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

April 8-9, 2015
Rockville, MD

Summary

INTRODUCTION

A panel of scientific and lay experts from across the United States, with expertise relevant to type 1 diabetes and its complications, convened in Rockville, Maryland on April 8-9, 2015. The goal of the 2-day workshop was to obtain input from panel members on draft concepts for research initiatives that could be pursued with funds from the *Special Statutory Funding Program for Type 1 Diabetes Research* ("*Special Diabetes Program"* or "the *Program*") in Fiscal Years (FY) 2016 and 2017. Furthermore, the panel was invited to propose other ideas for new and emerging opportunities for type 1 diabetes research that could be pursued with funds from the *Special Diabetes Program*. Thus, the workshop served as one of many key sources of input to the government for informing future research directions. A summary of initiatives that received enthusiasm from the panel is presented here, including descriptions of these proposals and summaries of the relevant panel discussion.

Background on Workshop: On April 14, 2015, the *Special Diabetes Program* was extended for 2 years through FY 2017 at a level of $150 million per year. 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 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) prospectively convened a panel of 22 scientific and lay experts to solicit input on future research directions. The 21 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. One 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-Department program of the U.S. Department of Health and Human Services (HHS), the NIDDK initiated a call for proposals to other Diabetes Mellitus Interagency Coordinating Committee (DMICC) member organizations for research that could be pursued in FY 2016 and/or FY 2017. 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*.

Thirty-nine proposals, submitted by four NIH Institutes and the Centers for Disease Control and Prevention (CDC), were presented to the panel. The proposals comprised 27 new initiatives and

12 continuations or expansions of ongoing programs. Written summaries including proposed cost and duration, background and justification, and goals and objectives for each of the 39 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 organized around eight broad topics related to type 1 diabetes research:

- Diabetes Complications
- Artificial Pancreas
- Clinical Management
- Resources
- Attracting New Talent to Type 1 Diabetes Research
- Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR)
- Autoimmune Etiology, Clinical Trials, and Epidemiology
- Beta Cell: Assessment and Therapies

The submitted proposals were grouped under the relevant topic area. For each proposal, an NIH or CDC 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. Two or three panel members were assigned to serve as primary discussants for each proposal and were asked to make initial comments and moderate the discussion. Panel members who were engaged with initiatives involving ongoing programs were asked to leave the room during relevant panel discussion periods. After all proposals had been discussed in a topic area, the panel members participated 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 panel 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 and emerging opportunities 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.

OPENING REMARKS

Dr. Rodgers welcomed the panel and thanked them for attending this important workshop. He also thanked the staff of the NIH and CDC for their efforts in preparing for the workshop and presenting the initiatives to be discussed. He emphasized that although the *Special Diabetes Program* is a special appropriation that the NIDDK administers on behalf of the HHS Secretary, it involves numerous NIH Institutes and Centers as well as the CDC. Dr. Rodgers described how, since its inception in 1998, the *Program* has supported numerous advances that have improved the lives of people with type 1 diabetes, and noted that many of these advances would not have been possible without *Special Diabetes Program* funding. The *Program* is extremely important to the NIDDK, and the Institute places a high priority on carefully administering the

funds and maximizing their value. The input provided by the panel would be critically important to the government in future planning efforts.

Overview of the *Special Diabetes Program*: Dr. Fradkin thanked the panel members for participating in the workshop and provided them with an overview of the *Special Diabetes Program*.

The *Special Diabetes Program* augments regularly appropriated funds that the NIH receives for diabetes research. Unlike regular appropriations, the funds from the *Special Diabetes Program* are limited in time and require renewal in law. In April 2015, the *Program* was extended for 2 years (FY 2016 and FY 2017) 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. The *Program* has been used to support large-scale, collaborative, high-risk, high-reward research consortia and clinical trials networks. More information is available at the Type 1 Diabetes Research website.

The *Program* is overseen by the NIDDK, with input provided by the statutory DMICC. By fostering coordination and collaboration across federal agencies, the DMICC has played an important role in guiding the *Special Diabetes Program*.

Dr. Fradkin noted that *Program* planning is a collaborative effort involving input from stakeholder government agencies (through the DMICC) as well as voluntary and charitable organizations, including the JDRF (formerly the Juvenile Diabetes Research Foundation), the American Diabetes Association (ADA), the Leona M. and Harry B. Helmsley Charitable Trust, the Endocrine Society, and the American Association of Clinical Endocrinologists. Additionally, planning and evaluation meetings such as this workshop have been pivotal to the effective use of *Program* funds. These meetings have allowed the NIDDK to obtain external input on research supported by the *Special Diabetes Program*. The feedback generated by these planning meetings has been critically important for identifying gaps and emerging opportunities for type 1 diabetes research funding. For example, input from the 2013 planning meeting resulted in a workshop on cardiovascular disease in type 1 diabetes, and the results of that workshop informed proposals to be presented at this meeting. Two strategic plans also serve 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 discussed examples of previous achievements supported in whole or in part by the *Program*, including comparative effectiveness studies in diabetic retinopathy, initial trials using artificial pancreas technologies, the development of Smart Insulin, the first national surveillance data on rates of childhood diabetes, trials to preserve beta cell function in people with new-onset type 1 diabetes and to prevent the disease in those at high risk, validation of best practices for islet manufacturing, and a method for large-scale production of beta cells. Additional information on *Program* achievements is available in the Special Statutory Funding Program for Type 1 Diabetes Research: Evaluation Report and "Type 1 Diabetes—Reaping the Rewards of a Targeted Research Investment." In addition, ongoing research holds great promise and may yield important new insights.

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. She noted that, 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 2016 and FY 2017 because of the uncertainty of future funding.

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 panel members had enthusiasm for 29 of the proposals—either as presented or with enhancements. Those 29 proposals are described below, grouped under the relevant topic area. These proposals include those for which there was enthusiasm for only part of the proposal or for which enthusiasm was contingent on resolution of an issue related to feasibility. Therefore, this summary includes proposals which may be partially supported, supported if contingencies are met, or supported through mechanisms other than a proposed Funding Opportunity Announcement.

TOPIC 1: DIABETES COMPLICATIONS

Current Efforts in Diabetes Complications

Dr. Fradkin noted that ongoing investigator-initiated grants supported by the *Program* include five Type 1 Diabetes Impact awards, five awards made under the "Biomarkers for Diabetes Complications – Non-invasive Measures in the Eye" Request for Application (RFA) (RFA-DK-13-027), and the Preventing Early Renal Loss trial. Several ongoing grants in this area are using biosamples from or participants in existing type 1 diabetes clinical trials. In addition, awards are expected to be made in FY15 under the following: Type 1 Diabetes Complications Impact Award (RFA-DK-14-017), Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies (PAR-14-257), and Research Using Subjects from Selected Type 1 Diabetes Clinical Studies (Living Biobank) (PAR-14-258).

Cardiovascular Disease in Type 1 Diabetes – Cohort, Registry, and Database Consortia

Primary discussants: Dr. Robert Eckel, Dr. Mark Espeland, and Dr. James Meigs

Cardiovascular disease (CVD) is the most frequent cause of death for people with type 1 diabetes. Despite differences between type 1 diabetes and type 2 diabetes with regard to metabolic parameters, as well as age of diabetes and CVD onset, the clinical management of

CVD in people with type 1 diabetes is based on clinical trials for people with type 2 diabetes. A jointly sponsored NIDDK and National Heart Lung and Blood Institute workshop was held on the NIH campus in October 2014, for a critical examination of the pathophysiology, risk factors, and clinical course of CVD for people with type 1 diabetes. Suggestions from the workshop were to: 1) facilitate joint analysis of CVD data from long-standing cohorts and registries of people with type 1 diabetes in North America and Europe and 2) define type 1 diabetes in a computable phenotype to allow research in the large databases of electronic medical records. These suggestions would address major knowledge gaps in the understanding of the risk factors for CVD in type 1 diabetes and the differences in pathogenesis and clinical course of CVD in type 1 diabetes and type 2 diabetes. Particularly needed is information on short- and long-term outcomes after acute events including the acute coronary syndrome and stroke. For the last point, development of information on how presentation, treatment, and other factors affect the course of the acute coronary syndrome or stroke in type 1 diabetes is needed. Additionally, the use of electronic databases to study these questions has been hindered by the difficulties of defining type 1 diabetes compared to type 2 diabetes using the data available in electronic medical records. Therefore, research is needed to better understand the clinical development and response to therapy of CVD in type 1 diabetes in order to tailor prevention and treatment to improve outcomes for people with type 1 diabetes.

This three-part initiative would support a consortium of investigators who oversee cohorts and registries of type 1 diabetes patients, and who have long-term follow up and data on CVD events and risk factors. Support would be provided for: 1) a central data coordinating center to facilitate a unified analysis of existing cohorts, registries, and databases; 2) research, using the consortium of cohorts and registries, on the development and response to therapy of CVD in type 1 diabetes; and 3) development and testing of a computable phenotype to identify people with type 1 diabetes in electronic medical records and research using the phenotype to answer questions on prevention and treatment of CVD in type 1 diabetes in electronic health records.

The panel stated that research on CVD in type 1 diabetes was needed. The panel had some reservations about the feasibility of certain components of the proposal (such as definition of a computable phenotype of type 1 diabetes and studies of cardiovascular therapeutic efficacy in people with type 1 diabetes and CVD). However, there was enthusiasm for studies on CVD involving combined analyses using existing cohorts to maximize previous investments in development of resources and to glean information from these sources to inform future efforts. One panel member proposed creating resources for access to vascular tissue from people with type 1 diabetes to foster mechanistic understanding of the differences between type 1 and type 2 diabetes. Others cautioned that this would be expensive and utility would be contingent on methods of tissue acquisition and processing.

Neurocognitive Effects of Glycemic Dysregulation in Type 1 Diabetes
Primary discussants: Dr. Nigel Calcutt, Dr. Robert Sherwin, Dr. Tim Wysocki

There is growing evidence that there are neurocognitive sequelae of type 1 diabetes. Early age of onset, repeated episodes of hyperglycemia and severe hypoglycemia, and increased clinical severity at the time of diagnosis may increase the risk for abnormal neurocognitive and emotional function, especially when metabolic disruption occurs in early development.

However, knowledge of how specific parameters associated with type 1 diabetes (*e.g*., age of onset and disease duration, glycemic control, frequency and severity of hypoglycemic episodes) may lead to changes in brain structure, function, and deficits in cognition, and of how susceptibility to these brain changes may vary across the lifespan is limited. Recent advances in neuroimaging, computerized neurocognitive assessment, and artificial pancreas system technologies could lead to improvements in characterizing brain structure/function, cognition, and glycemic control in type 1 diabetes.

The proposed initiative would support longitudinal human studies in individuals with type 1 diabetes. It would be further developed following a workshop to be held in 2016 to review the state-of-the-science, bring together experts at the intersection of metabolism and neurocognitive dysfunction, and identify major gaps in knowledge and opportunities for research Defining the glycemic parameters that adversely impact neurocognition, elucidating factors affecting susceptibility to these adverse effects, and identifying mechanisms underlying the effects of type 1 diabetes on neurocognition will inform future prevention and intervention strategies to minimize neurocognitive dysfunction.

The panel was enthusiastic about this initiative, noting that research in this area has been limited and that opportunities now exist due to advances in imaging and measurement technologies. Panel members encouraged NIDDK to foster collaborations between diabetes researchers and neuroscientists, to include research on insulin's role in neurocognition, to bring bioengineers into the discussion, to integrate this research with other complications research, and to include research on the effects of puberty on neurocognition. One panel member noted the impact of neurocognitive skills on self-management behaviors and decision making, and hoped that some creative solutions for that challenge could result from this initiative. Fundamental research could include study of glucose sensing neurons in the brain and of the impact of central nervous system carbohydrate metabolism on cognition. It was also suggested that neurocognitive studies could be incorporated into ongoing studies including artificial pancreas trials, The Environmental Determinants of Diabetes in the Young, and the SEARCH for Diabetes in Youth study.

Continuation of Diabetic Complications Consortium (DiaComp)
Primary discussants: Dr. Robert Eckel, Dr. Thomas Gardner

Strong evidence indicates that complications associated with type 1 diabetes, such as blindness, end-stage renal disease, painful neuropathy, lower extremity amputation, and premature death from cardiovascular disease and stroke, are linked through dysregulation of common pathways. The NIDDK-led Diabetic Complications Consortium (DiaComp) fosters communication and collaboration among investigators across diverse communities of complications research by soliciting and funding Pilot & Feasibility projects in high-impact areas of complications research; sponsoring meetings on cutting-edge topics that bring together investigators from multiple fields; supporting a website to serve the diabetic complications community with over 700 "members"; partnering with the NIDDK-funded Diabetes Centers to support summer research experiences in complications laboratories; and administering a Preclinical Testing Program to support the early stages of drug development.

The proposed continuation would sponsor an annual meeting or workshops and support Pilot & Feasibility projects that result from the meeting. The Pilot & Feasibility program is successful at funding high-quality projects that lead to publications and, in many cases, subsequent NIH funding. The program has had a steady increase in the number of applications and awards in a broad range of complications. However, the popularity of the program has led to a decrease in the success rate and a reduced ability to fund novel, ground-breaking projects. Due to increased demand and DiaComp's success in supporting important complications-related advances, funding from the *Special Diabetes Program* is being requested to allow funding of additional Pilot & Feasibility awards beginning in Fiscal Year 2016. These funds would be used to complement funding from the NIDDK regular appropriation that alone is insufficient to meet the increasing demand and maintain the vitality and success of DiaComp programs. Additional support provided to DiaComp would allow the conception of new ideas in type 1 diabetes research and their incubation through pilot testing within a short timeframe and streamlined process.

The panel felt that DiaComp was a strong program and filled an important need in funding high-risk high-reward projects. One panel member noted DiaComp may be one of the only sources for funding new ideas; another noted that this is the perfect program to support these types of projects. Panel members discussed different ways to evaluate the success of the program and encouraged NIDDK to collect more data. One approach to evaluation of the program would be to compare outcomes of funded projects with proposed projects that were not funded. It was suggested that DiaComp also foster research on neurocognitive complications.

Continuation of Diabetic Retinopathy Clinical Research Network (DRCR.net)
Primary discussants: Dr. Mark Espeland, Dr. James Meigs

The objective of the National Eye Institute-led Diabetic Retinopathy Clinical Research Network (DRCR.net) is to develop and maintain a collaborative network to facilitate multicenter clinical research on diabetic retinopathy, including proliferative diabetic retinopathy, diabetic macular edema, and associated conditions, which are a leading and growing cause of vision impairment and blindness in the United States and throughout the world. The general goals of the DRCR.net include: 1) continuing to develop protocols in a rapid and efficient manner while maintaining absolute scientific rigor and integrity; 2) continuously identifying and focusing upcoming studies on the most important, current medical and public health issues related to diabetes and its retina complications; and 3) continuing the legacy of innovative, novel approaches to clinical trial design and implementation, network structure, and education to patients, physicians, and the community interested in the Network's findings.

To accomplish these goals, the DRCR.net would like to explore biomarkers for retinopathy worsening within current and future protocols, expand genetic research initiatives within current and future protocols, and explore numerous new protocol ideas, including studying how to prevent proliferative diabetic retinopathy. Additional *Special Diabetes Program* funds to support the Network are being requested to support the clinical site costs to conduct the trials and the central coordination costs to design, conduct, monitor, analyze, and publish results from ongoing studies, studies currently in development, studies under consideration, and future ideas that will be reviewed by the Network. The DRCR.net plans to have eight studies ongoing in

2015 with seven of these studies continuing through at least 2016, and additional potential protocols are under consideration to be conducted by the Network.
The panel was enthusiastic about continuing to support the DRCR.net, calling it a tremendous program and a good use of funding. Panelists liked the DRCR.net's partnership with industry to maximize limited funds and provide quick translation and dissemination of results, and the DRCR.net's inclusion of effectiveness research. They were impressed with the Network's ability to recruit volunteers and discussed whether this model could apply to other complications. The panel suggested that DRCR.net could consider efforts towards prevention and early treatments; for example, efficacy of angiotensin converting enzyme inhibitors or receptor blockers might be studied in early proliferative diabetic retinopathy.

TOPIC 2: ARTIFICIAL PANCREAS

Current Efforts in Artificial Pancreas

Dr. Fradkin noted that in this area, ongoing investigator-initiated grants supported by the *Program* include one Type 1 Diabetes Impact award, two awards made under "Diabetes Impact Award—Closed-Loop Technologies: Clinical, Physiological, and Behavioral Approaches to Improve Type 1 Diabetes Outcomes" (RFA-DK-12-020), and five awards made under "Diabetes Impact Award—Closed-Loop Technologies: Development and Integration of Novel Components for an Automated Artificial Pancreas System" (RFA-DK-12-021). In addition, awards are expected to be made in FY 2015 under the following: Diabetes Impact Award—Closed-Loop Technologies: Clinical, Physiological, and Behavioral Approaches to Improve Type 1 Diabetes Outcomes (RFA-DK-14-014); Diabetes Impact Award—Closed-Loop Technologies: Development and Integration of Novel Components for an Automated Artificial Pancreas System (RFA-DK-14-015); and Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes (RFA-DK-14-024).

Expansion of Clinical, Behavioral, and Physiological Research Testing of Current and Novel Closed-Loop Systems

Primary discussants: Dr. Richard Bergenstal, Dr. Irl Hirsch, 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, and, together with integrated insulin delivery systems, may represent the next generation in type 1 diabetes management. These emerging and next-generation technologies require further translational 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 continue supporting 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 would expand and extend ongoing research supported through previously released NIDDK artificial pancreas Funding Opportunity Announcements (FOAs), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development-led Diabetes Research in

Children Network (DirecNet), JDRF, Helmsley Trust, and industry for the initial clinical testing of current and emerging closed-loop systems. It would build on current technology and ongoing clinical research to address barriers that limit progress toward a closed-loop system. Specifically, the initiative would support research to: 1) test and improve the accuracy, safety, reliability, utility, and clinical efficacy of these technologies in humans; 2) develop and test new approaches for use and integration of closed-loop components; 3) address behavioral factors that limit use of these systems; and 4) use the technologies as tools to advance understanding of glucose regulation in people with type 1 diabetes.

(NOTE: this proposal was discussed by the panel concurrently with the following initiative. Please see below for a summary of the combined panel discussion of these proposals.)

Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes
Primary discussants: Dr. Richard Bergenstal, Dr. Irl Hirsch, Dr. Robert Sherwin

New portable/wearable technologies to measure glucose levels and adjust delivery of insulin and other glucose-regulating hormones through an automated closed-loop artificial pancreas system have been developed recently. Initial clinical in-hospital and transitional/outpatient testing has shown very promising results, indicating improved maintenance of close to normal glucose levels with less variability when compared with non-automated open-loop systems. These results are very encouraging, as it is expected that an effective wearable automated system may lead to a reduction of the risk and incidence of complications and to a significant improvement of quality of life through mitigation of the burdens associated with diabetes management. *Special Diabetes Program*-supported research during the last 10 years has promoted significant progress in this field with single- and bi-hormonal systems which are being optimized to be tested in more definitive outpatient, real life studies. NIH has recently released a Funding Opportunity Announcement for long-term advanced validation studies, and the expectation is that the testing of new platforms will expand during the next decade. Thus, it is considered important to continue supporting these studies.

This initiative would build on current technology and clinical research resources to support the conduct of advanced trials designed to test the clinical and outpatient safety and efficacy of artificial pancreas device systems. This initiative would encourage investigative teams that have developed and initially tested a system with promising results to expand testing. These trials are expected to generate data able to satisfy safety and efficacy requirements by regulatory agencies for the approval of a user friendly and accessible integrated system. 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.

Panel discussion of initiatives: The panel was supportive of reissuing these initiatives, noting that the initiatives were complementary. Panel members encouraged NIDDK to continue collaborations with industry in this field, to consider strategies to prevent possible disparities that may accompany use of these technologies and promote broad accessibility of their use, and to include measures of complications outcomes in trials. One panel member suggested broadening these efforts to study unique populations such as older adults or pregnant women.

TOPIC 3: CLINICAL MANAGEMENT

Current Efforts in Clinical Management

Dr. Fradkin noted that ongoing investigator-initiated grants supported by the *Program* include five awards made under "Improving Adherence in Pre-Teens, Adolescents, and Young Adults with Type 1 Diabetes" (RFA-DK-11-029), one award under "Limited Competition for Clinical Trials in Type 1 Diabetes" (RFA-DK-12-511), three awards under "Improving Diabetes Management in Young Children with Type 1 Diabetes" (RFA-DK-13-022), and two awards under "Understanding Barriers and Facilitators to Type 1 Diabetes Management in Adults" (RFA-DK-13-023). In addition, awards are expected to be made in FY 2015 under the following: Improving Diabetes Management in Young Children with Type 1 Diabetes (RFA-DK-14-022).

Improving Adherence in Young Children with Type 1 Diabetes

Primary discussants: Dr. Georgeanna Klingensmith, Dr. Tim Wysocki

Diabetes management requires complex balancing of medication dosing, diet, and physical activity in order to achieve good glucose control while avoiding hypoglycemia. Even the most effective treatments for type 1 diabetes are limited when families struggle to follow the treatment regimen, and the diagnosis and management of type 1 diabetes can be a highly stressful experience for parents of young children. Given the unique challenges of managing type 1 diabetes in young children, there is a need to develop innovative and effective interventions to help families better manage diabetes and maintain good quality of life.

The goal of this initiative is to support multidisciplinary research teams to develop, refine, and pilot test innovative strategies to improve diabetes management and quality of life in families with young children with type 1 diabetes. At the end of the funding period, there should be 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. Research proposed could develop approaches to help families improve diabetes management, including addressing issues such as family conflict, stress, coping, problem solving and communication; over/under-prediction of risks and/or collaborative approaches to healthcare; and/or develop strategies to help families with the use of new or existing technologies, including addressing nocturnal hypoglycemia and/or barriers to use of the technologies.

(NOTE: this proposal was discussed by the panel concurrently with the following two initiatives. Please see below for a summary of the combined panel discussion of these proposals.)

Improving Adherence in Pre-teens, Adolescents, and Young Adults with Type 1 Diabetes

Primary discussants: Dr. Georgeanna Klingensmith, Dr. Tim Wysocki

Data from the Type 1 Diabetes Exchange demonstrate that diabetes management in adolescents and young adults is particularly problematic. Adolescents experience significant pubertal and developmental changes, increased peer influence, and issues related to emerging autonomy and

increased responsibility for life choices. Young and emerging adults are often faced with significant financial, health care, social, and interpersonal transitions that make it more challenging to adhere to a diabetes management regimen. There is a need to develop new and better interventions to improve the ability and motivation of adolescents and young adults to adhere to prescribed treatment regimens.

The goal of this initiative would be to support research to develop, refine, and pilot test innovative strategies to improve adherence to medications and medical regimens, including self-management, in pre-teens (ages 10-12), adolescents (ages 13-18), and young adults (ages 19-30) with type 1 diabetes. At the end of the funding period, there should be 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. Research proposed could address transition to adult care, health beliefs that reduce adherence, the use of new or existing diabetes technologies, and health care delivery, including enhanced collaborative communication, transitions in care, transitions in autonomy, adherence to the medical regimen, and patient-centered goal setting.

(NOTE: this proposal was discussed by the panel concurrently with the preceding and following initiative. Please see below for a summary of the combined panel discussion of these proposals.)

Understanding Barriers and Facilitators to Type 1 Diabetes Management in Adults
Primary discussants: Dr. Irl Hirsch, Dr. Tim Wysocki

Most of the observational and interventional research on diabetes self-management in type 1 diabetes has been conducted in youth and young adults, and data are limited on the psychosocial and behavioral issues that affect disease management as one ages. The data that exist about diabetes self-management in adults is often in mixed samples of individuals with type 2 or 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 without a more refined understanding of the context, barriers, and needs of this population.

The goal of this initiative is to support research that will identify barriers and facilitators to good diabetes self-management in adults with type 1 diabetes. Studies would focus on one or more adult age ranges: young working-age adults (25-44), older working-age adults (45-64), and older adults (65 and older). Research proposed could address health care team/system factors influencing self-management; unique risks related to life stage and context, including pregnancy/caring for children, work stress, transition to assisted living or nursing facilities, and/or adapting self-management to diabetes or aging related co-morbidities; barriers to adoption and use of new or existing technologies; and psychological co-morbidities interfering with self-care, such as depression, anxiety, or change in cognitive abilities.

Panel discussion of initiatives: The panel was enthusiastic for the reissue of these initiatives, noting the importance of addressing these issues and the needs of various unique populations. Specific populations suggested for study included: transition from pediatric to adult care;

pregnancy; older adults; individuals with cognitive impairment, low literacy, or depression; single parent families with children with type 1 diabetes; and people diagnosed with type 1 diabetes as adults. They suggested taking advantage of mobile technologies to conduct research in this field. Panel members also suggested encouraging research on diet, physical activity, smoking, alcohol, and drug use.

Impact of the Use of Glucose Monitoring and Control Technologies on Health Outcomes and Quality of Life in Older Adults with Type 1 Diabetes
Primary discussants: Dr. Irl Hirsch, Dr. Tim Wysocki

As life expectancy of people with type 1 diabetes is increasing, clinical studies are needed to determine whether the use (frequency and intensity) of current and emerging technologies for monitoring blood glucose and administering insulin improve health outcomes and quality of life in older adults with type 1 diabetes. Recent studies suggest that older adults, particularly those with longstanding diabetes, are more prone to hypoglycemia and hypoglycemia unawareness. Hypoglycemia and lack of awareness of it is especially risky in this older population, with associated emergency room visits, accidents, seizures, and cardiac events. Thus, this particular population could greatly benefit from the use of technologies that may maintain glycemic control with simultaneous avoidance of hypoglycemia.

This initiative seeks to design and conduct studies and trials addressing efficacy, quality of life, and cost when glucose control approaches, including higher frequency of self-monitoring of blood glucose or continuous glucose monitoring, are used in older adults with type 1 diabetes. Evidence derived from these studies could inform clinical decision making, payer decisions, and public health policies.

The panel felt that this initiative would be a good use of the *Special Diabetes Program* funding. Members encouraged including the Centers for Medicare & Medicaid Services in the design of these studies to ensure that resulting data could inform decisions. One panel member suggested expanding the target population beyond those with hypoglycemia unawareness to include people with glycemic variability, and also to demonstrate neurocognitive outcomes.

TOPIC 4: RESOURCES

Current Efforts in Resources
Dr. Fradkin noted that resources are generally not supported through investigator-initiated grants, but one such ongoing grant in this area, supported by the Program, was made under "Harvesting the Neuroimaging Cornucopia for Pancreatic Islet Imaging Reagents for Diabetes Research" (RFA-DK-13-024).

Human Pancreas Procurement and Analysis Program (HPPAP)
Primary discussants: Dr. Michael German, Dr. Ronald Gill

Documenting the series of events that lead to beta cell dysfunction and loss in type 1 diabetes could provide critical insights into the origin of the disease and help identify biomarkers and/or therapies for the earliest stages of disease. However, type 1 diabetes is a particularly difficult disorder to investigate because the pancreas is not an easily accessible organ. A deeper understanding of the origins and diversity of human type 1 diabetes would be greatly facilitated by access to extensively phenotyped human pancreatic tissues that could be used to develop comprehensive and integrated molecular, morphologic, and functional signatures of the normal, prediabetic, and type 1 diabetic human islet. Moreover, a parallel exploration of human pancreatic specimens collected from individuals with islet dysfunctions unrelated to type 1 diabetes (*e.g.*, Wolfram syndrome) or with conditions characterized by changes in beta cell mass or function (*e.g.*, pediatric obesity), could facilitate the discovery of molecular signatures with high specificity for beta cell dysfunction in type 1 diabetes, or the exploration of a residual regenerative capacity of pancreatic islets in people with type 1 diabetes.

The goal of this initiative is to create a Human Pancreas Procurement and Analysis Program (HPPAP) to develop and validate protocols and standards for the procurement and study of pancreata recovered from people with scarce or rare diabetes-related pathophysiologic conditions. HPPAP would devise strategies to obtain and collect high-quality pancreatic tissues from rare donors and design and implement approaches to maximize the information obtained from rare samples. HPPAP would also implement methods for sharing datasets and residual tissues with the broader research community. It is expected that HPPAP would leverage activities of existing programs through the formation of strategic partnerships, such as collaborations with the NIDDK-supported Integrated Islet Distribution Program and the JDRF-supported Network for Pancreatic Donors with Diabetes (nPOD).

The panel was supportive of this proposed new Program, saying that it would be an extremely valuable national resource. They suggested that HPPAP be coordinated with nPOD. One possibility is that HPPAP could be combined with nPOD to create a single, larger program. Another possibility is that the two programs could be separate but tightly coordinated—for example, they would integrate datasets and use the same protocols for procuring and treating samples to ensure that data are comparable. The panel also stressed the importance of collecting clinical data on the people from whom the organs are procured, of carefully phenotyping the type of diabetes, and of collecting organs from people who developed type 1 diabetes at various ages. In particular, they thought that having genetic data would be valuable, to identify maturity onset diabetes of the young (MODY) cases, for example. The panel noted that warm ischemia time and fixation of tissue are critical. It urged that collection methods should enable study of precursor cells, and suggested that protocols for freezing single cells and defining single cells in tissue should be developed, One panel member also suggested that people with cystic fibrosis-related diabetes be added to the list of rare disorders to study under HPPAP. Finally, the panel stated that HPPAP would need a strong Steering Committee to help define its scientific direction.

Continuation of the Integrated Islet Distribution Program (IIDP)
Primary discussants: Dr. Michael German, Dr. Stanislaw Stepkowski

The Integrated Islet Distribution Program (IIDP) is an ongoing effort organized by NIDDK to enhance the availability and reproducibility of human islets provided in support of type 1 diabetes research. The IIDP has facilitated many important scientific advances and accelerated the pace of human islet research. Given this success, demand for these valuable tissues has dramatically increased, and the need is expected to continue to rise. The IIDP now receives islets from six expert isolation laboratories and serves over 120 investigators pursuing peer-reviewed research programs.

The goal of this initiative is to renew support for a Coordinating Center that will be responsible for soliciting, implementing, and overseeing a national network designed to procure and distribute live human islets for basic research.

The panel felt that the IIDP is a valuable program that has enabled scientists to conduct research that otherwise would not have been possible. The panel was in favor of continuing the program, given its importance to investigators and the fact that procuring live human islets is a specialized area that requires a centralized resource. One issue to address in the next iteration of the program is that the distribution centers use different islet processing protocols, so the panel suggested that the NIDDK consider ways to standardize protocols across different centers. The panel also thought that enhancements could be made to improve the quality of islets. Other areas to consider in the future are for the IIDP to provide islets from people with diabetes, to obtain information on donor BMI, and for transplant centers to identify ways to increase the number of people who consent to donating their organs to research.

Continuation of Programs to Standardize C-peptide and HbA1c Assays
Primary discussants: Dr. Elizabeth Selvin, Dr. Robert Sherwin

This initiative discusses two ongoing, NIDDK-led programs: The C-peptide Standardization Program and the National Glycohemoglobin (HbA1c) Standardization Program (NGSP).

The C-peptide Standardization Program is responsible for standardizing C-peptide assays. The measurement of C-peptide provides information about intrinsic insulin secretion activity. Studies with laboratories and manufacturers showed that variability of C-peptide measurement can be reduced by incorporating serum calibrators with reference method-assigned values into the manufacturer's calibrator value assignment process. Future support is being requested for the next step: to prepare reference materials to enable manufacturers to re-calibrate their assays to match the proposed reference method and standardize assay results.

The purpose of the NGSP is to achieve standardization and reliability in measurement of HbA1c so that clinicians can use HbA1c optimally for diagnosis and treatment of diabetes and so that all research and clinical trial data can be compared. Although variability within and between HbA1c methods has improved tremendously, there is still room for improvement. Future support is being requested for continued implementation of the NGSP to further improve HbA1c measurement, especially near the diagnostic range and at clinically recommended target values.

The panel members were in favor of continuing these programs. They commented that the NGSP has been a major success and has made tangible and significant contributions to the research and public health fields; they also commended the NGSP website. The panel thought that one area for NGSP to consider addressing is point-of-care HbA1c testing, due to the large variability among different tests. Additionally, although the panel was supportive of using *Special Diabetes Program* funds to support these programs because of their contributions to both research and public health, they felt that the NIDDK should examine ways to make the programs self-supporting (*e.g*., with user fees) so that they would not need to be supported with *Special Diabetes* funds in the future. The panel also suggested that the program have a formal external evaluation committee assess the project.

Continuation of the Collaborative Islet Transplantation Registry (CITR)
Primary discussants: Dr. Ronald Gill, Dr. James Meigs

The mission of the ongoing, NIDDK-led Collaborative Islet Transplantation Registry (CITR) is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on transplants performed in North America. Through JDRF funding, the Registry has also collected data from selected European and Australian sites. The CITR consolidates islet, donor, and recipient data and disseminates the aggregate clinical results. The collection of these data enables researchers to track the progress of successfully engrafted patients, as well as to follow those who experience graft failure. The CITR allows islet transplant sites to have a single, comprehensive source database for all of their islet transplant activities, obviating the need for duplicate databases. These data are subjected to comprehensive biostatistical analyses and communicated in an annual report and in scientific presentations/publications. This effort is necessary to provide guidance for continued improvements and to identify the factors that contribute to sustained graft function and durability.

This proposal is for continuing support of the CITR for compilation and analysis of product and clinical data on allogeneic and autologous islet transplants within North America and—with complementary JDRF funding—on allogeneic islet transplant data from participating European and Australian centers. The Registry would continue to serve as a tool for the research community and address fundamental questions pertinent to the course of patient health status and graft survival following islet transplantation and maintenance immunosuppression.

The panel was supportive of continuing the CITR, calling it a unique resource. They thought that the Registry was critical to documenting progress in the islet transplant field, including detailing how the procedure benefits people. The panel felt that the introduction of data collection on autografts was a strength. Panel members thought that it would be beneficial to enhance the publication output of the Registry, although some panelists commented that the CITR is not intended to be a publication generator. Nonetheless, the panel members thought that data generation should be an important piece of the Registry's future. One suggestion to accomplish this was to incentivize the scientific community to analyze Registry data—*e.g.*, by funding ancillary studies for data analysis with the regular NIH appropriation.

TOPIC 5: ATTRACTING NEW TALENT TO TYPE 1 DIABETES RESEARCH

Current Efforts to Attract New Talent to Type 1 Diabetes Research

Dr. Fradkin noted that ongoing investigator-initiated grants supported by the Program include five awards made under "Career Development Programs in Diabetes Research for Pediatric Endocrinology (K12)" (RFA-DK-11-006), two awards made under "Bioengineering Interdisciplinary Training and Education for Type 1 Diabetes Research (R90/T90)" (RFA-DK-11-023), one award made under "Diabetes Research Training for Behavioral Scientists (T32)" (RFA-DK-11-027), and one award made under "Career Development Programs in Diabetes Research for Behavioral Scientists (K12)" (RFA-DK-11-028).

Type 1 Diabetes Pathfinder Award

Primary discussants: Dr. Ronald Gill, Dr. James Meigs

The Type 1 Diabetes Pathfinder Award was established in 2007 by NIDDK to attract new talent to type 1 diabetes research. The goal of the program was to support exceptional new investigators who propose creative new research approaches that had the potential to produce a major impact on important problems in biomedical and behavioral research relevant to type 1 diabetes and its complications. To be eligible for a Pathfinder Award, applicants needed to meet the NIH definition of "new investigator" as well as fulfill other requirements. The research proposed was not required to be in a conventional biomedical or behavioral discipline but had to be relevant to type 1 diabetes; investigators who had not previously studied diabetes were also encouraged to apply.

Based on the encouraging outcomes of the Type 1 Diabetes Pathfinder program awardees supported by this initiative in the past, the NIDDK is proposing to re-issue it to solicit new applications. The goal of the initiative remains the same. While R01 grants will continue to be the primary source of NIH support for new investigators, the Type 1 Diabetes Pathfinder Award would again be designed to support a small number of exceptionally creative new investigators whose research is focused on type 1 diabetes.

The panel was enthusiastic about this initiative, saying that it was critically important to encourage young scientists to pursue type 1 diabetes research. They also thought that it was appropriate to focus the program on new investigators rather than more established investigators. The panel suggested that, if a major goal of the program is to attract people outside of the type 1 diabetes field, the Request for Applications should state that goal. Another suggestion was to bring in more clinical investigators to the program because most of the awardees in the previous iteration of the program were basic scientists. Finally, the panel encouraged NIDDK to identify ways to connect the awardees with more established investigators, such as by inviting them to meetings of established research consortia (*e.g.*, the Human Islet Research Network, Type 1 Diabetes TrialNet). Such connections may help familiarize awardees with the broader type 1 diabetes scientific community; encourage them to pursue type 1 diabetes research after their award ends; and foster novel collaborations.

Career Development Programs in Diabetes Research for Pediatric Endocrinologists
Primary discussants: Dr. Rudolph Leibel, Dr. James Meigs

Management of diabetes in children is particularly arduous. Effective therapy for pediatric diabetes requires an exceptional level of effort from the children, their families, and their healthcare providers. These demands make it particularly challenging for pediatric endocrinologists involved in diabetes care to pursue research careers. Thus, it is imperative to enhance the diabetes research training and career development of pediatric endocrinologists to create the skilled investigators needed to build upon the foundation of current knowledge and to develop new approaches to the treatment, prevention, and cure of pediatric diabetes. To foster the development of a diverse and highly trained workforce of pediatric endocrinologists to assume leadership roles related to the Nation's biomedical and behavioral research efforts in the area of pediatric diabetes, the NIDDK previously solicited applications for the establishment of institutional career development programs in diabetes research for pediatric endocrinologists. Seven institutions received a T32 institutional training grant and a K12 physician scientist career development program grant as a result of this Funding Opportunity Announcement (FOA) using *Special Diabetes Program* funds. Due to the successes of the initial K12 grants, and a 3-year extension of funding for the *Special Diabetes Program*, a second K12 FOA was issued, and five K12 grants were funded.

Because of the success of the scholars supported by this program in the past, the NIDDK is proposing to extend/renew the K12 physician scientist career development program grants to eligible institutions. The awards would allow participants up to 3 years of supervised research experience that combine didactic studies with laboratory or patient-oriented research. The K12 programs would provide an opportunity for research career development after the clinical fellowship years to facilitate the transition to a fully trained independent investigator.

The panel thought that this was an essential program. They were pleased with the success of former trainees, many of whom went on to receive research funding after being supported by this program. The panel suggested that the prospective trainees could not only focus on clinical research, but also on basic research; they thought it was important for trainees to have a sophisticated understanding of basic research to inform what clinical research to pursue. Toward that goal, a suggestion was to encourage awardees to have mentors with knowledge about both basic and clinical research or to have separate mentors for the two research areas.

TOPIC 6: SMALL BUSINESS INNOVATION RESEARCH (SBIR) AND SMALL BUSINESS TECHNOLOGY TRANSFER (STTR)

Current Efforts in Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR)
Dr. Fradkin noted that ongoing investigator-initiated grants supported by the Program include one award made under "Small Business Innovation Research to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes: Towards an Artificial Pancreas" (RFA-DK-13-028). In addition, awards are expected to be made in FY 2015 under the following: PHS 2014-02 Omnibus Solicitation of the NIH, CDC, FDA, and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]) (PA-14-071); PHS 2014-02 Omnibus

Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42]) (PA-14-072); SBIR and STTR to Develop New Diagnostic, Monitoring and Therapeutics Technologies for the Complications of Type 1 Diabetes (T1D) (PAR-14-058; PAR-14-059); and Reagents for Glucagon and Incretin Research (R43/R44) (RFA-DK-14-008).

Towards a Bio-artificial Pancreas: Development of New Technologies for the Advancement of Cell Replacement Research for Type 1 Diabetes
Primary discussants: Dr. Ronald Gill, Dr. Maike Sander

Despite clear progress made during the last 15 years on cellular transplantation for type 1 diabetes, the most recent results demonstrate a long-term limited viability of engrafted islets, and, as a result, limited insulin independence under different novel modalities of immunosuppressive regimens tested. In addition, even the most innovative immunosuppressive regimens required for transplant survival still have significant immediate side effects, and long-term safety is uncertain. These problems, together with the scarcity of donor organs and the complexity of transplants, mandate a renewed emphasis on the investigation of novel methods within the field of tissue engineering for the development of a bio-artificial, cell-based hormone replacement therapy that may minimize the need for immunosuppression regimens. To support this, it is necessary to develop/optimize novel/smart/safe biomaterials, scaffolds, bio-matrices, and bio-barriers that may protect grafted cells from immune rejection and simultaneously promote appropriate vascularization/innervation with an efficient exchange of nutrients to optimize cellular long-term survival and proper function. These technologies may also be helpful for disease modeling and pre-clinical *in vitro* biomimetic testing.

The main goals of this initiative are for small businesses to create new biomimetic technologies and supportive resources for disease modeling, to improve pre-clinical testing, and to enable/optimize cell replacement therapies for type 1 diabetes.

The panel thought that this was an important area of science to pursue and thus was supportive of this proposal. They suggested taking a focused approach in the Request for Applications, stating which types of technologies the applicants should address.

Towards an Artificial Pancreas: Expansion of Support for Research to Develop New Therapeutics and Monitoring Closed-Loop Automated Technologies for Type 1 Diabetes
Primary discussants: Dr. Bergenstal, Dr. Hirsch

The development of an affordable, automated, mechanical artificial pancreas able to mimic normal pancreatic beta cell function has enormous potential benefit for a substantial proportion of people with diabetes. 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 with commercial potential. Additionally, approved devices and current technologies still have significant limitations, and it is important to put renewed emphasis on the creation of the next generation of devices that will reduce the burden of diabetes self-management and help people with type 1 diabetes achieve recommended levels of blood glucose control. Several relevant projects are being supported as a

result of the publication of a recent, similar Funding Opportunity Announcement, but given the pace of technical progress in this field, it is important to continue supporting research in this field.

This proposal would stimulate and support small business innovative research on novel and current 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, physiologists, bio-behavioral researchers, and designers in academic centers and industry to develop new approaches to create devices with enhanced accuracy and less patient burden that will represent improvements in the safety and effectiveness of currently available technology.

The panel had enthusiasm for this proposal, saying that it, like the other Small Business Innovation Research and Small Business Technology Transfer proposals presented, addresses a compelling scientific opportunity. They stated that there is a particular need for improved infusion sets for insulin pumps, which could potentially be addressed by research supported under this proposal.

Small Business Innovation Research (SBIR) to Develop New Methods and Technologies for Assessment of Risk and for Early Diagnosis and Prognosis of Type 1 Diabetes
Primary discussants: Dr. Betty Diamond, Dr. Jane Salmon

Early identification of type 1 diabetes risk and the onset of autoimmunity provides the basis for a variety of major ongoing studies seeking to prevent or delay the disease. Investigators have used a combination of islet autoantibody positivity, autoantibody seroconversion, biomarkers of genetic susceptibility, and beta cell functional assays as criteria to select individuals at high risk of developing type 1 diabetes. However, current technology for identification of at-risk individuals is costly, requires the participation of research laboratories, and may not be suitable for public health screening that would ensue should effective preventative interventions be established. Methods for more efficient identification of individuals at risk of type 1 diabetes who may be eligible for preventative intervention would include low-cost, high-throughput, accurate and predictive assays/devices that could be used at the point of care level. A reissue of a previous initiative is considered important to continue promoting and supporting novel developments in this field as new biomarkers/assays/devices are needed.

The main goals of this proposal are for small businesses to create new technology resources to improve the identification of individuals at risk of developing type 1 diabetes, predict prognosis and monitor disease progression, and assess the efficacy of therapeutic interventions.

The panel supported this proposal and felt that it addressed a compelling scientific opportunity. They underscored the importance of identifying people at risk for type 1 diabetes, even potentially before a prevention strategy is identified. For example, they noted that many children, particularly those younger than 3 years old, often are hospitalized with diabetic ketoacidosis (DKA) when they are diagnosed with type 1 diabetes; DKA is a life-threatening condition. This often happens because parents are unfamiliar with type 1 diabetes and its

symptoms. Thus, identifying children at risk would enable pediatricians to educate parents about type 1 diabetes so that they recognize signs and symptoms earlier and seek medical attention before the child develops DKA.

TOPIC 7: AUTOIMMUNE ETIOLOGY, CLINICAL TRIALS, AND EPIDEMIOLOGY

Current Efforts in Autoimmune Etiology, Clinical Trials, and Epidemiology

Dr. Fradkin noted that ongoing investigator-initiated grants supported by the Program include one Type 1 Diabetes Impact award, three awards made under "Function of Type 1 Diabetes Genes" (RFA-DK-11-019), four awards made under "Research Using Subjects from Selected Type 1 Diabetes Clinical Studies (Living Biobank)" (PAR-11-349; PAR-13-028; PAR-14-064), and five awards made under "Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies" (PAR-11-350 PAR-13-013; PAR-14-065). In addition, awards are expected to be made in FY15 under the following: Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies (PAR-14-257) and Research Using Subjects from Selected Type 1 Diabetes Clinical Studies (Living Biobank) (PAR-14-258).

Mechanisms Underlying the Contribution of Type 1 Diabetes Risk-associated Variants

Primary discussants: Dr. Peter Gregersen, Dr. Rudolph Leibel

Genome-wide association studies have identified more than 50 genetic loci that contribute to type 1 diabetes susceptibility (http://www.t1dbase.org). Fine mapping of these and other autoimmune susceptibility loci using a custom genotyping array (Immunochip) has succeeded in reducing the size of the type 1 diabetes loci and the number of potential candidate genes, and has identified several additional novel type 1 diabetes risk loci that have been implicated in other autoimmune diseases. The result of the Immunochip analysis now accounts for nearly 80% of the genetic risk of type 1 diabetes; however, the mechanisms underlying the contribution of these risk-associated genes and their variants for type 1 diabetes remain to be clarified. Understanding the functional consequences of these loci could then be translated to clinical benefits, including reliable biomarkers and effective strategies for screening and disease prevention. Combining fine-resolution genomic data with gene expression profiles and proteomic data for construction of integrated gene networks—taking into account gene-gene interactions (epistasis) as well as epigenetic and environmental factors—will be necessary to understand the pathophysiology of type 1 diabetes. A previous Funding Opportunity Announcement (FOA) in Fiscal Year 2012 addressed novel approaches to studying the function of type 1 diabetes risk-associated genes/loci. Reissuance of this funding opportunity would expand this promising beginning and allow additional genes/loci to be evaluated.

As such, a future FOA supported under this proposal would be focused on recruiting integrative teams and individual investigators for projects to determine the mechanisms underlying the contribution of the risk-associated variants for type 1 diabetes. The proposed studies would identify causal variants and elucidate the mechanisms whereby changes in the function or regulation of these variants are likely to affect risk of type 1 diabetes.

The panelists were supportive of this initiative. They felt that it identified an excellent opportunity to encourage translational research that would capitalize on the current basic research investment and would lead to new insights into causes of type 1 diabetes. Discussants suggested that this initiative would also benefit diabetes research as a whole, as it may reveal causes of disease heterogeneity in type 2 diabetes as well as type 1 diabetes. The panel stressed the importance of encouraging approaches that would work in synergy with the efforts and existing sample sets of other ongoing studies and research cohorts. The panel urged that the focus be on humans rather than rodent models, and encouraged better phenotyping of the human population to identify subtypes based on age of disease onset and other characteristics.

SEARCH for Diabetes in Youth
Primary discussants: Dr. James Meigs, Dr. Elizabeth Selvin

The SEARCH for Diabetes in Youth (SEARCH) study was established in 2000 to provide population-based estimates of the prevalence and incidence of diabetes by type in U.S. youth < 20 years of age. SEARCH is co-led by the Division of Diabetes Translation of the Centers for Disease Control and Prevention (CDC) and the NIDDK and consists of five clinical sites, a coordinating center, and a central laboratory. The SEARCH study estimated that, in 2009, 166,984 youth aged <20 years lived with type 1 diabetes and that every year ~18,400 youth are diagnosed with the disease. Moreover, SEARCH found that, from 2001 to 2009, the prevalence of type 1 diabetes in youth increased by 23%. This increase is likely due to increases in the number of new cases. Indeed, from 2002-2009 among non-Hispanic white youth, SEARCH found that the incidence (per 100,000 per year) of type 1 diabetes increased from 24.1 in 2002 to 27.2 in 2009, a relative increase of 2.7% per year.

By the end of the current funding cycle (2010-2014), SEARCH will be able to assess trends in the incidence of type 1 and type 2 diabetes from 2002 to 2012 by age, sex, and race/ethnicity. However, continued surveillance of diabetes with onset in childhood and adolescence is crucial for understanding the disease burden at the population level, for identifying subgroups most at risk, for planning health care delivery, and for increasing understanding of the clinical course of the disease. The CDC and NIDDK have issued a Funding Opportunity Announcement for continuation of the SEARCH Registry study for 5 years starting in Fiscal Year 2015. This proposal is requesting funds to supplement the SEARCH Population Based Registry in order to perform an in-person visit in newly diagnosed incident cases in 2016. An in-person clinical visit provides more detailed ascertainment of diabetes type through the measurements of diabetes autoantibodies and markers of insulin resistance.

The panel supported this proposal and felt that the proposed research would be a valuable use of the *Special Diabetes Program* funds. The panel noted that SEARCH has been tremendously productive, generating many influential publications of great benefit to the diabetes research community. Additionally, panel members felt that SEARCH is a good incubator for the work of young investigators, which will benefit both the SEARCH project as well as possible SEARCH ancillary studies in the future. One panel member suggested that measurement of acute insulin secretion might be valuable in diabetes classification.

Surveillance for Type 1 Diabetes among Young Adults
Primary discussants: Dr. James Meigs, Dr. Elizabeth Selvin

Although previous research suggests that almost half of type 1 diabetes cases occur in adulthood, very limited data are available in the United States on the prevalence and incidence of type 1 diabetes in adulthood. Recent data on the prevalence of type 1 diabetes in adults come from the 1999-2010 National Health and Nutrition Examination Survey (NHANES). NHANES does not collect information on diabetes type or measure type 1 diabetes immune biomarkers. Therefore, in NHANES, type 1 diabetes was defined based on age at diagnosis and treatment patterns. There is a paucity of data also on the incidence of type 1 diabetes in adults. One study conducted among U.S. military personnel assessed the incidence of insulin-requiring diabetes during 1990-2005 in active duty military personnel aged 18-44 years. However, it is unclear if the cases described are all type 1 diabetes or also include those with type 2 diabetes that require insulin. Findings on temporal trends in type 1 diabetes incidence in the adult population have also been inconclusive. Diabetes registries in Finland, Italy, and in the United Kingdom have indicated an increase in incidence. Whether the cumulative incidence of type 1 diabetes is increasing or the observed increase in children is due to a shift to younger age of onset is unknown, and long-term population-based surveillance efforts of children and young adults is necessary to enhance understanding.

The research goal of this proposal is to investigate the feasibility of determining the incidence and prevalence of type 1 diabetes among young adults (age 20 to 45 years) in the United States. The initiative proposes to establish one or more sentinel sites that would have access to data that covers a large geographic area with a range of ages and races/ethnicities. Specific objectives include establishing a diverse, population-based registry and an electronic cohort to identify cases of diabetes among young adults; determining the prevalence and incidence of type 1 diabetes; and accessing laboratory and pharmacy data related to diabetes autoantibodies and insulin use from electronic health records.

The expert panel stated that this initiative addressed an important and interesting question that could have significant clinical implications. Panelists expressed concern about relying solely on electronic health records to identify cases of type 1 diabetes, as these records may reflect misdiagnoses. The panelists felt that the initiative should be strengthened by gathering blood samples from study participants. These blood samples could be studied at a central laboratory for the presence of multiple relevant type 1 diabetes autoantibodies, which would clarify diabetes status. The panel felt that such an analysis of participant blood samples would be required to validate the data gained from analysis of electronic health records.

Research Using Biosamples and Subjects from Selected Type 1 Diabetes Clinical Studies
Primary discussants: Dr. Irl Hirsch, Dr. Jane Salmon, Dr. Elizabeth Selvin

This proposal is intended to continue to encourage projects requesting access to a "Living Biobank" comprised of: 1) people who have been characterized for risk of developing type 1 diabetes through the Type 1 Diabetes TrialNet (TrialNet) Pathway To Prevention Study and in ongoing TrialNet prevention studies; and 2) participants currently enrolled and followed for

diabetic complications in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Additionally, archived samples would also be available from the Type 1 Diabetes Genetics Consortium, Trial to Reduce IDDM in the Genetically at Risk, Type 1 Diabetes Prevention Trial-1, Immune Tolerance Network, Genetics of Kidneys in Diabetes, Network for Pancreatic Organ Donors With Diabetes, Clinical Islet Transplantation Consortium, and SEARCH for Diabetes in Youth. Providing support for type 1 diabetes ancillary studies increases the return from large investments in clinical studies and repositories. Over time, new type 1 diabetes trials and studies are completed and observational studies are expanded, resulting in the addition of new samples to the collections and new opportunities for research in well-characterized participants. In addition, new mechanistic questions and new technologies provide new research opportunities every year.

This initiative would support ancillary studies expected to generate scientific discoveries on type 1 diabetes primary pathogenesis or the pathogenesis of complications, and on biomarkers of disease progression or clinical responses to interventions. Where appropriate, a strong emphasis would be placed on highly collaborative, cooperative projects designed to maximize biomarker discovery and validation from limited sample resources. Studies of intermediate endpoints of disease progression or biomarkers that could be used to design cheaper, smaller, and shorter clinical trials would be especially encouraged.

The panel was enthusiastic about this proposal. The proposed initiative was felt to be a cost-efficient way to capitalize on existing data and sample repositories. Additionally, the support of ancillary studies was seen as a good method to introduce young investigators to the large studies providing the samples as well as maximizing use of available samples and existing infrastructure.

Type 1 Diabetes TrialNet: Charting New Routes on the Pathway to Prevention
Primary discussants: Dr. Betty Diamond, Dr. Robert Eckel, Dr. Jane Salmon

The NIDDK-led Type 1 Diabetes TrialNet (TrialNet) is an international consortium of clinical research centers aiming to prevent or delay onset of type 1 diabetes. TrialNet researchers are working to achieve this goal through understanding of the natural history of the disease, identifying persons at risk, and evaluating new therapies that balance potential risks and benefits. The goals of the consortium are: 1) prevention of type 1 diabetes; 2) conduct of mechanistic studies; and 3) conduct of trials and pilot studies in new-onset or at-risk populations to prepare for new type 1 diabetes prevention trials.

This proposal would aim to pursue all three of the above-stated goals. First, TrialNet would continue to screen relatives of people at risk for disease and to recruit and follow them in existing and future clinical trials for prevention of type 1 diabetes. Second, specific mechanistic Requests for Proposals would be developed by the TrialNet Biomarkers and Mechanisms Panel, other working groups, and the TrialNet Steering Committee. Third, though new-onset trial designs depend on the specific agent and therapeutic goals, the overall objective would be for smaller, faster trials. Short mechanistic or preliminary metabolic endpoint pilot trials would be conducted in at-risk populations. Studies would also be done, as needed, to determine drug formulation or dosing requirements once efficacy and safety information had been obtained.

The panel was supportive of TrialNet and felt that it is a valuable resource providing unique opportunities for people to take part in type 1 diabetes prevention trials. They emphasized that as research into the genetic and environmental causes of diabetes bears fruit and new possible prevention strategies come to light, TrialNet would allow these strategies to be efficiently tested. One panel member suggested that TrialNet should attempt as much as is practical to expand the racial and ethnic diversity of its participants. Additionally, several panelists pointed out that TrialNet has a unique opportunity to determine the possible effects of type 1 diabetes prevention interventions on neurocognitive development, as TrialNet continues to follow some participants who took part in type 1 diabetes prevention trials.

Immune Tolerance Network (ITN)
Primary discussants: Dr. Nigel Calcutt, Dr. Robert Eckel, Dr. German, Dr. Peter Gregersen, Dr. Jane Salmon

The Immune Tolerance Network (ITN) is a National Institute of Allergy and Infectious Disease-led 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 after kidney, liver, and pancreatic islet transplantation. The goals of the ITN with respect to type 1 diabetes are: 1) to develop and test novel immune therapies to prevent and treat type 1 diabetes through the induction of robust and long-lasting immunological tolerance; 2) to develop and validate assays to monitor the impact of these therapies on type 1 diabetes disease progression; 3) to gain new understanding of the immunologic mechanisms involved in the natural history and progression of type 1 diabetes and to use such information to formulate new treatment approaches; and 4) to develop bioinformatics and data analysis strategies for the interpretation of complex clinical and mechanistic data across type 1 diabetes trials and to define common features of immunity that may be shared between this and other autoimmune disorders.

(NOTE: all ITN proposals were discussed by the panel concurrently. Please see below for a summary of the combined panel discussion of these proposals.)

Sub-proposal A: Preserving Beta Cell Function with Immune Modulators in New-Onset Type 1 Diabetes
Despite progress toward understanding the genetic, environmental, and immunologic basis for type 1 diabetes, the prevention and cure of this condition remains elusive. While the autoimmune pathogenesis of type 1 diabetes is well established, and clinical trials with immunotherapeutic agents have demonstrated preservation of insulin secretion, these effects have not been long lasting. Nevertheless, preservation of even modest amounts of endogenous insulin secretion significantly improves quality of life and reduces long-term complications.

Ongoing and planned ITN studies are testing whether various interventions can preserve remaining beta cells in individuals with recently diagnosed type 1 diabetes. All of these studies examine the safety of these interventions and also conduct associated mechanistic assessments that are relevant to the specific interventions under investigation. Ongoing support for these studies to obtain safety data and type 1 diabetes outcome data, as well as detailed mechanistic

work, is critical to foster rational decisions in the design of future studies to promote a tolerogenic environment and sparing of beta cell death.

Sub-proposal B: A Robust Technology Platform for Assessing Islet-specific Autoimmunity in Type 1 Diabetes Clinical Trials

There is a compelling need for: 1) assays that will stratify people for entry into trials, to maximize the efficiency of enrollment; 2) assays that will elucidate mechanisms of clinical response in treatment or prevention trials; and 3) assays that predict poor outcomes early in the course of the trial, potentially enabling the use of flexible, adaptive trial designs. Rapid improvements in immunological assay technology, coupled with availability of genome-wide RNASeq and informatics resources, have transformed the ability to detect subtle changes in immunologic status within individuals. Advances in biomarker development utilizing similar technologies in other autoimmune diseases demonstrate the potential for type 1 diabetes research in this area.

Over the last year the ITN has partnered with leading investigators to perform pilot studies that create a type 1 diabetes assay pipeline, starting with frozen peripheral blood mononucleated cells in clinical trial specimens and now including informative RNASeq and cytometry profiling on individual participants. This subproposal would perform validation and optimization studies that would establish a proof-of-concept for use of this technology platform across multiple type 1 diabetes intervention studies. Such a platform may, in the future, benefit type 1 diabetes prevention studies conducted by Type 1 Diabetes TrialNet, and the initial testing of this cohort would be performed in collaboration with the Type 1 Diabetes TrialNet mechanistic studies group.

Sub-proposal C: ITN NOD Preclinical Consortium

The ITN NOD (non-obese diabetic mouse) Preclinical Consortium provides a platform for the rapid assessment of selected combinations of therapeutic agents for their efficacy in arresting progression of autoimmune-mediated beta cell loss in hyperglycemic NOD mice. This preclinical data assists the ITN in prioritizing novel therapeutic combination regimens and provides the basis for the development of future clinical trials treating people with new onset type 1 diabetes.

Two future combination protocols are being developed as preclinical studies for the consortium. First, the ITN Network Steering Committee has conceptually encouraged trials of Treg cells in combination with agents that should promote Treg cell durability and function. The preclinical consortium is designing a protocol to assess dose and timing of the Treg combination therapy, using the same NOD disease protocols successfully used in previous consortium studies. Second, pro-tolerogenic adjuvants are an attractive option in trials of antigen-specific therapy in type 1 diabetes, but none currently are validated for use in humans. This sub-proposal would carry out a preclinical combination protocol to test the combination of anti-IL6 plus antigen (likely insulin or proinsulin). An outcome that documents pro-regulatory boosting in the absence of effector cell expansion will be important for proceeding to develop future antigen delivery therapy for ITN trials in people.

Panel discussion of ITN proposals: The panel supported all three of the ITN proposals presented. The ITN was viewed as an effective and innovative program, and panelists were enthusiastic about the ITN's proposed focus on combination immunotherapies. The panel acknowledged that there is both possible risk and reward from such studies, with some panelists cautioning that long term risks of these agents are unknown but most feeling the benefits justified trials of carefully selected agents. The technology platform for assessing islet-specific autoimmunity was viewed as a useful step toward making type 1 diabetes trials more user-friendly, which might encourage people with type 1 diabetes to participate in clinical trials. Panelists supported the NOD Preclinical Consortium as an efficient and cost-effective way to test approaches before they are considered for clinical trials. The discussion acknowledged that although the NOD mouse model does not perfectly replicate type 1 diabetes in humans (and thus can give false positive or false negative results for treatment regimens compared to those regimens' effectiveness in clinical trials in people), this model is still a valuable preclinical screening step.

The Environmental Determinants of Diabetes in the Young (TEDDY)
Primary discussants: Dr. Betty Diamond, Dr. Mark Espeland, Dr. Gregersen, Dr. Rudolph Leibel

The Environmental Determinants of Diabetes in the Young (TEDDY) is an NIDDK-led observational cohort study with the goal of identifying 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 may result in new strategies to prevent, delay, or reverse type 1 diabetes. TEDDY's international consortium of six Clinical Centers and a Data Coordinating Center completed recruitment in 2010. The study was designed to follow participants for 15 years to accrue approximately 800 participants who develop autoantibodies and 400 participants who develop diabetes. As of November 2014, 605 participants have reached the primary endpoint (*i.e.*, appearance of one or more islet autoantibodies confirmed at two consecutive visits), and 194 participants have reached the second primary outcome (*i.e.*, development of type 1 diabetes).

(NOTE: all TEDDY proposals were discussed by the panel concurrently. Please see below for a summary of the combined panel discussion of these proposals.)

Sub-proposal A: Continued Follow-up of TEDDY Subjects
Continued follow-up of TEDDY participants is needed to achieve the overall goals of TEDDY and build on the investment to date. TEDDY plans to conduct analyses from participant samples in two phases. TEDDY has initiated the first phase of analysis of specific demographic, genetic, genomic, epigenetic, psychosocial, dietary, infectious, environmental, metabolomic, and proteomic measures. The second phase of analyses will relate these measures to the development of islet autoimmunity and type 1 diabetes at the conclusion of follow-up. TEDDY has designed and implemented an imbedded case-control study from which samples from selected participants are being analyzed for gene expression, the microbiome, plasma viral metagenomics, metabolomics, and proteomics. Also, DNA from these same participants will undergo whole genome sequencing and analysis, making it possible to analyze each of the

"omics" studies in the same population and to integrate findings across several "omics" studies. The continued follow-up would validate the findings observed from the case-control study analysis as well as allow testing for other hypotheses for which additional power is needed.

Sub-proposal B: Immunological Assessments of TEDDY Subjects
Over 500,000 serum, 700,000 plasma, and 70,000 peripheral blood mononuclear cell (PBMC) samples have been collected from TEDDY participants. These specimens provide a unique opportunity for scientists to test novel hypotheses. In the next phase, the plan is to interrogate samples from TEDDY participants regarding key questions concerning the etiology of type 1 diabetes. This would be done by assessing PBMC, serum, and plasma samples using different immunologic assays for development of islet autoimmunity and diabetes, such as large-throughput multiparameter protein and gene profiling of global immune cells and of antigen-specific T and B cells at the single cell level.

Sub-proposal C: Epigenetic Modifications in TEDDY Subjects
TEDDY offers a unique opportunity to study the role of epigenetic modifications in the development of type 1 diabetes. The biological processes underlying states of health and disease—involving interactions between many genes and external influences—are likely to be driven by DNA sequence variants as well as non-coding modifications that affect the transcriptional capacity of these genes. Transcriptional profiles depend on the interplay between epigenetic modifications, interacting proteins, non-coding RNAs, and inter- and intra-chromosomal interactions, as well as on factors yet to be discovered, and perturbation of these regulatory elements may have profound consequences on health. TEDDY has collected DNA samples from TEDDY participants 2 to 4 times per year throughout their participation in the study, and cord blood samples are also available. TEDDY would like to characterize the occurrence and potential functions of epigenetic modifications in these samples, toward understanding how epigenetic regulatory mechanisms contribute to beta cell autoimmunity and type 1 diabetes.

Panel discussion of TEDDY proposals: All three TEDDY proposals were met with high enthusiasm from the panel. The panelists viewed the TEDDY study and its collected samples as an invaluable resource, and they felt that TEDDY follow-up should continue. The analysis of the TEDDY sample set, including the immunological and epigenetic assessments suggested, are expected to yield significant insights into the causes of type 1 diabetes. Panel members noted that TEDDY's sample archive is an irreplaceable resource and that great care should be taken to carefully choose analysis methods and to coordinate that analysis to maximize the data that can be gleaned from the limited samples available. There was support for studies using abundant samples (such as DNA) from TEDDY and a general feeling that the use of precious samples (such as PBMCs) should be reserved for the most critical and hypothesis-driven studies. Making iPSC from TEDDY biosamples would be valuable. The panelists noted that TEDDY is a good opportunity to collect neurocognitive assessment data, and several neurocognitive assessment tools aimed at pediatric populations were discussed.

Trial to Reduce IDDM in the Genetically at Risk (TRIGR)
Primary discussants: Dr. Betty Diamond, Dr. Mark Espeland, Dr. Peter Gregersen

The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) trial, led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, tests the hypothesis that weaning to an extensively hydrolyzed infant formula reduces the cumulative incidence of type 1 diabetes by the age of 10-14 years in children at risk of developing type 1 diabetes. The trial randomized 2,159 infants with at least one family member affected by type 1 diabetes and a human leukocyte antigen (HLA) genotype conferring increased disease susceptibility. Infants were weaned either to an extensively hydrolyzed casein-based formula or a conventional cow's milk-based formula. TRIGR participants have been tightly monitored for the appearance of diabetes-associated autoantibodies. The first endpoint (*i.e.*, positivity for ≥2 autoantibodies by the age of 6 years) was reached in 2013. There was no significant difference between the two treatment groups in the cumulative incidence of positivity for multiple autoantibodies at that time. This outcome does not exclude the possibility that the intervention may have an effect on clinical development of type 1 diabetes.

The purpose of this proposal would be to complete the follow-up of each TRIGR participant to age 10 years (February 2017) and to complete all data analyses. When accrual and follow-up are completed, the TRIGR study would have the world's largest and longest experience in the identification, recruitment, and follow-up of newborn infants with a first-degree relative with type 1 diabetes and increased HLA genetic risk. In addition, TRIGR would have amassed an extremely valuable repository of dietary data and blood samples for analysis. Completion of this trial to its designed endpoint would help to resolve the controversy regarding the role of early cow's milk feeding in the etiology/pathogenesis of type 1 diabetes.

The panel supported follow-up of the TRIGR participants up to the age of 10 years and recognized that the TRIGR cohort was a valuable resource. The panel also supported the sharing of TRIGR resources with other clinical trials for further analysis. Since TRIGR's sample collection is the same protocol as that used for the family component of The Environmental Determinants of Diabetes in the Young, the TRIGR sample database also may contribute to other datasets, especially since at the end of the study, samples will be widely available and perhaps available through programs such as the Living Biobank.

TOPIC 8: BETA CELL: ASSESSMENT AND THERAPIES

Current Efforts in Beta Cell Assessment and Therapies

Dr. Fradkin noted that ongoing investigator-initiated grants supported by the Program include five awards made under the "Human Islet Research Network: Consortium on Targeting and Regeneration (HIRN-CTAR)" RFA (RFA-DK-13-015); four awards made under the "Human Islet Research Network: Consortium on Human Islet Biomimetics (HIRN-CHIB)" RFA (RFA-DK-13-016)"; four awards made under the "Human Islet Research Network: Consortium on Modeling Autoimmune Interactions (HIRN-CMAI)" RFA (RFA-DK-13-017); and six awards made under the "Human Islet Research Network: Consortium on Beta-cell Death and Survival (HIRN-CBDS)" RFA (RFA-DK-13-018). In addition, awards are expected to be made in FY 2015 under the following: Consortium on Beta-cell Death and Survival (HIRN-CBDS) (RFA-DK-14-021).

Cellular Therapies for Type 1 Diabetes Consortium
Primary discussants: Dr. Ronald Gill, Dr. Maike Sander, Dr. Robert Sherwin
The current cellular therapy for type 1 diabetes is human allogeneic islet transplantation, which requires immunosuppression for graft survival. The Clinical Islet Transplantation (CIT) consortium (co-led by the NIDDK and National Institute of Allergy and Infectious Disease) has been conducting pivotal (phase III) islet alone and islet after kidney trials, as well as pilot studies, in islet transplantation. The islet alone pivotal trial has been completed, and the results have been submitted for publication and are being prepared for submission to the U.S. Food and Drug Administration (FDA). The FDA will evaluate the results and determine if they are sufficient for licensure of the human islet as a biologic product. Despite the excellent results from the islet alone pivotal study, important limitations remain. Pancreas availability limits the number of people who could be treated with human organ-derived islets, and the current immunosuppression regimen has significant adverse effects.

The major goal of this proposal is to advance research on cellular therapies used to treat type 1 diabetes through either investigator-initiated clinical research or a clinical consortium. The approaches could include evaluating additional pharmacologic or cellular treatments to significantly improve human islet transplantation or the use of alternative insulin-producing cellular or bio-artificial products. Additionally, next-generation regulated insulin-producing cells and other products are being developed and could be available for study when the consortium will be launched.

The panel felt that the recent advances in cellular therapy have been extremely encouraging and there was some support for this proposal. The panelists commented that the type 1 diabetes cellular therapy field is at a crossroads and future initiatives should be determined based on the evolving state of the field. While further advancements require continued investment in this area, the costs of research will become much more manageable after regulatory approval of cell-based therapy. Such approval and subsequent insurance coverage would greatly facilitate leveraging the important infrastructure maintained by the CIT consortium. Panelists noted that there is a need in this area to determine best practices to support the use of next-generation cellular therapy products in people, such as how to encourage engraftment and prevent rejection.

PATIENT PERSPECTIVE

Ms. Ellen Leake provided comments on the proposals from the patient perspective. She emphasized that it was extremely exciting to hear about the research opportunities described at the meeting and to see the variety of projects that may be supported by the *Special Diabetes Program*. She encouraged further type 1 diabetes research, including research into type 1 diabetes biomarkers and efforts to make continuous glucose monitors more user friendly for both people with type 1 diabetes and clinicians. Ms. Leake was particularly struck, she said, by discussion of type 1 diabetes genetics research and how such research moving forward might reveal even more gaps in our knowledge about type 1 diabetes. It is, she said, difficult to distinguish between research that needs to be done and research that we do not yet know we need to do, as there is still so much more to learn. Finally, she thanked the panelists and NIH and CDC staff and encouraged all present to work to fill the knowledge gaps about type 1 diabetes and move the field forward.

ADDITIONAL DISCUSSION

The expert panel also 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:

- Standardization of continuous glucose monitor (CGM) data to ease use and clinical analysis— Glycemic control was central to many discussions, and with CGMs becoming the standard of care, panelists identified the need for standards to guide the analysis and use of CGM data. The field could benefit from agreement among clinicians in areas such as how to define hypoglycemia and how to measure time in range. One panelist proposed a workshop to standardize glucose metrics and definitions for clinical and research work involving CGMs, as such a workshop could influence many of the issues discussed at this planning meeting.
- Defining type 1 diabetes to allow identification of different disease subgroups – Discussion at several points acknowledged that it is sometimes difficult to define type 1 diabetes, particularly in cases when insulin is not immediately needed or when older children who are overweight or obese present with diabetes. Panelists acknowledged that beta cell function, for example, is often used as a defining metric but also pointed out that many things affect beta cell function and that current technologies for assessing beta cell function are insufficient. There is a need for a clear definition(s) of type 1 diabetes (with acknowledgement that type 1 diabetes may include several sub-diseases) so that the type 1 diabetes population can be further defined. Such definition(s) may allow subgroup analyses that will aid in determining how best to treat these different sub-populations.
- Defining diabetes type for people on dialysis as a result of end-stage kidney disease – The panel noted that some doctors do not know whether their dialysis patients have type 1 or type 2 diabetes; they just know that they have some form of diabetes. One area of opportunity is to determine which type of diabetes people on dialysis have. Although this could be difficult to discern, it would be important since optimal care of these patients may be influenced by diabetes type.
- Continued and enhanced collaboration among large clinical trials to enhance efficiency – In many discussions of proposals for large clinical trials, increased or continued collaboration with other trials and consortia was suggested. The panelists urged consortia spearheading trials to facilitate the merging of sample sets (where appropriate) to conserve resources and to glean as much information as possible. For example, a panelist suggested offering participants screened for one trial the opportunity to participate in another that might better suit their needs, thus allowing their previous efforts and samples to be conserved and to benefit different protocols.
- Linking new investigators with established investigators – The panel suggested that, when research efforts involve young investigators, the NIH should find ways to connect them with more established investigators (*e.g.*, in ongoing research consortia) in order to foster collaborations and expose the new investigators to the broader type 1 diabetes community. This could help retain the young investigators in the type 1 diabetes research field.

APPENDIX 1: PANEL MEMBERS

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APPENDIX 2: ACRONYMS

Organizations

ADA	American Diabetes Association
CDC	Centers for Disease Control and Prevention
DMICC	Diabetes Mellitus Interagency Coordinating Committee
HHS	U.S. Department of Health and Human Services
JDRF	Juvenile Diabetes Research Foundation
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health

Research Programs

CITR	Collaborative Islet Transplantation Registry
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
HPPAP	Human Pancreas Procurement and Analysis Program
IIDP	Integrated Islet Distribution Program
ITN	Immune Tolerance Network
nPOD	Network for Pancreatic Organ Donors with Diabetes
NGSP	National Glycohemoglobin (HbA1c) Standardization Program
NHANES	National Health and Nutrition Examination Survey
SBIR	Small Business Innovation Research
STTR	Small Business Technology Transfer
TEDDY	The Environmental Determinants of Diabetes in the Young
TRIGR	Trial to Reduce IDDM in the Genetically At-Risk

Other Acronyms

CVD	cardiovascular disease
DKA	diabetic ketoacidosis
DNA	deoxyribonucleic acid
FOA	funding opportunity announcement
FY	fiscal year
HbA1c	hemoglobin A1c
HLA	human leukocyte antigen
PBMC	peripheral blood mononuclear cell
RFA	Request for Applications
RNA	ribonucleic acid