Type 1 Diabetes Research

The overall objective of this initiative 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 expertise relevant to type 1 diabetes research. The intent is to attract new research talent to type 1 diabetes research; strengthen the on-going 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.

Discussant Comments

- 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 to fund 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 its 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 two years. This increase would permit more time for researchers to build productive partnerships and perform collaborative research.

Highlights of Panel Discussion

Attracting New Talent Through Focused Innovative Partnerships: The panel endorsed the recommendation to support a "focused" innovative partnership initiative to attract specific types of researchers, such as neuroscientists and bioengineers, to type 1 diabetes research. The panel felt that future innovative partnership initiatives should not be completely defined, but rather still permit researchers to propose novel partnerships that can propel research.

Research Training and Career Development in Pediatric Diabetes

Through this initiative, the NIDDK, JDRF, and ADA have provided support for research training and career development 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. These integrated programs are designed to prepare pediatricians, selected by the institution, for such careers.

Discussant Comments

- This program is extremely important for 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.

Highlights of Panel Discussion

Retaining Researchers in Pediatric Diabetes by Enhancing Communication: The panel stressed that it is critical for the NIH to keep lines of communication open with the trainees in order to hear their concerns, which could potentially help to retain investigators in this field of research. The NIH noted that the trainees are brought to the NIH campus in Bethesda in order to meet the NIH staff members who will most likely be

the program directors for their independent R01 grants. The goal of the meeting is to assist the researchers in their transition from being "trainees" to "independent investigators." In addition, the meeting provides an opportunity for the NIH to receive feedback from the trainees.

Submitted Innovative Ideas

Discussant Comments

The eclectic group of interesting ideas is highlighted below:

- Measuring the state of beta cell viability: The oxidation state of mitochondria indicates the health of the cell. Measuring the intrinsic autofluorescence of mitochondrial flavoproteins could indicate if cells are viable for transplantation.
- Promoting gene therapy targeted to beta cells: Adenovirus vectors that molecularly target beta cells could deliver agents like BCL2 that would make them more resistant to apoptosis.
- Protecting transplanted islets with immunorejection resistant gene: Testicular Sertoli cells are resistant to immunorejection, possibly due to some factor that they express. The panel recognized the potential of screening Sertoli cells for the anti-rejection factor. However, the panel noted that this resistance might also be explained if Sertoli cells did not express any surface molecules recognized by T-lymphocytes.
- Converting embryonic stem cells into beta cells: The sequence of steps would be very complex and challenging, but the panel agreed about the potential impact of generating beta cells from a renewable resource. The NIH noted that investigators in the Beta Cell Biology Consortium are studying methods to promote maturation of embryonic stem cells into beta cells.
- Applying computer-based imaging techniques to automate morphometric measurements (e.g., size, shape, total numbers) of isolated islet cells.

Discussion of Opportunities

The discussion of Goal VI was organized around three themes: (1) Incorporating New Technologies; (2) Recruiting New Talent; and (3) New Mechanisms of Funding.

Incorporating New Technologies

Analyzing Large Datasets and Models With Computational Biology

The panel discussed the need to incorporate quantitative methods into biology to analyze multidimensional databases, to produce mathematical models of complex biological phenomena, and to develop technologies for large-scale analyses of

images. Producing complex models 10 years from now requires training biomathematicians today. One possibility would be the creation of a bioinformatics consortium; however, modular steps in existing consortia might have more immediate results in the context of current efforts than a large scale restructuring. It may be possible to take advantage of the bioinformatics efforts under way as part of the NIH Roadmap (accessible at http://nihroadmap.nih.gov/bioinformatics/index.asp).

Facilitating Transplantation Research With Humanized Mouse Models

The panel identified a long-term opportunity to genetically engineer "humanized" mouse lines for transplantation and autoimmunity studies. In a "humanized" animal model, the copies of certain animal genes have been replaced by the homologous human version. Although small scale efforts to this end have been driven by investigator-initiated projects, the panel recommended developing a 10-year trans-NIH plan to develop such a mouse model. The panel suggested that this project would be an excellent opportunity to employ partnerships with small businesses.

Recruiting New Talent

Investing in Promising Investigators With Career Development Awards

The panel supported the idea of career development awards to recruit and retain top young investigators and to promote high-risk, high-impact research. Similar in concept (but not in mechanism) to the NIH Director's Pioneer Awards and the program of the Howard Hughes Medical Institute, these awards might raise the profile of type 1 diabetes research by providing an attractive monetary recognition to recipients. The panel noted that, in a recent JDRF report tracking the progress of 600 recipients of JDRF funding over the past 30 years, the retention rate of investigators still working in diabetes-related research was 80 percent. Furthermore, the retention rate for recipients of Career Development Awards was around 98 percent.

Raising the Profile of Diabetes Research

The panel discussed the need to raise the profile of the type 1 diabetes field to attract talent from other fields and to recruit graduate students into diabetes laboratories. To this end, research questions in general immunology, developmental biology, or neurobiology could be posed from the type 1 diabetes perspective. For example, "What does it take to induce immune tolerance?" and "What causes a cell to differentiate into one as sophisticated as a beta cell?" Additionally, the panel suggested holding annual diabetes meetings for students.

Inspiring Future Generations of Diabetologists by Rewarding Mentors

The panel recognized the influence leaders can have to guide students into a particular field. De-

signing a creative way to recognize and award good mentors could yield significant dividends.

New Mechanisms of Funding

Solving the Grand Challenges in Diabetes With Self-Aggregating Consortia

The panel strongly encouraged the funding of self-assembled research teams to tackle priorities identified by the type 1 diabetes community. Unlike consortia whose members are defined by the reviewing authority, this model represents a paradigm shift in the culture of collaboration and competition. Self-aggregating assemblies would identify their own research gaps and barriers and could encourage their home institutions to invest in infrastructure to promote team science.

Providing Safeguards for Academic Career Vulnerabilities With Bridge Funding

The panel identified the key points at which early-career scientists leave research for industry or private practice. Although the NIH budget may fluctuate, the future of diabetes research requires recruiting students into research by assuring available research funding. The panel proposed bridge-funding mechanisms to safeguard faculty trying to renew their first R01 grants—possibly extending grants from 5 to 7 years. Additionally, the panel suggested positions that would permit junior faculty to bridge different research labs of senior scientists from different fields and to bridge NIH intramural research with academia.

Commendation to the NIH and NIDDK in Administration of the Special Funding Program:

The panel and the voluntary diabetes advocacy organizations (ADA and JDRF) commended the efforts of the NIDDK and the NIH and CDC in assembling a major research effort in a short time frame and in an administratively streamlined fashion.

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ABBREVIATIONS AND ACRONYMS

Organizations

ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
JDRF	Juvenile Diabetes Research Foundation International
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NCMHD	National Center on Minority Health and Health Disparities
NEI	National Eye Institute
NHGRI	National Human Genome Research Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
ODS	Office of Dietary Supplements

Research Programs and URLs

ACE	Autoimmunity Centers of Excellence
AMDCC	Animal Models of Diabetic Complications Consortium http://www.amdcc.org
BCBC	Beta Cell Biology Consortium http://www.betacell.org

CIT	Clinical Islet Transplantation Consortium http://www.isletstudy.org/
DASP	Diabetes Autoantibody Standardization Program http://www.idsoc.org/committees/antibody/dasphome.html
DCCT	Diabetes Control and Complications Trial
DirecNet	Diabetes Research in Children Network http://public.direc.net/
DPT-1	Diabetes Prevention Trial—Type 1
DRCR.net	Diabetic Retinopathy Clinical Research Network http://www.drcr.net
EDIC	Epidemiology of Diabetes Interventions and Complications http://www.bsc.gwu.edu/bsc/studies/edic.html
FIND	Family Investigation of Nephropathy and Diabetes
GoKinD	Genetics of Kidneys in Diabetes Study http://www.gokind.org/access/home.html
ICRs	Islet Cell Resource Centers http://www.infosci.coh.org/icr
ITN	Immune Tolerance Network http://www.immunetolerance.org
NGSP	National Glycohemoglobin Standardization Program http://web.missouri.edu/~diabetes/ngsp
NHPCSG	Non-Human Primate Transplantation Tolerance Cooperative Study Group
SEARCH	SEARCH for Diabetes in Youth http://www.searchfordiabetes.org
T1DGC	Type 1 Diabetes Genetics Consortium http://www.t1dgc.org
T1D-RAID	Type 1 Diabetes-Rapid Access to Intervention Development http://www.niddk.nih.gov/fund/diabetesspecialfunds/T1D-RAID
TEDDY	The Environmental Determinants of Diabetes in the Young http://www.teddystudy.org
TrialNet	Type 1 Diabetes TrialNet http://www.diabetestrialnet.org
TRIGR	Trial to Reduce IDDM in the Genetically at Risk http://www.trigr.org

Other Abbreviations and Acronyms

AGE	advanced glycation endproduct
DMICC	Diabetes Mellitus Interagency Coordinating Committee
DSMB	Data and Safety Monitoring Board
EAB	External Advisory Board
FY	Fiscal Year
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
IDDM	insulin-dependent diabetes mellitus
IRB	Institutional Review Board
NMR	nuclear magnetic resonance
PI	Principal Investigator
P.L.	Public Law
RFA	Request for Applications
RFI	Request for Information
ROS	reactive oxygen species
SBIR	Small Business Innovation Research
SNP	single nucleotide polymorphism

ACKNOWLEDGEMENTS

Special appreciation is extended to the members of the expert panel of scientific and lay experts for their time and effort in reviewing the research consortia and networks supported by the Special Funding Program for Type 1 Diabetes Research. The panel's discussion of the importance of the efforts, and their recommendations for enhancing current programs and future directions in type 1 diabetes research, will be a significant guide to the NIH and CDC as they develop future initiatives. The many NIH and CDC participants are recognized for their important contributions at the meeting and during review of the summary report.

The efforts of Mary Hanlon, Ph.D., and Shefa Gordon, Ph.D., NIDDK Office of Scientific Program and Policy Analysis, in coordinating the meeting and preparing the summary report are gratefully acknowledged.

Of great assistance to the expert panel was background material on the research consortia and networks supported by the Special Funding Program. This material was provided in advance of the meeting by:

Centers for Disease Control and Prevention
National Center for Research Resources
National Eye Institute
National Institute of Allergy and Infectious Diseases
National Institute of Child Health and Human Development
National Institute of Diabetes and Digestive and Kidney Diseases