Diabetes Mellitus Interagency Coordinating Committee (DMICC) Workshop on Research Supported by the Special Statutory Funding Program for Type 1 Diabetes Research

June 6-7, 2013
Rockville, MD

Summary

INTRODUCTION

A panel of 19 scientific and lay experts from across the United States, with expertise relevant to type 1 diabetes and its complications, convened in Rockville, Maryland on June 6-7, 2013. The goal of the 2-day workshop was to obtain input from panel members on draft concepts put forth by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) for research initiatives that could be pursued with funds from the *Special Statutory Funding Program for Type 1 Diabetes Research* (*Special Diabetes Program*) in Fiscal Year (FY) 2014. Concepts were also prospectively considered for funding in FY 2015, should the *Special Diabetes Program* be renewed. Furthermore, the panel was invited to propose other ideas for new and emerging opportunities for type 1 diabetes research that could be pursued with the Special Funds. Thus, the workshop served as a key source of input to the government for informing future research directions.

Overview of the Special Program for Type 1 Diabetes Research: The *Special Diabetes Program* is a special appropriation that the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) administers on behalf of the Secretary of the U.S. Department of Health and Human Services (HHS), in collaboration with multiple NIH Institutes and Centers and the CDC. The *Special Diabetes Program* is overseen by the NIDDK, with input provided by the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC). The DMICC was created by Congress to coordinate diabetes research activities and health programs among federal agencies. By fostering coordination and collaboration across federal agencies, the DMICC has played an important role in guiding the *Special Diabetes Program*.

The *Special Diabetes Program* augments regularly appropriated funds that the NIH receives for diabetes research. Unlike regular appropriations, the Special Funds are limited in time and require renewal in law. In January 2013, the *Program* was extended for 1 year (FY 2014) at a level of $150 million per year. The *Program* provides funds for the support of a wide range of basic, pre-clinical, and clinical research on the prevention, treatment, and cure of type 1 diabetes and its complications. More information is available at the Type 1 Diabetes Research website.

Overview of Program Planning: To ensure the most scientifically productive use of the *Special Diabetes Program* funds, the NIDDK has instituted a collaborative planning process that involves the participation of most NIH Institutes and Centers; members of the DMICC; and the

two major diabetes voluntary organizations, JDRF (formerly the Juvenile Diabetes Research Foundation) and the American Diabetes Association (ADA).

Also critical to the planning process is scientific input that the NIH has garnered from diabetes researchers, the broad research community, and the public. Sources of input include a variety of scientific workshops and conferences, diabetes research strategic planning processes, and a series of planning and evaluation meetings to assess current research and future opportunities. The planning and evaluation meetings have convened panels of experts external to the NIH to provide input on research supported by the Special Funds. These meetings have been critically important to informing program planning.

Background on Workshop: In January 2013, the *Special Diabetes Program* was extended for 1 year through FY 2014. This extension provides an opportunity to support new and emerging research in type 1 diabetes and its complications. To inform decisions about how best to use the new funds, the NIDDK convened a panel of external experts to solicit input on future research directions. The Institute asked DMICC members to suggest names of possible panel members. With this input, the NIDDK invited 19 scientific and lay experts to serve on the panel. The 18 scientists had expertise in a variety of areas, including type 1 diabetes, type 2 diabetes, diabetes complications, genetics, immunology, beta cell biology, behavioral research, neurology, drug development, clinical trial design, epidemiology, and islet transplantation. A lay panel member with broad expertise in type 1 diabetes was also invited to provide important input from the patient perspective.

Because the *Special Diabetes Program* is a trans-HHS program, the NIDDK initiated a call for proposals to other DMICC member organizations for research that could be pursued in FY 2014 and/or FY 2015. Specifically, the NIDDK requested:

1. New concepts for basic, pre-clinical, or clinical research that could advance understanding of type 1 diabetes or its complications; or
2. Continuations or expansions of ongoing programs supported by the *Special Diabetes Program*. This included programs that were requesting funds to support a new funding cycle or programs that were seeking additional funds to support new activities in the current funding cycle (*e.g.*, launch of new clinical trials).

Thirty proposals, submitted by four NIH Institutes and Centers and the CDC, were presented to the panel: 24 new initiatives and six continuations or expansions of ongoing programs. Write-ups of the 30 proposals were provided to the panel members prior to the workshop.

Workshop Agenda: The workshop began with opening remarks from Dr. Griffin Rodgers, Director, NIDDK, followed by an overview of the *Special Diabetes Program* given by Dr. Judith Fradkin, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK.

The workshop was then organized around six broad topics related to type 1 diabetes research:

- Artificial Pancreas
- Autoimmune Etiology and Epidemiology
- Clinical Management
- Resources

- Diabetes Complications
- Beta Cell Biology

The submitted proposals were grouped under the relevant topic area. For each proposal, a government staff member gave a presentation to describe the concept and goals. The presentation was followed by a question and answer period and a panel discussion period. One or two panel members were assigned to serve as primary discussants for each proposal and were asked to make initial comments and moderate the discussion. After all proposals had been discussed in a topic area, the panel members engaged in an overarching discussion of the proposals, which gave them an opportunity to suggest other ideas for future research directions that could propel progress in that topic area.

At the conclusion of the workshop, the lay member gave a short presentation of her observations and suggestions, and there was a closing discussion during which panel members were asked to comment on any gaps in the overall *Special Diabetes Program* research portfolio and suggest other new and emerging areas of research that could be pursued to advance type 1 diabetes research progress.

OPENING REMARKS

Griffin P. Rodgers, M.D., M.A.C.P., Director, NIDDK, welcomed the panel and thanked them for attending this important workshop. He emphasized that though the *Special Diabetes Program* is administered by NIDDK, it involves numerous NIH Institutes and Centers as well as the CDC. He described how the *Program* is extremely important to the NIDDK and how the Institute places the highest priority on administering the funds and maximizing their value. He stated that the purpose of the workshop was to discuss how best to use new funds from the recent extension of the *Special Diabetes Program* to support research to combat type 1 diabetes and its complications. Therefore, the input provided by the panel will be critically important to the government in its planning efforts.

Overview of the *Special Diabetes Program*: Judith Fradkin, M.D., Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, thanked the panel members for participating in the workshop and provided them with an overview of the *Special Diabetes Program* (see previous Introduction section). The *Program* has been used to support large-scale, collaborative, high-risk, high-reward research consortia and clinical trials networks. The funding supplements, but does not replace, research supported by regular NIH appropriations. It is a time-limited funding stream requiring renewal in law, with the funds currently available through FY 2014. Dr. Fradkin clarified that, though *Program* funding is only currently available through FY 2014, the panel was asked to consider how funds might be used in FY 2015 as well, should the *Program* be extended.

Dr. Fradkin noted that this workshop is one of a series of planning and evaluation meetings that the NIDDK has convened to obtain external input on research supported by the *Special Diabetes Program*. Proposals that generated high levels of enthusiasm at the 2011 planning meeting, for instance, have since been awarded or will be awarded in fall of 2013. The input generated by

these planning meetings has consistently informed funding decisions and also identified gaps and emerging opportunities for type 1 diabetes research funding. For example, the input gained from previously convened meetings has resulted in new initiatives and programs to improve coordination across consortia, to expand artificial pancreas research, and to foster development of type 1 diabetes animal models, among others. The NIDDK expects that input from today's workshop will be similarly important for informing decisions about future research. In addition to planning and evaluation meetings, two strategic plans are serving as important guideposts for type 1 diabetes research: a Type 1 Diabetes Strategic Plan (2006) and a Diabetes Research Strategic Plan (2011). These Plans were developed under the auspices of the DMICC with broad input from the scientific community, patient advocacy groups, and the public.

Dr. Fradkin explained that, because the *Special Diabetes Program* is time-limited, the NIDDK has employed different management strategies for the *Program* than it uses for regular appropriations. For example, since 2009, the Program has been extended in increments of 1-2 years, but most typical research grants are 5 years in duration. Therefore, the NIH cannot fund traditional 5-year research grants with short-term funds because of the uncertainty of out-year funding. To address the challenge of supporting new, multi-year research projects with short-term funding, the NIDDK has made use of special types of grants, such as the Type 1 Diabetes Targeted Research Award. The NIDDK expects that special types of grants will also be used to support research in FY 2014 because of the uncertainty of funding beyond that fiscal year. Dr. Fradkin also reminded the panel that the sequester applies to *Program* funding as well, and thus FY14 funding levels would be reduced under sequester.

Dr. Fradkin also noted that the same set-aside requirements regarding research conducted by small businesses that apply to the NIH regular appropriation also apply to the *Special Diabetes Program* (for more information, see the NIH SBIR/STTR website). Dr. Fradkin asked the panel members to consider opportunities to utilize those funds.

DISCUSSION OF PROPOSALS

The workshop focused on discussion of 30 proposals, submitted by the NIH and CDC, for initiative concepts that could be pursued with Special Funds in FY 2014 and possibly FY 2015, should the *Program* be continued. The panel members had enthusiasm for 23 of the proposals—either as presented or with enhancements—and thought these proposals were of high scientific merit. Those 23 proposals are described below, grouped under the relevant topic area.

TOPIC 1: ARTIFICIAL PANCREAS

Current Efforts Toward an Artificial Pancreas

Dr. Fradkin provided an overview of the current research portfolio related to development of artificial pancreas technology. A broad Request for Applications (RFA) in 2012 resulted in funding one Type 1 Diabetes Impact Award, and three projects to develop new therapeutics and monitoring technologies were funded via SBIR awards. In addition, two RFAs that were endorsed by a previous expert panel are currently accepting applications. One is focused on clinical and behavioral research related to the use of closed-loop technologies, and another is focused on developing and integrating novel components for automated artificial pancreas systems. There is also one active SBIR Funding Opportunity Announcement (FOA) for FY 2013. Dr. Fradkin pointed out that many artificial pancreas projects previously funded through the Special Diabetes Program have been completed or are in their final year, so there is opportunity to support new and emerging research in this field.

Type 1 Diabetes-Impact Awards on the Development of an Artificial Pancreas: Expansion of Support for the Testing of Current Novel Closed-Loop Systems Through Clinical, Behavioral, and Physiological Studies

Primary discussant: Dr. Robert Sherwin

New technologies for monitoring blood glucose, which provide detailed information about daily glucose patterns, are already in clinical use and are steadily improving in terms of ease of use and accuracy. Together with integrated insulin delivery systems, these monitoring devices may represent the next generation in type 1 diabetes management. Furthermore, telemedicine platforms with remote monitoring capacity through portable miniaturized devices are quickly evolving. These emerging and next-generation technologies require further translation research to evaluate and improve their safety, accuracy, and efficacy as research progresses from animal and simulated models to human trials. It is therefore important to stimulate additional collaborative research to clinically test current and new technologies in order to optimize their operability, taking into consideration patient preferences and behavioral and physiological factors, to achieve the goal of viable, functionally-integrated, closed-loop systems for routine use.

This initiative will expand and extend ongoing research supported through the previously released NIDDK artificial pancreas FOAs, DirecNet (led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD]), JDRF, and industry. New projects supported through this initiative will build on the ongoing work and provide support for testing of improved devices and integrative technologies and for new approaches to the use and integration of these devices. Research would be sought in three key areas: a) clinical/behavioral research focused on enhancing the application of new technology for glucose sensing and insulin delivery to improve glucose control and reduce hypoglycemia/hypoglycemia unawareness in people with diabetes; b) studies that use new technologies to better understand physiological mechanisms affecting glucose control in type 1 diabetes; and c) research to test and improve the efficacy, safety, accuracy, and reliability of these new technologies in humans in inpatient and outpatient settings. Long-term research goals include improved metabolic control

with decreased glycemic excursions, prevention of acute and chronic complications, and improved quality-of-life in people with diabetes.

The panel was enthusiastic in its support of artificial pancreas research, identifying this area as having great potential to significantly affect patient care in a short timeframe with a relatively small investment. The panel supported modest, focused clinical studies testing state-of-the-art artificial pancreas technologies in real-world situations. Such trials could be performed by a small, multi-center consortium. A particular need in these trials would be to investigate what real-world challenges exist to adoption of artificial pancreas technology by healthy people with type 1 diabetes. Data from such trials is expected to drive further innovation in the artificial pancreas field.

Towards an Artificial Pancreas: Expansion of Support for Research to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes
Primary discussant: Dr. Edward Damiano

Despite the availability of increasingly effective treatment modalities, including insulin analogues, continuous glucose monitors, and continuous subcutaneous insulin infusion devices, a substantial proportion of people with type 1 diabetes cannot achieve adequate glycemic control or avoid acute complications such as hypoglycemia. NIDDK has long supported research in this field, especially through small business projects, and this support has contributed substantially to the development of new, approved devices that are increasingly widely used in clinical practice. Nonetheless, the approved devices and current technologies have many limitations, and it is important to put renewed emphasis on the creation of the next generation of devices that will further the goals of relieving patients of the burden of diabetes self-management and achieving good blood glucose control to prevent acute and chronic complications.

This initiative is intended to stimulate and support innovative research on novel technologies that may lead to the development or optimization of a portable, personalized, automated closed-loop/artificial pancreas system for more efficient metabolic control of diabetes. The goal is to stimulate bioengineers in academic centers and industry to develop new approaches to creating devices with enhanced accuracy and less patient burden that will represent improvements in the safety and effectiveness of currently available technology. It is important to stimulate collaborative research that may generate new technologies or optimize the operability of current systems in order to achieve the goal of clinically viable, functionally integrated closed-loop systems.

The panel saw this proposed program as a valuable contribution to the health of those with type 1 diabetes. The panel acknowledged the SBIR/STTR program's success in stimulating innovation and investment in this area by small businesses. This innovation then incentivizes larger companies to invest in cutting-edge technology and drives the field forward. The panel agreed that, though great advances in glucose sensor technology have been made, improvements would be welcome. Other identified areas where technological innovation could be stimulated were stable, pumpable glucagon formulations, rescue treatments for severe hypoglycemia, and point of care glucose monitors for use in artificial pancreas calibration.

TOPIC 2: AUTOIMMUNE ETIOLOGY AND EPIDEMIOLOGY

Current Efforts in Autoimmune Etiology and Epidemiology

Dr. Fradkin provided an overview of the current autoimmune etiology and epidemiology research portfolio, including discussion of programs that will be funded through non-competing commitments, such as the National Institute of Allergy and Infectious Disease (NIAID)'s Cooperative Study Group for Autoimmune Disease Prevention and NICHD's ongoing clinical Trial to Reduce IDDM in the Genetically at Risk (TRIGR). The Special Diabetes Program also funds grants focusing on the function of type 1 diabetes-associated HLA (human leukocyte antigen) genes, as well as Type 1 Diabetes Impact Awards related to autoimmune etiology and epidemiology. The "Research Using Subjects from the Type 1 Diabetes TrialNet Natural History Study" and "Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies" RFAs are also currently supporting awards, and proposals put forward below call for re-issue of these two RFAs.

Function of Non-MHC (Major Histocompatibility Complex) Loci for Type 1 Diabetes

Primary discussants: Dr. Jeffrey Bluestone and Dr. Rudolph Leibel

Type 1 diabetes is a polygenic disease involving multiple genes as well as environmental components. Previous research has made type 1 diabetes unique among polygenic diseases in that researchers have identified the genes or gene regions accounting for approximately 75 percent of the genetic risk. It is estimated that the highly polymorphic HLA MHC class II molecules are central to susceptibility to type 1 diabetes and contribute 40-50 percent of the risk. However, candidate gene studies carried out by the *Special Diabetes Program*-supported Type 1 Diabetes Genetics Consortium and other researchers have identified over 40 non-MHC loci significantly associated with the disease. Further analysis of the predicted functional impact of these loci has suggested that they encode molecules involved in lymphocyte activation and signaling and in the release of, and response to, cytokines such as *IL2RA*, *IL10*, and *IL27*. The functional mechanism of other non-MHC, type 1 diabetes-associated genes are not yet defined. Additional research is needed to identify the mechanism of these non-MHC loci's effect on type 1 diabetes risk.

This initiative would support research to determine the function of type 1 diabetes-associated non-HLA loci and to study the mechanism of how these loci and their encoded genes confer disease risk. This research may reveal pathways involved in the earliest pathogenic mechanisms of type 1 diabetes and elucidate how innate and adaptive immune systems are engaged to produce massive beta cell destruction and clinical disease. Such insights could provide leads for new therapeutic targets and further the development of genetic tests to predict who may develop type 1 diabetes and to personalize drug treatment regimens.

The panel recognized the importance of learning more about this topic, particularly as much effort has been invested in identifying these loci and little is known about their function. These loci also include some beta cell genes, and further study of these genes could reveal overlapping susceptibility factors for both major forms of diabetes. Additionally, non-MHC loci may hold the key to understanding why certain immunotherapy drugs treat some autoimmune diseases but not others, and identifying the function of these loci might aid in predicting which

immunotherapies could successfully treat type 1 diabetes. These studies will require a more focused, concerted effort—as suggested by this initiative—than standard genome-wide association studies. The panel acknowledged that study of identified non-MHC loci might be an important, though long-term, investment.

The Environmental Determinants of Diabetes in the Young (TEDDY)
Primary discussant: Dr. Jeffrey Bluestone

TEDDY, an ongoing program led by NIDDK, was established to develop and carry out studies to identify environmental triggers of type 1 diabetes, such as infectious agents, dietary factors, and/or psychosocial factors, in genetically susceptible individuals. Identification of such factors will lead to a better understanding of disease etiology and pathogenesis and result in new strategies to prevent, delay, or reverse type 1 diabetes. TEDDY has completed recruitment of over 8,000 participants, and the study will follow them for 15 years, which is predicted to lead to approximately 800 children developing autoantibodies and 400 children developing diabetes within the timeframe. As of March 2013, 460 children reached the primary endpoint (*i.e.*, appearance of one or more islet autoantibodies), and 117 children reached the second primary outcome (*i.e.*, development of type 1 diabetes).

Over 2 million prospectively collected specimens (DNA, RNA, serum, plasma, cells, and other samples) have been collected from TEDDY participants. These specimens provide a unique opportunity for scientists within and outside the TEDDY consortium to test novel hypotheses by performing otherwise impossible critical studies, and both humoral and cellular assays can be applied to sample sets from TEDDY children followed longitudinally from 3 months of age. This new initiative would support the TEDDY study in its main goal to identify environmental factors that predispose to or protect from beta cell autoimmunity and type 1diabetes. Specifically, the initiative would support the use of immunological assays to investigate the links between environmental exposures, genotype, immunological responses (cellular, humoral, or both), beta cell autoimmunity, and/or type 1 diabetes progression. Such questions may include (but are not limited to) how environmental factors influence children's immune status, whether certain immunological profiles predict beta cell autoimmunity and subsequent progression to type 1 diabetes, and whether children with different risk genotypes have altered immune profiles that may affect their risk of progression to diabetes.

The panel agreed that the TEDDY samples are a resource with great promise to support studies of type 1 diabetes onset and progression. However, it was also noted that this sample set is an irreplaceable resource, and discussion focused on how to best capitalize on the TEDDY archive and gain the most out of limited samples. The panel agreed that any use of TEDDY samples should be highly coordinated and ideally involve parallel studies of a single thawed sample. Concerns were raised about whether current FACS (fluorescence-activated cell sorting) technology could work efficiently with small sample sizes, whether control samples would be overburdened, and whether knowledge of type 1 diabetes onset was sufficient to generate the best hypotheses to interrogate the TEDDY sample archive. The panel also noted, however, that TEDDY samples might lose their viability over time and that the sample set must not become a "museum" that is never used for lack of the perfect hypothesis. The panel suggested that projects using the TEDDY samples be solidly hypothesis-driven and rigorously selected to reveal the most data possible from the limited samples available.

Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies
Primary discussants: Dr. Megan Sykes

NIDDK is committed to providing access to research resources including biosamples, repositories, and databases from NIDDK-supported type 1 diabetes clinical trials. Biosamples archived in the NIDDK Central Repository and those held by consortia include those from the Diabetes Prevention Trial-Type 1 (DPT-1), Genetics of Kidneys in Diabetes study, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), and Type 1 Diabetes TrialNet. Samples are also available from the SEARCH for Diabetes in Youth Study funded by the CDC and NIDDK, and plans are being developed to make available selected samples from Immune Tolerance Network studies, Clinical Islet Transplant Consortium studies, and from the Network for Pancreatic Organ Donors with Diabetes (nPOD) collections. There have been three prior versions of this proposed initiative which have garnered high-quality applications, and additional studies have expressed interest in participating. Additionally, new samples from completed type 1 diabetes trials and from continuing observational studies expand the collections and offer new insight regarding the full spectrum of autoimmunity and/or complications. In addition, new assays are constantly being developed, and discoveries in the basic science of type 1 diabetes and its complications and of other autoimmune diseases continually result in new testable hypotheses.

This initiative would support ancillary studies using archived, non-renewable (non-DNA) samples from participating type 1 diabetes clinical trials and studies, such as those listed above. Ancillary studies are expected to generate scientific discoveries on the primary pathogenesis of type 1 diabetes, pathogenesis of complications, and/or biomarkers of disease progression or clinical responses to interventions. Projects that plan to identify biomarkers of clinical response to therapy in new-onset type 1 diabetes studies, as well as progression to disease in prevention or natural history studies, would be highly encouraged. Identification of biomarkers that can be used as surrogate endpoints in clinical trials is a major goal of this program. Projects that aim to identify diabetes risk at early stages, and imminent clinical onset of disease at later stages, would also be important to pursue.

There was significant enthusiasm for this initiative. The panel reiterated that the original study personnel should be prepared to provide patient phenotypic information to facilitate patient selection and asked for clarification about how projects would be selected. It was also pointed out that the studies included in this initiative provide, through TrialNet, older children and relatives of those with type 1 diabetes, in comparison to TEDDY, which enrolls younger children and also screens the general population. In addition, NIDDK Central Repository samples offer the opportunity to interrogate samples obtained during a particular intervention or perturbation of the immune system. The panel suggested that the scientific community be educated (perhaps through a webinar or workshop) about the sample sets available to them through this initiative so that they might make informed choices about study sample selection. Such education might aid in attracting young investigators and researchers outside of the type 1 diabetes field.

Research Using Subjects from Selected Type 1 Diabetes Clinical Studies (Living Biobank)
Primary discussant: Dr. R. John Looney

The NIDDK seeks to accelerate the pace of scientific research toward more effective prevention, treatment, and cure of type 1 diabetes and its complications. To this end, NIDDK is committed to providing access to research resources that will increase understanding of type 1 diabetes pathogenesis, and pathogenesis of its complications, in humans. The Type 1 Diabetes TrialNet Pathway to Prevention study and DCCT/EDIC have phenotypically and genetically characterized people at risk for developing type 1 diabetes. Opportunities to access these persons have been offered previously—most recently through an FOA with an April 2013 receipt date. Two awards have been made to date, but many applications were promising, and there is a strong need for additional opportunities.

This initiative would provide a means to access and perform ancillary studies using the unique at-risk population enrolled in the Type 1 Diabetes TrialNet Pathway to Prevention study OR the unique population being followed in DCCT/EDIC. Mechanistic studies can be cross-sectional or longitudinal. Applicants may propose to perform tests on participants and/or collect samples "on demand" at regularly scheduled visits. Access to Pathway to Prevention study participants for mechanistic studies that may require some brief and safe intervention may also be proposed. Studies are expected to generate scientific discoveries on disease mechanisms, pathogenic processes, and biomarkers of disease progression, clinical responses, or type 1 diabetes complications.

The panel supported the open sharing of patient access and believed that this initiative represented a tremendous resource to the research community. The panel observed that there are other living biobanks available, though these other biobanks do not include at-risk individuals as TrialNet does. Lack of cross-talk between registries and biobanks (living and otherwise) was discussed, and more such cross-talk was encouraged to reduce duplication and to allow researchers to easily identify and utilize resources from multiple biobanks. Panel members suggested that perhaps the Living Biobank and Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies initiatives could be merged to allow researchers access to both archived and fresh samples via the same application. Such a merging of initiatives would allow study of diabetes pathogenesis in addition to risk factors.

Type 1 Diabetes TrialNet
Primary discussants: Dr. R. John Looney and Dr. Ronald Gill

The ongoing Type 1 Diabetes TrialNet, led by the NIDDK, is an international consortium of clinical research centers focused on the delay and prevention of type 1 diabetes. TrialNet has created an extensive network of experienced sites capable of screening large numbers of relatives of people with type 1 diabetes as a source of participants for prevention trials, and the Network is currently screening at least 15,000 people per year. In addition, TrialNet has spearheaded clinical trials for type 1 diabetes prevention in relatives of people with the disease, as well as for beta cell preservation in new-onset patients. Among its accomplishments, TrialNet has determined that the drugs rituximab (which targets B lymphocytes) and abatacept (which inhibits T cell costimulation) slow progression of type 1 diabetes in the newly diagnosed. TrialNet is currently conducting three ongoing prevention trials, with another in active development. TrialNet also conducts studies to optimize the conduct of type 1 diabetes trials and to gain a mechanistic understanding of tested interventions.

The aim of this initiative is to optimize TrialNet's risk screening performance and cost efficiency by establishing a TrialNet Clinical Network Hub to centralize and support selected activities at TrialNet Clinical Centers and Affiliate Sites. The Hub will, among other responsibilities, develop a coordinated program to enhance screening and recruitment, ensure consistency in clinical operations across sites, and provide centralized oversight in various areas, including a centralized institutional review board. The major goal of this organizational change is to increase productive screening rates, streamline decision-making processes, improve collaboration, and make TrialNet's clinical activities more consistent, efficient, and effective. This initiative also aims to improve TrialNet by increasing the geographical distribution of Centers and thus reducing patient burden. Finally, the initiative aims to provide support to the existing TrialNet Coordinating Center for performance of a prevention study in single autoantibody-positive relatives of individuals with type 1 diabetes. TrialNet currently is following a large number of single autoantibody-positive individuals, but no trials currently target those individuals. This initiative would enable the conduct of a prevention trial in this population using *Tichuris suis* ova.

The panel encouraged the proposed goal of increasing efficiency of screening among sites and also encouraged TrialNet to prioritize, propose, and perform mechanistic studies to capitalize on the screened TrialNet population. Additionally, the panel recognized that although TrialNet has been productive in screening, the percentage of screened individuals eligible for trials is very low and that more screening is required to fill the pipeline with participants for trials of promising treatments. The panel also discussed the importance of framing in the request to participate in a clinical trial, as there could be multiple psychological and sociological barriers that often need to be overcome. Also mentioned was the fact that not being able to choose what arm of a trial a participant will be in can be a significant obstacle, especially to parents of children with type 1 diabetes, and especially if the intervention is expected to have side effects. The expert panel further recognized that there is a currently untapped opportunity for prevention trials focusing on those who are single autoantibody-positive. Having trials available in which single autoantibody-positive people could enroll is an important step toward taking full advantage of the Pathway to Prevention population, particularly since there is typically only a small window of opportunity when a person will remain single autoantibody-positive before progressing to being multi-autoantibody-positive or diabetic.

Treatment of Silent Type 1 Diabetes
Primary discussant: Dr. Robert Sherwin

The screening and follow-up of people at risk for type 1 diabetes in international studies such as TrialNet, TRIGR, and TEDDY has led to the identification of people with disease onset (based on an oral glucose tolerance test [OGTT] in the diabetic range) prior to symptomatic hyperglycemia. These individuals with "silent" type 1 diabetes also have significantly lower insulin resistance compared to those with symptomatic disease. These data suggest that silent type 1 diabetes could be an intermediate step on the path to symptomatic diabetes and thereby could be an opportunity to slow or reverse disease progression. Silent diabetes presents a therapeutic challenge, however, because the use of standard intensive insulin therapy, with its associated risks, is not uniformly accepted at this stage of disease. When early type 1 diabetes is detected in asymptomatic people (especially children), many endocrinologists withhold therapy unless and until there are symptoms such as clear-cut fasting hyperglycemia or increasing

hemoglobin A1C (HbA1C) levels. Thus, there is a compelling need to test whether there is a relative benefit to intensive versus "wait and see" treatment approaches and to determine what therapeutic choices can be offered to asymptomatic patients to slow beta cell loss and development of insulin resistance. Furthermore, studies of those with silent diabetes, who may have greater beta cell reserves, may offer unique opportunities to test beta cell preservation strategies that have proven less effective in those with more advanced, symptomatic disease.

The research goals of this initiative would be to develop therapies for cases of "silent" type 1 diabetes and test the associated mechanism of these therapies, possibly studying people with silent diabetes in TrialNet, TRIGR, and TEDDY. Possible projects include but are not limited to:

- Comparison of insulin versus other treatments (*e.g.*, lifestyle, metformin, incretins, or other agents) on time to elevated fasting glucose, HbA1C, or C-peptide preservation;
- Treatment studies with a focus on understanding the variables that determine progression; and
- Trials of immunomodulatory agents proven effective in preserving C-peptide with a focus on assessing clinically meaningful preservation or restoration of beta cell function.

The panel acknowledged that there is a knowledge gap about how to treat those presenting an abnormal OGTT result but no other symptoms. Also, the silent diabetes stage might be a powerful time to intervene and halt diabetes progression. Panel members further suggested several questions that need to be addressed in this population, including how much residual beta function remains and whether promising beta cell modulator treatments might have more prominent effects in those with more remaining beta cells. Another suggestion was to alter the inclusion criteria for TrialNet to allow this silent diabetes population to enroll in existing trials. However, there were concerns about the lack of consensus on how silent diabetes could be defined and about what studies could be constructed to effectively utilize this relatively small patient population. The panel encouraged organization of a meeting or workshop to discuss these issues, before a new initiative is pursued.

Immune Tolerance Network
Primary discussants: Dr. John Buse and Dr. R. John Looney

The ongoing Immune Tolerance Network (ITN), led by NIAID, is an international consortium dedicated to advancement of tolerance-inducing therapies for the treatment of autoimmune diseases, asthma, and allergic diseases, and for the prevention of graft rejection following kidney, liver, and pancreatic islet transplantation. The ITN develops and conducts phase I-III clinical trials of novel tolerance strategies that investigate safety and efficacy, as well as the basic biological features and potential biomarkers of tolerance through mechanistic studies integrated into each trial. Among its type 1 diabetes-related accomplishments, ITN completed the first multicenter clinical trial of islet transplantation, paving the way for other islet consortia studies now in progress. In addition, ITN continues to conduct trials to advance anti-T cell therapeutics for treatment of new-onset type 1 diabetes.

The proposal requested support for the ITN, which would enable design and implementation of 1-2 type 1 diabetes clinical trials per year. These clinical trials would include single or combination therapies (including cell-based therapies) to slow autoimmune destruction of beta

cells. There is an emerging consensus that durable responses and re-establishment of immunologic tolerance in type 1 diabetes will require combination therapies that target more than one arm of the dysregulated immune system. One such promising combination is teplizumab and rilonacept, which would combine a T cell-directed therapy with an agent that blocks inflammatory responses. This combination may favor the restoration of a favorable T cell balance. The first proposed study of teplizumab and rilonacept will test whether the drug combination can preserve remaining beta cells in individuals recently diagnosed with type 1 diabetes.

The ITN was acknowledged for its unique efforts and successes in testing tolerance strategies, as were the NIAID's contributions to the program. The panel agreed that combination therapies are the next logical step in type 1 diabetes immunotherapy and that there are many possible agents that could be tested in combination. However, there is limited data available about the safety issues involved in combining biological agents. The panel believed that the ITN's choice of teplizumab and rilonacept was reasonable, but stressed that combination immunotherapies are usually most effective when they have shown some efficacy when administered separately. Another suggestion was to test combination biologic therapy with islet transplantation in an attempt to functionally cure diabetes, rather than to simply re-establish tolerance in patients who might not have any beta cell function remaining.

Search for Diabetes in Youth
Primary discussants: Dr. Robert Eckel and Dr. James Neaton

SEARCH is an ongoing multi-center epidemiological study conducted in geographically dispersed and racially/ethnically diverse populations in the United States. The study aims to identify the number of children and youth under age 20 who have type 1 or type 2 diabetes; examine how the two forms of the disease differ, including how they differ by age and race/ethnicity; learn more about the risk for acute and chronic complications of diabetes; investigate the different types of care and medical treatment received; and learn more about how diabetes affects the daily lives of children and youth in the United States. SEARCH has already provided estimates of type 1 diabetes burden, and ongoing assessment of incidence from 2002 to 2014 will allow SEARCH to be uniquely positioned to estimate trends in type 1 diabetes incidence among American youth, including among minority groups. In addition, SEARCH is poised to explore whether temporal trends in type 1 diabetes incidence are associated with genetic, biological, or immunological factors and whether severity of type 1 diabetes onset is changing over time. These findings could lead to the development of novel etiologic hypotheses.

This initiative would continue to support SEARCH enrollment and data collection, including enrollment and a patient survey for incident cases in 2015-2018 and in-person visits for 2015-2017 incident cases; ongoing ascertainment of incident cases is needed to establish trends in incidence. Prevalence would also be assessed in 2015 by age, sex, race/ethnicity, and diabetes type, an assessment which has not been done since 2009 and which is continuously needed for health care delivery planning and to identify high-risk groups. Other possible efforts would be to expand surveillance of racial/ethnic groups already under study or of groups (*e.g.*, those of Puerto Rican descent or additional American Indian tribes) or geographic regions (*e.g.*, U.S. Northeast) not well-represented in SEARCH. SEARCH will also continue evaluating and improving criteria for diabetes case classification to simplify surveillance. Additionally, possible

studies could include conducting a follow-up visit for the 2012 incident cohort or expanding prospective follow-up of type 1 diabetes youth (including minority youth). Such an expansion of follow-up could study risk factors for and natural history of micro- and macrovascular complications, occurrence of acute complications, and sub-clinical vascular abnormalities. Addition of a non-diabetic control group could allow comparison of the natural history of subclinical vascular abnormalities in those with and without diabetes.

Since SEARCH is the only effort in the United States that provides incidence data on type 1 diabetes, it was lauded by the panel for providing invaluable information and laying the groundwork for future studies. SEARCH's ancillary studies are extremely valuable to identify the incidence of complications in this population, and the panel encouraged further studies on complications such as neuropathy, on the interactions between obesity and islet failure, and on what types of interventions work in high- and low-prevalence localities. The panel was also concerned about the misdiagnosis of diabetes in children, both of obese children with type 1 diabetes who are assumed to have type 2 diabetes, and the inclusion in SEARCH of children with type 2 diabetes misdiagnosed as type 1 diabetes. Additionally, the panel encouraged follow-up of SEARCH enrollees to identify children with insulin resistance that developed after puberty. Overall, the panel was extremely enthusiastic about continuing support for SEARCH and its ancillary studies.

TOPIC 3: CLINICAL MANAGEMENT

Current Efforts in Type 1 Diabetes Clinical Management

Dr. Fradkin provided an overview of the current research portfolio related to clinical management of type 1 diabetes. For example, the NIDDK supports an initiative on Clinical Trials in Type 1 Diabetes to test interventions to improve clinical management of type 1 diabetes across the lifespan by improving glycemic control and/or treating or reducing diabetes complications. Two planning grants were awarded to support administrative study group activities that are required to begin recruitment of participants; one of these planning grants related to behavioral research to improve outcomes for youth with type 1 diabetes, and that project is eligible to apply for full trial funding in response to RFA-DK-12-511 (Limited Competition for Clinical Trials in Type 1 Diabetes). In addition, the NIDDK supports investigator-initiated grants through an initiative on Improving Adherence in Pre-Teens, Adolescents, and Young Adults with Type 1 Diabetes (RFA-DK-11-029).

Improving Adherence in Young Children with Type 1 Diabetes

Primary discussant: Dr. Georgeanna Klingensmith

Diagnosis and management of type 1 diabetes can be a highly stressful experience for parents of young children. Treatment regimens for tight glucose control can be especially challenging for very young children and their families. For example, smaller insulin doses can be more challenging to calculate, and young children are more susceptible to hypoglycemia, particularly at night. Additionally, parents of young children with type 1 diabetes often report stress related to constant vigilance and fear of hypoglycemia, difficulty differentiating between diabetes-related symptoms and normal behavior, disrupted sleep schedules due to nocturnal blood glucose testing, fear/challenges in leaving the child with other caregivers, and feelings of anxiety and/or

depressed mood associated with caring for a child with type 1 diabetes. Given these unique challenges of managing type 1 diabetes in young children, there is a need to develop innovative and effective interventions to better help families manage diabetes and maintain good quality of life.

The goal of this initiative is to support research to develop, refine, and pilot test innovative strategies to improve adherence to treatment in young children with type 1 diabetes (5 years old and under). At the end of the funding period, the goal is to have well-developed and well-characterized intervention(s) that have been demonstrated to be safe, feasible to implement, effective, acceptable in the target population, and ready to be tested in a larger efficacy trial.

The panel supported this initiative, as there has been little research done studying adherence in young children with type 1 diabetes. They noted that the research needs to focus on the parents (and in most cases the mother) as primary caregivers, since young children cannot manage their own disease. The panel also suggested that this research be influenced by the broader field of developmental psychology research on children in this age range. Finally, it could be beneficial to examine ways to help families utilize new and emerging technologies to manage their child's type 1 diabetes.

Understanding Barriers and Facilitators to Type 1 Diabetes Management in Adults
Primary discussant: Dr. John Buse

Most of the observational and intervention research on diabetes self-management in type 1 diabetes has been conducted in youth. Data that exist about diabetes self-management in adults is often in mixed samples of individuals with type 2 and type 1 diabetes without adequate power to detect unique factors related to managing type 1 diabetes. Without a better understanding of the barriers and facilitators for good self-management in adults, it is difficult to develop treatment approaches that are tailored to specific risk factors or high-risk groups.

The goal of this initiative is to support research designed to elucidate the factors (*e.g.*, social, economic, environmental, behavioral, emotional) that influence diabetes self-management, in a positive or harmful way, in adults. This research could help to identify barriers and facilitators to good diabetes self-management in adults with type 1 diabetes. Factors associated with poor adherence in adults could be possible targets for intervention.

The panel acknowledged this area as an important research gap that should be addressed, given the lack of studies in adult populations. They stressed the need to strongly encourage applicants to pursue longitudinal, rather than cross-sectional, studies. They also suggested considering ways to partner with the Type 1 Diabetes Exchange, which includes a clinic registry of over 26,000 people of all ages with type 1 diabetes.

TOPIC 4: RESOURCES

Current Efforts in Research Resources
Dr. Fradkin provided an overview of the current research portfolio related to research resources. For example, the NIDDK supports training and career development programs for bioengineers

and pediatric endocrinologists pursuing diabetes research. The Institute also supports an Integrated Islet Distribution Program, which processes and distributes high-quality human cadaveric islets to scientists to use for basic diabetes research, and the Type 1 Diabetes Mouse Resource, which distributes mouse models important to type 1 diabetes research to the broad community. The NIDDK Central Repositories store data and biological samples from NIDDK-funded clinical studies, including several type 1 diabetes studies.

Harvesting the Neuroimaging Cornucopia for Pancreatic Islet Imaging Reagents
Primary discussant: Dr. Ronald Gill

Biomarkers for human islet cell mass, especially the beta cell, remains an important goal in order to elucidate the natural history of diabetes and monitor therapy. The goal remains elusive due to large differences between animal models and humans, the current dearth of beta cell-specific imaging targets, and the difficulty and expense of developing radiochemicals for human use. However, there are many hundreds of existing reagents with investigational new drug (IND) applications that have been designed for imaging the human brain and which target pathways present in the islet, specifically in the beta cell, suggesting they could be used to image the beta cell.

This new initiative would build on ongoing research in neuroimaging PET (positive emission tomography) probes. It would provide funding to PET Centers with a high volume of human neuroimaging studies and access to a large selection of imaging agents and allow PET center personnel to quickly screen the pancreas in people already undergoing various PET brain studies. This approach would be used as a screen to identify agents with the highest likelihood of success, leveraging the investment already being made in the brain imaging studies. Promising agents could then be further developed to image islet cell mass, function, or disease state.

The panel felt that using this type of approach to leverage ongoing neuroimaging research was a feasible and efficient way to possibly move forward the islet imaging field and thus endorsed the new initiative. The pancreatic imaging would require additional consent from the patient, but the panel thought that could be addressed fairly easily by the Centers conducting the studies. They stated that an important question remains as to whether beta cell mass correlates with beta cell function, and that question could be addressed with progress in islet imaging.

Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID)
Primary discussant: Dr. Ronald Gill

The T1D-RAID program is designed to assist translation from the research bench to the clinic of novel therapeutic interventions for type 1 diabetes and its complications. T1D-RAID helps bridge the gap by providing access to contract resources to address the most common barriers between laboratory discoveries and clinical trials of new molecular entities. This facilitates efficient translation of promising discoveries even in the absence of pre-clinical development capacity in the organization where the discovery was made. T1D-RAID does not sponsor clinical trials; it sponsors the work needed to get ready to do clinical trials.

The T1D-RAID program currently supports three projects and has another recently positively reviewed agent in queue. Special Funds are requested to continue to support the ongoing

projects. The longer-term goal of the program is to restructure to better leverage the current translational activities occurring across the NIH. Therefore, no new applications are currently being accepted.

The panel thought that it was important for the NIH to provide resources to assist scientists with translational research, including for type 1 diabetes. However, in moving forward, they agreed with NIDDK's plans for determining how best to fit type 1 diabetes into the broader NIH translational research landscape, especially in light of the creation of the new National Center for Advancing Translational Sciences (NCATS). They also suggested giving thought to what projects needed NIH support versus projects that would be done by the private sector (*e.g.*, development of difficult formulations of compounds, which may not be done by contract organizations), in order to prioritize projects to support with limited funding.

TOPIC 5: DIABETES COMPLICATIONS

Current Efforts in Diabetes Complications

Dr. Fradkin provided an overview of the current research portfolio related to diabetes complications. The NIDDK supports the Diabetes Complications Consortium, which provides an environment to foster communication and collaboration between investigator communities involved in complications research. The Institute also supports an initiative on Clinical Trials in Type 1 Diabetes to test interventions to improve clinical management of type 1 diabetes across the lifespan by improving glycemic control and/or treating or reducing diabetes complications. Two planning grants were awarded to support administrative study group activities that are required to begin recruitment of participants; one of the planning grants related to diabetes complications, and that project is eligible to apply for full trial funding in response to RFA-DK-12-511 (Limited Competition for Clinical Trials in Type 1 Diabetes). There are also ongoing, investigator-initiated grants related to diabetes complications that have been funded through the following initiatives: Type 1 Diabetes Impact Award (RFA-DK-10-012) and Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies (PAR-11-350).

Biomarkers for Type 1 Diabetes Complications through Imaging the Eye

Primary discussant: Dr. John Penn

A major obstacle for the development of therapies for type 1 diabetes complications is the paucity of validated biomarkers for detecting the early, reversible stages of complications and for measuring the response to interventions in clinical trials. Imaging of the blood vessels in the retina and the nerves in the cornea offers the opportunity to visualize directly the development of diabetes complications in the eye and to provide a marker of complications in other tissues. A workshop, sponsored by NIDDK, the National Eye Institute (NEI), JDRF, and the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium was held in October 2011. The presentations and panel discussions at the workshop highlighted the technologic advances in imaging and image analysis that now allow visualization of molecules and quantitation of vascular and nerve patterns. In many cases, these tools have not been applied to diabetes complications, so one goal of this initiative is to attract investigators to the field of diabetes complications.

The new initiative aims to develop non-invasive or minimally invasive biomarkers for diabetes complications that use visualization of the nerves and vessels of the eye. The initiative would support human studies, as well as pre-clinical research with high potential to be translated to human studies.

The panel was enthusiastic about this initiative and optimistic that it could make a short-term impact on the diabetes complications research field. One example cited was that there is currently a dearth of basic and clinical research in diabetic neuropathy, in part because of a lack of biomarkers. Thus, identification of new biomarkers could potentially stimulate progress in this area. The panel also felt that NIDDK should consider supporting the research through a consortium mechanism or employ strategies to ensure that funded researchers communicate regularly. They said that researchers with varying expertise (*e.g.*, vascular biology, physiology, molecular biology) are needed to realize progress in this area, but they do not often interact at their academic institutions, so this effort would be an excellent opportunity to bring these groups together to tackle an important research topic.

Type 1 Diabetes Impact Awards in Diabetic Complications Research
Primary discussant: Dr. Ann Marie Schmidt

This new initiative builds on a successful initiative supported by the NIDDK in 2011 for Type 1 Diabetes Impact Awards. In that effort, applications were solicited in four areas, one of which was diabetes complications. Out of 111 submissions, over half were focused on diabetic complications. Ultimately, five complications-oriented grants were funded. This robust response, coupled with subsequent community input from multiple NIDDK-sponsored workshops and strategic planning exercises, suggests a continuing unmet demand for investigator-initiated high-risk, high-reward projects in the area of diabetes complications.

The proposed new initiative is to support Impact Awards focused solely on diabetes complications. The goal is to solicit research projects proposing ground-breaking studies that address fundamental questions or major obstacles in type 1 diabetes complications research. Of particular interest will be studies that challenge current dogma or address a clear and compelling need. The initiative is designed to provide an avenue for submission of highly innovative and/or hypothesis-generating studies that are difficult to support with standard NIH grant mechanisms, such as the R01.

The panel thought that this initiative was a good way to support high-risk, high-reward research on diabetes complications. They also noted that for the past solicitation, an added benefit was attracting new talent to complications research, so it is hoped that the new initiative would do the same. They cautioned that the initiative should not support research that would normally be funded through the regular R01 funding mechanism, but rather support transformative projects that could make a major impact on the complications field. Another suggestion was to encourage studies on the long-term effects of type 1 diabetes treatment on neurocognition by partnering neurologists with endocrinologists.

Small Business Innovation Research to Develop New Diagnostic, Monitoring, and Therapeutic Technologies for the Complications of Type 1 Diabetes
Primary discussant: Dr. Matthew Breyer

Diabetes impairs quality of life and shortens lifespan primarily through premature cardiovascular mortality, peripheral/central/autonomic neuropathy, nephropathy, retinopathy, and wound healing compromise. In addition to its devastating toll in human suffering, type 1 diabetes and its complications result in significant health care expenditures for families and constitute a major societal economic burden. New emphasis is needed on novel and more effective biomarkers, therapies, and technologies based on current scientific advances that may be developed as commercial products by the biotech/small business sector.

This new initiative would stimulate and support innovative research by small business concerns for the development of biomarkers, therapies, and technologies for the early diagnosis, monitoring, and treatment of micro- and macrovascular complications of type 1 diabetes. A goal of this initiative is to stimulate basic, translational, and bioengineering researchers from academic centers and industry to work in collaboration on complications of type 1 diabetes.

The panel was in favor of supporting this initiative. They felt that telemedicine approaches could be particularly useful to pursue, as many people who develop diabetes complications do not have easy access to care, although the panel also noted that limitations related to third-party reimbursement are currently a barrier to implementing telemedicine approaches. Biomarker development is also important, and could, for example, help to predict which patients are likely to develop complications. Samples from well-characterized patient populations, such as the DCCT/EDIC may be a rich resource for identifying novel biomarkers.

Clinical Trials for Cardiovascular Disease in Type 1 Diabetes
Primary discussants: Dr. Robert Eckel and Dr. Ann Marie Schmidt

People with type 1 diabetes have at least a 10-fold increase in the risk of cardiovascular disease (CVD) compared to age-matched controls. The DCCT/EDIC study showed that a period of intensive glycemic control is associated with a significant reduction in major CVD outcomes. However, hyperglycemia and traditional CVD risk factors do not completely explain the increased CVD burden in people with type 1 diabetes. Additionally, despite the differences in the pathophysiology of atherosclerosis in type 1 versus type 2 diabetes, the clinical management of CVD in people with type 1 diabetes is based on clinical trials for people with type 2 diabetes because of the absence of large clinical trials for CVD prevention and treatment in type 1 diabetes.

The initiative would support clinical trials to test interventions designed to prevent or treat CVD in people with type 1 diabetes. If successful, the results of the clinical trials should be of practical importance to clinical management and applicable immediately.

The panel agreed with the need to study this area, as there is no published literature on the underlying mechanisms that lead to acute coronary syndromes (*e.g.*, heart attack) in type 1 diabetes. Because of the paucity of data in this field, the panel felt that it was premature to conduct a clinical trial until more research is conducted to better understand the underlying disease. The panel suggested several options for utilizing Special Funds to examine this research area, including using intravascular ultrasound (IVUS) to examine atherosclerosis in people with type 1 diabetes, such as in the well-characterized DCCT/EDIC patient population; leveraging

studies in animal models to move promising therapies into the clinic; or supporting a consortium to study the underlying mechanisms of acute coronary syndromes in type 1 diabetes. They suggested that as a next step, NIDDK consider convening a small group of experts to provide input on the most pressing questions to address, which could inform the development of a future initiative.

Clinical Trials to Study the Neurological Impact of Dysglycemia in Type 1 Diabetes
Primary discussants: Dr. Eva Feldman and Dr. Robert Sherwin

The achievement of tight glycemic control in children with type 1 diabetes is limited by the risk of hypoglycemia and the associated potential for impaired neurocognitive development. Data in animal models and humans suggest that both hypoglycemia and hyperglycemia can be deleterious to the developing brain.

The goal of the proposed initiative is to solicit applications for clinical trials designed to identify the neurologic consequences of dysglycemia and glucose variability on the young developing brain in children and to focus on the development of future treatments. This area of research will add to understanding of the neurocognitive consequences of type 1 diabetes and would forge new partnerships between the endocrinology and neurology fields. Additionally, important questions might be answered related to the short- and long-term effects of dysglycemia on brain development, as well as possible targeted prevention strategies and future therapies.

The review panel commented that studies are needed to address both cognition and behavior, which are areas that are usually studied separately. In past years, researchers have not had the tools necessary to pursue such studies, but technologic advances in brain imaging allow structural changes in the brain that may affect cognitive function to be examined in real time. Overall, the panel felt that the study of neurocognitive effects of type 1 diabetes in children and adolescents is of vital importance, and recommended this area of investigation be studied through Impact Awards (described above).

Diabetic Retinopathy Clinical Research Network (DRCR.net)
Primary discussants: Dr. James Neaton and Dr. John Penn

Even with advances in the diagnosis and management of ocular disease in people with diabetes, eye complications associated with the disease continue to be the leading cause of vision loss and new onset blindness in working-age individuals throughout the United States. The ongoing DRCR.net, led by the NEI, develops and maintains a collaborative network to facilitate multicenter clinical research on diabetic retinopathy, diabetic macular edema (DME), and associated conditions. The Network currently consists of approximately 130 active clinical sites in 39 states. The network has initiated 21 multicenter studies involving 8,595 study participants, as of the end of 2012. Among other accomplishments, the DRCR.net completed a landmark phase III clinical trial demonstrating the comparative effectiveness of ranibizumab combined with laser treatment for reversing vision loss caused by DME compared to laser treatment alone.

The proposal presented was for continuing *Special Diabetes Program* funding of the DRCR.net, which would support the completion of ongoing trials and enable new trials to be launched. The

Network has several potential protocols and research studies that are currently under consideration, and thus the Network is well positioned to build on its proven track record of identifying, implementing, and completing trials that meet its objective through its process of protocol development, independent review, implementation, and publication.

The panel felt that the DRCR.net was a model clinical trials network, particularly with respect to how they leverage industry support. The panel's comments focused on how to build on the tremendous success of this effort, such as by examining whether the Network could potentially be utilized to propel progress in using telemedicine for diabetic retinopathy and to look at differences in the development of complications between people with type 1 and type 2 diabetes, as the Network enrolls people with both forms of the disease.

TOPIC 6: BETA CELL BIOLOGY

Current Efforts in Beta Cell Biology

Dr. Fradkin provided an overview of the current research portfolio related to beta cell biology and beta cell replacement strategies. She discussed the Beta Cell Biology Consortium (BCBC), which will sunset in FY2013. A new effort, called the Human Islet Research Network (HIRN), which was presented for consideration at this meeting, would build on the tremendous success of the BCBC. Other ongoing programs include the Clinical Islet Transplantation Consortium, co-led by NIDDK and NIAID, which is conducting studies to improve the safety and long-term success of methods for islet transplantation; the Collaborative Islet Transplantation Registry, led by NIDDK, which expedites progress and promotes safety in islet transplantation through the collection, analysis, and communication of comprehensive and current data on all islet transplants performed in North America; and the Non-human Primate Transplantation Tolerance Cooperative Study Group, led by NIAID, which is collaboratively developing and evaluating the safety and efficacy of novel therapies to induce immune tolerance in non-human primate models of islet, kidney, heart, and lung transplantation.

Glucagon and the Glycemic Dysregulation of Type 1 Diabetes

Primary discussant: Dr. Rudolph Leibel

Glucagon is a hormone secreted by alpha cells in the pancreas. Glucagon and insulin are regulated in opposition to one another—when insulin is secreted, glucagon levels are suppressed and vice versa. Glucagon is also known to prevent/reverse hypoglycemia, but this action can be disrupted in type 1 diabetes. Some glucagon antagonists and agonists are being tested in clinical trials for the treatment of type 2 diabetes, but their application to type 1 diabetes has not been thoroughly explored. Additionally, there is a dearth of basic research on the molecular mechanisms related to glucagon action that could inform future studies and trials.

The purpose of this initiative is to support research conducted by small businesses and academic laboratories to explore the role of glucagon in regulation of glycemia in animal models and in people at different stages of type 1 diabetes, and to provide the necessary tools for the study of glucagon's secretion and action. The long-term goal would be to determine whether pharmacologic modulation of glucagon secretion or downstream activity could be an effective adjunct to insulin in treating people with type 1 diabetes.

The panel felt that research on glucagon and its regulation is a key topic to study, particularly because many type 2 diabetes drugs relate to glucagon suppression. Importantly, hypoglycemia is a major challenge to the management of type 1 diabetes, so understanding how glucagon function is dysregulated in the disease could lead to important insights to benefit disease management. The panel also encouraged NIDDK to support human studies, if possible, as mouse models may not be an ideal system in which to pursue research in this area.

Imaging Pancreatic Beta Cell Mass and Function
Primary discussant: Dr. Domenico Accili

Finding robust biomarkers of pancreatic beta cell mass, function, and inflammation is important to better support clinical research in type 1 diabetes pathogenesis and to monitor therapies aimed at restoring beta cells or their function. Although there is an ongoing international research effort in imaging, still needed are well-defined imaging targets on or in the beta cell and ligands that can bind to them, as well as novel means of delivering these imaging agents to the cell surface. There is an interest in the scientific community to pursue research on beta cell imaging; however, the NIDDK has observed that beta cell imaging grants do not fare well when compared to more classical R01 grant applications when reviewed by regular NIH study sections.

To bolster research in this area and to help overcome the barrier faced during peer review, the proposed initiative would support a Program Announcement Reviewed in an Institute (PAR) to establish a specially-convened study section focused only on grant applications for beta cell imaging. The PAR would encompass methods appropriate for *in vivo* studies in humans, as well as for studies in animals with promise for moving toward human application.

The panel encouraged support of research on beta cell imaging. From an industry perspective, they thought that advances in this area could aid the ability to test new therapies, for example if trials could utilize imaging technology to determine if drugs slow disease progression. The panel suggested that NIDDK consider whether it would be beneficial to combine the beta cell imaging initiatives presented at the workshop into one larger initiative (*i.e.*, combining this initiative with the "Harvesting the Neuroimaging Cornucopia for Pancreatic Islet Imaging Reagents" initiative found in the "Resources" Topic Area above).

Human Islet Research Network (HIRN)
Primary discussants: Dr. Mark Espeland, Dr. Domenico Accili, Dr. Megan Sykes, and Dr. Ronald Gill

The Human Islet Research Network (HIRN) consists of six interrelated components, each supported under a separate FOA. Below is an overview of HIRN, a description of the six FOAs, and the panel's input on the overall effort.

Overview: The HIRN is a proposed new team-based effort designed to support discovery-based research and resource and technology development for type 1 diabetes translation. It would build on the tremendous success of the consortium-based approach to research pioneered by the NIDDK's BCBC, which will sunset in 2013 after 13 years in existence. The HIRN's centralized

administrative team would help NIDDK coordinate the activities of a limited number of small-to medium-size consortia, each defined by a specific set of research priorities. This network structure would help to facilitate interactions between small communities of investigators organized around common biological and/or technological challenges, with the overall goal of developing innovative strategies for the treatment, prevention, and monitoring of type 1 diabetes. It is anticipated that the modular structure proposed for the HIRN will support evolution of the program over time in response to emerging scientific and technological advances.

FOA 1: HIRN Coordinating Center: One component of the HIRN would be a coordinating center to provide needed organizational and bioinformatics support. The coordinating center would consist of an administrative component designed to promote collaborations among current and future Network participants, and to facilitate communication between the Network and the broader scientific community, including managing regular teleconferences and annual meetings; developing and maintaining a central website; and managing opportunity pool programs. Bioinformatics functions would include developing and maintaining a centralized internet-based archive of HIRN research findings; developing methods to track and facilitate movement of data from HIRN sites into the central repository; provision of training for HIRN investigators to ensure rapid and timely data release to the Network and to the community; and facilitating coordination of the HIRN with other related database efforts.

FOA 2: HIRN Consortium on Regeneration, Reprogramming, and Targeting: The life-threatening side effects of poor insulin management in type 1 diabetes and severe type 2 diabetes underscore the need for new therapeutic strategies to replenish beta cell mass. The promising outcome of islet transplantation has prompted the search for alternative and abundant sources of beta cells for replacement therapy, and much progress has been made in differentiating insulin-producing cells from stem/precursor cells for possible clinical use. At the same time, new developments in areas such as islet plasticity, epigenetic control of cell identity, cellular reprogramming, genome editing, and cell targeting could be leveraged to develop an alternative to cell or islet transplantation: the controlled, *in vivo* replenishment of functional beta cells using a patient's own cells and tissues. The HIRN Consortium on Regeneration, Reprogramming, and Targeting would consist of five to six collaborative teams of investigators with projects aimed at furthering the understanding and control of the human islet's cellular diversity and plasticity; finding innovative and efficient means to reprogram adult human cells of various origin into functional beta cells or beta-like cells; or developing reagents and strategies for the *in vivo*, targeted delivery of regulatory factors that would result in an increase of functional human beta cell mass.

FOA 3: HIRN Consortium on Human Islet Biomimetics: Scientists have made great strides in recent years in generating human pancreatic progenitors *in vitro*. However, the efficient generation of fully functional, glucose-responsive, insulin-secreting beta-like cells *in vitro* remains elusive, and there remains a critical need for clonal and expandable human islet cell sources capable of full maturation *in vitro*. This Consortium on Human Islet Biomimetics would support two to three collaborative teams of investigators focused on generating new sources of human islet cells in conjunction with the development of a cell-based platform through combining expertise in areas such as stem cell biology, beta cell biology, and tissue

bioengineering. It is expected that platforms developed may be used to discover and test novel therapeutics and to further understand human beta cell biology and diabetes pathophysiology.

FOA 4: HIRN Consortium for Modeling Autoimmune Interactions: Animal models have been used to advance type 1 diabetes research by supporting the exploration of cellular and molecular mechanisms that may contribute to beta cell autoimmunity. However, a true understanding of human type 1 diabetes requires that the disease be studied in the context of the human cells, genetics, and environments that drive development of clinical disease. Better model systems are needed to reveal how the human islet interacts with immune cells to initiate type 1 diabetes and to enhance preclinical testing of new disease-modulating drugs. The Consortium for Modeling Autoimmune Interactions would address this problem by creating the reagents, resources, and protocols needed to measure human cell populations as they interact in an autoimmune, *in vivo* environment. The Consortium would consist of groups of investigators developing novel approaches to assay human type 1 diabetes autoimmunity *in vivo* using animal model platforms. The goal of the program would be to develop and export assays that are capable of defining and measuring the early events that lead to autoimmune destruction of human beta cells.

FOA 5: HIRN Consortium on Measuring Beta Cell Death and Survival: Many questions remain regarding the root causes of beta cell loss in type 1 diabetes. The relative contributions of various mechanisms of beta cell injury to disease initiation (including metabolic stress, inflammation, and autoimmunity) are yet to be defined. Addressing such issues will require new approaches and novel technologies, including the development of techniques that are capable of measuring molecular events occurring inside beta cells and inflammatory cells, as well as methods to monitor changes in local environments where islet and immune cells interact. Defining these pathophysiologic events and devising strategies to manipulate them could lead to novel therapeutic solutions. The ultimate goal would be to use this information to protect, and even renew, the population of residual beta cells in people with type 1 diabetes, resulting in the normalization of both beta cell mass and function. The HIRN Consortium on Measuring Beta Cell Death and Survival would support four to six bold and creative research projects to develop the tools and technologies needed to confront major unanswered questions relevant to the loss of beta cell function in early type 1 diabetes.

FOA 6: HIRN Consortium on Bioengineering and Synthetic Biology Program: The HIRN Consortium on Bioengineering and Synthetic Biology Program would support a group of investigators proposing the development of highly-innovative bioengineering or synthetic biology solutions relevant to type 1 diabetes research and/or therapy. Researchers would be assigned to the HIRN consortium most relevant to their proposed project, and they would also participate in the yearly meeting of the entire Network. It is anticipated that interactions between investigators in this Consortium and investigators in other HIRN consortia will lead to new projects and collaborations that will further contribute to the mission and success of the HIRN.

Panel discussion: The panel was extremely supportive of the HIRN and felt that it built on landmark research done by the BCBC. They endorsed the modular structure proposed, which gives flexibility in terms of ending or starting new consortia based on scientific opportunity and available funding. However, they cautioned against top-down management in terms of

disassembling and assembling teams too often, as that could potentially detract from productivity and prevent longer-term projects from coming to fruition.

Some panel members felt that it was important for the HIRN to focus on research related to keeping remaining beta cells alive and put less focus on beta cell regeneration research. Panel members also felt that a lack of tools to conduct autoimmunity research was a key research barrier and thus important to pursue through the HIRN. The panel also discussed proposed research to develop mouse models that have greater fidelity to human disease. Although there was some concern that the development of such mouse models is a high-risk project that will take a long time to complete, panel members thought that it was an important area to pursue. In particular, they thought it was a good investment of *Special Diabetes Program* funds that could reap benefits in years to come by leading to key research resources that could be used by the broad research community. Additionally, research to develop such mouse models is typically not supported through the regular R01 grant mechanism, so it would be appropriate for the NIDDK to support the research through a new initiative, like the HIRN. Overall, the panel felt that supporting the HIRN was a good use of *Special Diabetes Program* funds, as it is research that could inform a cure, which is the ultimate goal of type 1 diabetes research.

PATIENT PERSPECTIVE

Ms. Judy Hunt provided comments on the proposals from a patient's perspective. She stated that patients want to live safely and avoid developing disease complications. She also felt that patients want a safe and long-lasting cure, even if that will take more time for researchers to develop. She encouraged the different NIH Institutes and Centers to work together on research areas that could benefit from wide-ranging expertise. Likewise, she encouraged researchers studying seemingly disparate areas to share knowledge with one another, as findings in one area could benefit progress in another. She also stressed that it is important to support research that could benefit people with type 1 diabetes of all ages and life stages. Ms. Hunt closed her comments by saying that this has been a very exciting meeting, with numerous promising scientific opportunities presented.

ADDITIONAL DISCUSSION

The expert panel identified topic areas in type 1 diabetes research that were not addressed in the proposals presented at the workshop. Fostering research in these areas could accelerate progress on the understanding, prevention, and treatment of type 1 diabetes and its complications. Areas of opportunity identified by the panel included:

- Research is needed on the long-term effects of insulin use in type 1 diabetes and the underlying mechanisms related to insulin resistance in this population.
- Research using nanoparticles as a novel approach to deliver immunotherapies could be of benefit. It may require attracting engineers to pursue the problem.
- The panel felt that it was important to support career development awards (K awards), particularly for physician-scientists, as it remains critical to train the next generation of scientists pursuing type 1 diabetes research. In addition, efforts should also focus on helping

people with K awards transition to independent faculty positions. The panel suggested that NIDDK consider expanding its meeting in which they convene their K awardees to include awardees from other NIH Institutes and Centers.

- Research could examine factors related to reimbursement by third-party payers, including whether reimbursement issues may effect whether patients adhere to diabetes treatment guidelines or have access to state-of-the art treatments.
- The panel suggested that research focus on treating two key components of type 1 diabetes: the lack of beta cells and the underlying autoimmune disease. Both areas need to be addressed to ultimately develop a cure.
- Researchers studying diabetes complications tend to be in academic siloes. To encourage cross-talk and sharing, the panel suggested making initiatives focused on a specific complication broader to include other complications.
- Because research shows that the immune system is plastic, studies are needed to identify ways to manipulate the immune system from a pathogenic to a tolerogenic state.
- The panel commented on balancing research supported by the *Special Diabetes Program*. They thought that it was important to pursue research that could provide results in the short-term and thus have a more near-term impact. However, they also felt that it was important that the Program funds be used to invest in longer-term projects that could reap major benefits for future research (*e.g.*, development of new research tools that could be used by the broad scientific community).

Appendix 1: Panel Members

Domenico Accili, M.D.
Professor of Medicine
Columbia University
College of Physicians and Surgeons

Jeffrey Bluestone, Ph.D.
UCSF Executive Vice Chancellor and Provost
AW and Mary Clausen Distinguished Professor of Medicine, Pathology, Microbiology, and Immunology
UCSF Diabetes Center

Matthew Breyer, M.D.
Chief Scientific Officer
Lead Generation Biology
Biotechnology Discovery Research
Lilly Research Laboratories

John Buse, M.D., Ph.D.
Professor of Medicine
Chief, Division of Endocrinology
Executive Associate Dean for Clinical Research
University of North Carolina

Edward Damiano, Ph.D.
Associate Professor
Department of Biomedical Engineering
Boston University

Robert Eckel, M.D.
Charles A. Boettcher Endowed Chair in Atherosclerosis
Professor of Medicine - Division of Endocrinology, Metabolism and Diabetes, and Cardiology
Professor of Physiology and Biophysics
Program Director, Adult General Clinical Research Center
University of Colorado Denver

Mark Espeland, Ph.D.
Professor, Department of Biostatistical Sciences
Division of Public Health Sciences
Wake Forest University Health Sciences

Eva Feldman, M.D., Ph.D.
Russell N. DeJong Professor of Neurology
Director, Program for Neurology Research and Discovery
University of Michigan

Ronald Gill, Ph.D.
Professor of Surgery
Scientific Director, Colorado Center for Transplantation Care, Research, and Education
University of Colorado

Judy Hunt
NIDDK Council Member

Georgeanna Klingensmith, M.D.
Chief, Pediatric Clinics
Professor of Pediatrics
University of Colorado
Barbara Davis Center for Childhood Diabetes

Rudolph Leibel, M.D.
Professor of Pediatrics and Medicine
Director, Division of Molecular Genetics and the Naomi Berrie Diabetes Center
Columbia University
College of Physicians and Surgeons

R. John Looney, M.D.
Professor of Medicine
Division of Allergy/Immunology and Rheumatology
University of Rochester

James Neaton, Ph.D.
Professor of Biostatistics
Division of Biostatistics
School of Public Health
University of Minnesota

John S. Penn, Ph.D.
Phyllis G. and William B. Snyder Professor
Vice Chairman
Department of Ophthalmology and Visual Sciences
Assistant Dean for Faculty Development
Vanderbilt University School of Medicine

Ann Marie Schmidt, M.D.
Dr. Iven Young Professor of Endocrinology
Professor, Departments of Medicine, Biochemistry and Molecular Pharmacology, and Pathology
NYU Langone Medical Center

Robert Sherwin, M.D.
C. N. H. Long Professor of Medicine
Section Chief, Endocrinology
Director, Yale Center for Clinical Investigation
Yale University

Megan Sykes, M.D.
Professor of Medicine and Surgery and Microbiology & Immunology
Director, Columbia Center for Translational Immunology
Columbia University
College of Physicians and Surgeons

Timothy Wysocki, Ph.D.
Director, Center for Pediatric Psychology Research, Department of Biomedical Research
Nemours Children's Clinic

Appendix 2: Acronyms

Organizations

ADA	American Diabetes Association
CDC	Centers for Disease Control and Prevention
DMICC	Diabetes Mellitus Interagency Coordinating Committee
FNIH	Foundation for the National Institutes of Health
HHS	U.S. Department of Health and Human Services
JDRF	Juvenile Diabetes Research Foundation
NCATS	National Center for Advancing Translational Sciences
NEI	National Eye Institute
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health

Research Programs

BCBC	Beta Cell Biology Consortium
DCCT	Diabetes Control and Complications Trial
DPT-1	Diabetes Prevention Trial-Type 1
DRCR.net	Diabetic Retinopathy Clinical Research Network
EDIC	Epidemiology of Diabetes Interventions and Complications
HIRN	Human Islet Research Network
ITN	Immune Tolerance Network
nPOD	Network for Pancreatic Organ Donors with Diabetes
SBIR	Small Business Innovation Research
STTR	Small Business Technology Transfer
T1D-RAID	Type 1 Diabetes-Rapid Access to Intervention Development
TEDDY	The Environmental Determinants of Diabetes in the Young
TRIGR	Trial to Reduce IDDM in the Genetically At-Risk

Other Acronyms

CVD	cardiovascular disease
DME	diabetic macular edema
DNA	deoxyribonucleic acid
FACS	fluorescence-activated cell sorting
FOA	funding opportunity announcement
FY	fiscal year
HbA1C	hemoglobin A1C
HLA	human leukocyte antigen
IND	investigational new drug
IVUS	intravascular ultrasounds
MHC	major histocompatibility complex
OGTT	oral glucose tolerance test
PAR	Program Announcement Reviewed in an Institute
PET	positron emission tomography
RFA	Request for Applications
RNA	ribonucleic acid