

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

**April 26-27, 2017  
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 26-27, 2017. 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) 2018 and 2019. 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:** To inform decisions about how best to use a possible extension of the *Special Diabetes Program* funds, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) prospectively convened a panel of 24 scientific and lay experts to solicit input on future research directions. The 23 scientists had expertise in a variety of areas, including type 1 diabetes, type 2 diabetes, diabetes complications, genetics, immunology, beta cell biology, behavioral research, clinical trial design, epidemiology, translational research, 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/initiatives to other Diabetes Mellitus Interagency Coordinating Committee (DMICC) member organizations for research that could be pursued in FY 2018 and/or FY 2019, if the funds were extended. Specifically, the NIDDK requested proposals for:

- 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-two proposals, submitted by four NIH Institutes and the Centers for Disease Control and Prevention (CDC), were presented to the panel. The proposals comprised 20 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 32 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 five broad topics related to type 1 diabetes research:

- Autoimmune Etiology, Clinical Trials, and Epidemiology
- Beta Cells: Assessment and Therapies
- Diabetes Complications
- Clinical Management
- Artificial Pancreas

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 involved in an ongoing program were asked to leave the room during the relevant panel discussion. 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, including contributing to the development of the first hybrid artificial pancreas that was recently approved by the U.S. Food and Drug Administration (FDA), and noted that many of these advances would not have been possible without *Special Diabetes Program* funding. He stated that the NIDDK places a high priority on administering the *Special Diabetes Program* funds and maximizing their value. The input provided by the panel at today's meeting 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. 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 [Special Statutory Funding Program for 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, the American Diabetes Association (ADA), and the Leona M. and Harry B. Helmsley Charitable Trust. Additionally, planning and evaluation meetings such as this workshop have been pivotal to the effective use of *Program* funds. These meetings are one way that the NIDDK obtains 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. A [Diabetes Research Strategic Plan](#) (2011) also serves as an important guidepost for type 1 diabetes research. This Plan was 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, the recent FDA approval of a hybrid artificial pancreas and additional ongoing trials testing novel devices, 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, completion of an islet transplantation trial aimed at validating a process for islet cell manufacturing for submission to the FDA as a biologic product, a method for large-scale production of beta cells, and identification of distinct beta cell subtypes. Additional information on *Program* achievements is available in the [Special Statutory Funding Program for Type 1 Diabetes Research: Progress Report](#). 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. Additionally, *Program* funding has been used to create major new long-term initiatives, such as The Environmental Determinants of Diabetes in the Young (TEDDY), the Beta Cell Biology Consortium, the Human Islet Research Network (HIRN), and the Type 1 Diabetes TrialNet (TrialNet). These large-scale, long-term, ambitious efforts were designed to

promote progress in type 1 diabetes research that could not be achieved by a single laboratory and may not have been possible otherwise. *Special Diabetes Program*-supported research has made major scientific accomplishments, and has also created a foundation for future advances in the years to come.

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 high enthusiasm for 26 of the proposals—either as presented or with enhancements. Those 26 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 the proposed Funding Opportunity Announcement.

### **TOPIC 1: AUTOIMMUNE ETIOLOGY, CLINICAL TRIALS, AND EPIDEMIOLOGY**

#### ***Current Efforts in Autoimmune Etiology, Clinical Trials, and Epidemiology***

Dr. Fradkin provided an overview of the current autoimmune etiology, clinical trials, and epidemiology research portfolio, including discussion of ongoing programs in which funding decisions have already been made, such as the SEARCH for Diabetes in Youth Study and Programs to Standardize C-peptide and HbA1c Assays. Dr. Fradkin also noted that ongoing investigator-initiated grants supported by the *Program* include one “Type 1 Diabetes Pathfinder Award” (RFA-DK-15-030), two awards made under “Research Using Subjects from Selected Type 1 Diabetes Clinical Studies (Living Biobank)” (PAR-14-258), one award made under “Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies” (PAR-14-257), three awards made under “Understanding the Pathogenesis and Etiology of Type 1 Diabetes Using Biosamples and Subjects from Clinical Studies” (RFA-DK-15-018), and six awards made under “Mechanisms Underlying the Contribution of Type 1 Diabetes Risk-Associated Variants” (RFA-DK-15-025). In addition, new awards are expected to be made in Fiscal Year 2017 under “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 (R43/R44)” (RFA-DK-15-024).

#### ***Mechanisms Underlying the Contribution of Type 1 Diabetes Disease-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. 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 risk loci and the number of potential candidate genes; has identified several additional novel type 1 diabetes risk loci that have been implicated in other autoimmune diseases; and, in nearly one-half of the loci, found association with one putatively causal gene. The result of the ImmunoChip analysis now accounts for nearly 80 percent 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. New biological insights that arise from studying the function of these genes could be translated to clinical benefits, including identifying reliable biomarkers and developing effective strategies for screening and disease prevention.

This proposal would focus on recruiting integrative teams and individual investigators for projects to determine the mechanisms underlying the contribution of the disease-associated variants for type 1 diabetes. The proposed studies would be expected to 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 commented that there has been significant effort in the genetics field to find causal and protective variants of disease, and type 1 diabetes has led the way. They felt that the focus of this proposal should be on understanding the function of already identified genetic regions, rather than on identifying new regions, as that is being pursued in other venues. Understanding function could shed light on the pathophysiology of type 1 diabetes, illuminate new prevention or treatment targets, and be applicable broadly to type 2 diabetes. The panel suggested that the type 1 diabetes genetics field consider increasing interaction with the type 2 diabetes genetics field, building on efforts such as the Accelerating Medicines Partnership (<https://www.nih.gov/research-training/accelerating-medicines-partnership-amp>); think about how to prioritize which genetic regions are studied for function; consider studying families of people with type 1 diabetes to identify high-penetrance genetic factors; and pursue research to determine how genetic penetrance is influenced by other factors in the genome.

***Incidence of Type 1 Diabetes among Young Adults: Diabetes in Young Adults (DIYA) Study***  
*Primary discussants: Dr. James Meigs, Dr. Trevor Orchard, Dr. Elizabeth Selvin*

A current gap in knowledge is that, although half of the cases of type 1 diabetes occur in adulthood, there are limited data on the incidence of type 1 diabetes in the U.S. adult population. This is due, in part, to the difficulty of distinguishing between type 1 and type 2 diabetes in this population and performing complete case ascertainment in fragmented health care systems. Findings on temporal trends in type 1 diabetes incidence in the adult population have also been inconclusive. The Incidence of Type 1 Diabetes Among Young Adults: Diabetes in Young Adults (DIYA) Study is a Centers for Disease Control and Prevention-led program that aims to answer important questions related to incidence of type 1 diabetes in the young adult population. The current 2-year DIYA study includes one site to assess the feasibility, costs, accuracy, and timeliness of a surveillance system for type 1 diabetes in this population.

The goal of this proposal is to support the second phase of the DIYA study. While the current study is powered to determine differences in type 1 diabetes incidence among males and females,

it is unlikely to provide information about differences by race/ethnicity and is not long enough to detect trends in incidence. The exact research goals and objectives of the second phase will depend on the initial results from the current 2-year project. Possible directions include expanding the study to multiple sites and including a central laboratory for the measurement of diabetes autoantibodies (DAA); or expanding the study to additional sites using electronic health records (EHRs), without the measurement of DAA.

The expert panel stated that this was an extremely important initiative because it is currently unknown how many people in the United States have type 1 diabetes. Additionally, physicians do not have the clinical tools to diagnose adults with new-onset diabetes as having type 1 or type 2. Obese adults with type 1 diabetes may be misdiagnosed as having type 2 diabetes and treated with type 2 diabetes drugs, such as SGLT2 inhibitors, that could lead to diabetic ketoacidosis. Thus, it is critical not only to determine the incidence and prevalence of type 1 diabetes in the U.S. young adult population, but also to develop clinical tools that physicians could use to make correct diagnoses. Generally, the panel was in favor of expanding the number of sites, to get national representation; they also thought that use of EHRs alone may not be sufficient and encouraged the inclusion of DAA measurement. They also felt that performing additional phenotyping would be critical to the success of this effort. However, because the 2-year pilot study was recently launched and no data are yet available, the panel felt that it was important to wait for pilot data before moving forward. They suggested holding a workshop, to include representatives from different health systems, when those data are available, to develop an approach for the second phase of the study.

### ***The Environmental Determinants of Diabetes in the Young (TEDDY)***

*Primary discussants: Dr. Mark Espeland, Dr. James Meigs, Dr. Matthias Von Herrath*

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, collecting data and biosamples, to accrue approximately 800 participants who develop autoantibodies and 400 participants who develop type 1 diabetes. As of November 2016, 658 participants have reached the primary endpoint (*i.e.*, appearance of one or more islet autoantibodies confirmed at two consecutive visits), and 246 participants have reached the second primary outcome (*i.e.*, development of type 1 diabetes).

#### ***Sub-proposal A: Continued Follow-up of TEDDY Subjects***

The purpose of this proposal was to support the continued follow-up of TEDDY participants. Continued follow-up 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 and will relate these measures to the development of islet autoimmunity and type 1

diabetes. The second phase of analyses will interrogate these measures in participants who have reached the outcomes at a later age, thus potentially representing a different phenotype of disease. The continued follow-up could, for example, also allow testing for other hypotheses for which additional power is needed.

*Sub-proposal B: Assessments of Toxins and Other Environmental Factors in TEDDY Samples*  
Toxins and toxicants in foods or water might activate autoimmune mechanisms in genetically susceptible individuals, and exposure to them might result in pancreatic islet cell death. The list of elements, man-made chemicals, and naturally occurring mycotoxins that have been suggested to be associated with type 1 diabetes is long, and the list of chemical agents capable of producing or exacerbating autoimmune manifestations in susceptible individuals is constantly growing. This proposal would interrogate TEDDY's unique resources to determine the chemical exposomes and answer key questions about the etiology of type 1 diabetes.

Both TEDDY proposals were met with high enthusiasm from the panel. The panelists commented that the TEDDY study and its collected samples were an invaluable resource, and they felt that follow-up should continue. They suggested that the NIDDK consider holding a bioinformatics workshop to discuss and develop overarching plans for understanding the massive amount of data that is emerging from the study. The panel was also highly supportive of the proposal to investigate the role of environmental toxins. TEDDY is a unique resource with which to examine this area, and conducting a study of toxins may also help to retain the interest and enthusiasm of TEDDY families who are interested in learning about the contribution of toxins to disease development. The panel encouraged the TEDDY investigators to take an unbiased approach when examining toxins, suggested that TEDDY coordinate its efforts with the NIH's Environmental Influences on Child Health Outcomes program (<https://www.nih.gov/echo>), and noted that the study may find several toxins that contribute small effects rather than a single toxin that causes a large effect. To find the latter, it may be necessary to study populations at low genetic risk of developing type 1 diabetes.

### ***Type 1 Diabetes TrialNet***

*Primary discussants: Dr. Robert Eckel, Dr. Mark Espeland, Dr. R. John Looney*

The NIDDK-led Type 1 Diabetes TrialNet (TrialNet) is a 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 to conduct: 1) prevention trials, 2) mechanistic studies, and 3) 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 continue TrialNet to pursue all three of the above-stated goals. First, if TrialNet's Oral Insulin Trial shows positive benefit in the delay of disease, the Network would build on the positive results by conducting new trials of oral insulin, most likely in combination with other agents; TrialNet is also making plans for new prevention trials if the oral insulin treatment provides no benefit. Second, TrialNet has identified key scientific questions that will guide future studies and new trials, and plans to begin integrated, multi-dimensional studies

using innovative statistical designs with TrialNet clinical data and samples. Third, TrialNet has two new-onset studies in protocol development that could be supported. 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 enthusiastic about TrialNet and commended the Network on its productivity, including its impressive publication record. They thought that the mechanistic studies conducted by TrialNet have been informative and should continue. They also felt that the TrialNet infrastructure was important to support. As research into the genetic and environmental causes of diabetes identifies new possible prevention strategies, TrialNet would allow these strategies to be efficiently tested. There was discussion among the panel members about the types of agents to test through TrialNet. They recommended future prevention studies be guided by the results of ongoing prevention and new onset studies. They also suggested that future therapies tested through the Network focus on immunomodulatory drugs that have long-lasting effects with short-term treatment—so that people do not have to take the drugs for the rest of their lives—or are antigen based (*e.g.*, oral insulin). It is also possible that combination therapy will be needed—*e.g.*, treatment with a drug to “reset” the immune system followed by maintenance therapy. The panel felt that TrialNet is well positioned to determine what approaches may work best at preventing type 1 diabetes in those at risk for developing the disease.

### ***Immune Tolerance Network (ITN)***

*Primary discussants: Dr. Robert Eckel, Dr. Mark Espeland, Dr. R. John Looney*

The Immune Tolerance Network (ITN) is a National Institute of Allergy and Infectious Diseases (NIAID)-led consortium dedicated to the 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 to: 1) develop and test novel immune therapies to prevent and treat type 1 diabetes through the induction of robust and long-lasting immunological tolerance, 2) develop and validate assays to monitor the impact of these therapies on type 1 diabetes disease progression, 3) 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, 4) 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, and 5) encourage and provide open access for the biomedical community to ITN’s type 1 diabetes trial data.

This proposal would continue support for the ITN and advance therapeutic strategies that will stop progressive autoimmune destruction of pancreatic beta cells in people with recent-onset or developing type 1 diabetes by exploiting immune tolerance mechanisms and immunomonitoring tools in the context of innovative clinical trials. In particular, three components of ITN’s Strategic Plan for Type 1 Diabetes, developed in collaboration with NIAID, NIDDK, and JDRF, are ready for implementation in Fiscal Years 2018-2019: 1) strategic immunomodulation, 2)

clonotypic profiling—a precision medicine initiative, and 3) type 1 diabetes immune biomarker validation.

The panel was supportive of the ITN, saying that it has made good progress and that it remains worthwhile to continue to fund studies in new-onset type 1 diabetes, including testing approaches toward antigen-specific tolerance. A panel member commented that the ITN could provide much needed information about how to “rank” immune modulators by determining, for example, how long drugs need to be given to patients to be effective—*e.g.*, for other autoimmune diseases, a drug may need to be administered for a year, but may require a shorter administration for treating new-onset type 1 diabetes. A panel member thought that, related to the clonotypic expansion of islet-antigen specific T cells, it may be necessary to expand T cells from islets in addition to the peripheral blood. Another panel member encouraged the ITN to involve and leverage the expertise of non-diabetes experts participating in the Network on the type 1 diabetes studies.

### ***Immune System Engineering for Targeted Tolerance in Type 1 Diabetes***

*Primary discussants: Dr. Megan Levings, Dr. R. John Looney, Dr. Matthias von Herrath*

Type 1 diabetes results from the autoimmune destruction of the insulin-producing pancreatic beta cells. It may be possible to change the course of the disease, or to prevent it entirely, by interfering with pathways that lead to autoimmune pathogenesis and thus re-establishing tolerance. Toward this goal, personalized, effective, and organ-targeted therapies are needed. Advances in cancer therapy could provide an opportunity for such new therapies in type 1 diabetes. Recent discoveries in the field of cancer immunology demonstrate that tumors can evolve to evade the immune system. They do this, in part, by activating the normal mechanisms by which undamaged or uninfected cells turn off immune responses after an infection. Several new, highly effective cancer therapies in use today subvert that process and reawaken immune cells, or engineer immune effector cells to recognize cancer cells and directly bypass inhibitory mechanisms. Building on this success and focusing on autoimmunity, developing interventions based on targeting mechanisms of tolerance has the potential to lead to novel therapeutic agents to prevent or treat disease, including both immunomodulatory drugs and cellular therapy.

The purpose of this proposal is to support research on novel ways to safely restore self-tolerance in people with autoimmune diseases like type 1 diabetes. It would explore, first in a workshop, and later through a Funding Opportunity Announcement (FOA), research on de-activating immune responses specifically and safely through the development of tolerizing vaccines and/or inhibitory compounds. It would also explore the prospects for engineering immune regulation in the context of autoimmune attack through the direct manipulation of regulatory and other cells types for applications in cell therapy.

The panel had high enthusiasm for this proposal, and felt that pursuing it now was timely to build on the recent successes in cancer immunotherapy. The proposed studies would be done in a pre-clinical setting, but would benefit from the clinical infrastructure that has been built for cancer. The panel members encouraged the FOA to include assay development for measuring tolerance, as well as to challenge researchers with testing their tolerance approaches in the context of combination therapies. The panel also suggested ensuring that approaches that move forward to

a clinical setting be appropriately robust, as sometimes there are robustness issues when testing therapies in different models. The panel also encouraged the NIDDK to involve the allergy research community in this effort, in addition to the cancer community.

### ***The Characterization and Discovery of Novel Autoantigens in Type 1 Diabetes***

*Primary discussants: Dr. Peter Gregersen, Dr. Matthias von Herrath*

Type 1 diabetes is an autoimmune disease that is thought to be caused, in part, by a T cell-mediated destruction of insulin-producing beta cells. High risk for disease, in those with genetic susceptibility, is predicted by the presence of two or more autoantibodies with different specificities. Autoantibodies against insulin, GAD65, IA-2, and ZnT8 are commonly known as the major specificities in type 1 diabetes. Despite this knowledge, it is still unknown what leads to the breakdown of tolerance, and there is a poor understanding of type 1 diabetes etiology and pathophysiology. The continued identification and characterization of type 1 diabetes-relevant antigen epitopes for both autoantibodies and T cells is critically important for understanding the etiology and pathophysiology of type 1 diabetes. Powerful new technologies provide opportunities to facilitate a more complete discovery and characterization of autoantigens and the immune response to them. Indeed, several neoantigens like insulin hybrid peptides and other post-translationally modified peptides have been recently reported but their responses need to be better characterized.

The overarching goal of this initiative is to discover new autoantigens and characterize the T-cell and humoral responses of both new and previously identified autoantigens in type 1 diabetes. The longer-term goals are to use these autoantigens/epitopes, and their responses, to monitor disease progression and treatment and, potentially, to inform the use of autoantigens as therapeutics. To achieve these goals, the proposal would first bring together technology and diabetes experts in a workshop to discuss the current state-of-the-science. This workshop would then help to inform the development of a Funding Opportunity Announcement (FOA) on this topic. Both the workshop and FOA would facilitate the formation of interdisciplinary teams.

The panel was supportive of this proposal—identifying new autoantigens can inform novel therapeutic approaches and provide insights about how to interpret genetic findings. They stated that it was important to consider post-translationally modified proteins as possible autoantigens, and to determine which newly discovered peptides are found in the pancreas. Additionally, the panel encouraged the NIDDK to take a systematic approach to identifying new autoantigens, like has been done through other NIH-supported efforts such as the Immune Epitope Database and Analysis Resource (IEDB; <http://www.iedb.org/>). Collaboration with the IEDB could enhance this effort.

### ***Mass Spectrometric Assays for the Reliable and Reproducible Detection of Proteins/Peptides of Importance in Type 1 Diabetes Research***

*Primary discussants: Dr. Rudolph Leibel, Dr. Megan Levings*

Many assays in basic and clinical science research rely on antibodies. However, there are no widely accepted guidelines or standardized methods to determine the validity of these reagents. Furthermore, many recent publications have highlighted that commercial antibodies often fail to detect the intended target, and concerns have been raised about several questionable assays used to detect and/or quantify peptides or proteins. The rigor and reproducibility of many commonly used immunoassays could be improved substantially by applying mass spectrometry (MS) instead of relying only on antibodies. Within the last decade, major improvements in instrumentation and data handling have made MS-based targeted proteomics a highly reproducible methodology for detecting and quantifying proteins/peptides. Reliable MS assays and internal standards to harmonize different laboratory practices would be of value and could be developed for commonly quantified proteins relevant to type 1 diabetes. The major advantages of targeted MS assays are that they are highly reproducible across laboratories, they can be easily multiplexed, and they are relatively less expensive when compared to a typical ELISA.

The purpose of this proposal is to develop reliable and reproducible MS assays for some key proteins and peptides of interest in type 1 diabetes research. To determine the target list and the matrix in which the assays should be developed, a Request for Information (RFI) would be published to solicit suggestions. Responses to the RFI would inform the publication of a Funding Opportunity Announcement to establish an interdisciplinary team with expertise in physiology, type 1 diabetes, and MS.

The panel was enthusiastic about this proposal. They felt that this research was needed not just because of the problems with immunoassays described above, but also because it could be used to discover novel molecules and, ultimately, be used to study those novel molecules in clinical samples. A panel member suggested that a clinical chemist be included in the proposed interdisciplinary team.

### ***Research Using Subjects from Selected Type 1 Diabetes Clinical Studies***

*Primary discussants: Dr. Robert Eckel, Dr. Georgeanna Klingensmith, Dr. Elizabeth Selvin*

Ancillary studies to type 1 diabetes clinical studies increase the return on the large investments made in the parent studies. Over time, new type 1 diabetes trials and studies are completed and observational studies are expanded, resulting in the addition of samples to the collections and new opportunities for research in well-characterized participants. In addition, novel mechanistic questions and emerging technologies provide new research opportunities.

This proposal is intended to encourage projects requesting access to participants in clinical studies—a “Living Biobank.” Examples of participating studies include Type 1 Diabetes TrialNet and the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Other studies could be included as well, such as artificial pancreas clinical trials. The supported ancillary studies would be 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 bring new topic experts to the parent study. 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 very supportive of this proposal. They felt that it was a cost-effective way to capitalize on the investment that has already been made in existing studies. It also provides a good opportunity to pursue research, for example, on psychological issues affecting people with type 1 diabetes, particularly with respect to artificial pancreas studies. The panel also commented that the support of ancillary studies is especially important for junior investigators, to introduce them to the large studies providing the samples, as well as to provide them with access to the studies' senior scientists and existing infrastructure.

## **TOPIC 2: BETA CELLS: ASSESSMENT AND THERAPIES**

### ***Current Efforts in Beta Cell Assessment and Therapies***

Dr. Fradkin provided an overview of the current research portfolio, including discussion of ongoing programs in which funding decisions have already been made, such as the Integrated Islet Distribution Program, the Collaborative Islet Transplant Registry, and the Clinical Islet Transplantation Consortium. She also noted that there is one ongoing investigator-initiated grant supported under the Type 1 Diabetes Pathfinder Award (RFA-DK-15-030). In addition, awards are expected to be made in Fiscal Year 2017 under “Therapeutic Targeting of the Human Islet Environment” (RFA-DK-17-003) and “Competitive Collaborative Projects for Human Islet Biology” (RFA-DK-17-004).

### ***Development of New Technologies and Bioengineering Solutions for the Advancement of Cell Replacement Therapies for Type 1 Diabetes***

*Primary discussants: Dr. Vincent Poitout, Dr. Robert Sherwin*

Even with significant recent progress in the field of islet transplantation, there is still limited viability of engrafted islets and even the most innovative immunosuppressive regimens required for transplant survival still have significant side effects. There is, therefore, a need to support innovative research, in both academic centers and small businesses, for the development of novel technologies for bioartificial cell replacement therapy that minimize the need of immunosuppression.

This initiative would support research to develop: 1) novel, smart, and safe biomaterials, scaffolds, matrices, and barriers to protect grafted cells from immune rejection; 2) methods to promote appropriate vascularization with efficient nutrition and oxygenation to optimize long-term survival and function; 3) optimization of islet isolation, preservation, transportation, and storage methods to improve islet transplantation; and 3) techniques to maintain and expand human, physiologically responsive, insulin-producing cells for cell replacement and disease modeling.

The panel was supportive of this initiative, noting that this research is incredibly important. They felt that a biological cure is highly desirable to patients, that the time is right to accelerate this research, and that the opportunities exist to improve the basic science needed to make islet

transplantation safer, more effective, and more accessible to people with type 1 diabetes.

### ***High-resolution Exploration of the Human Islet Tissue Environment***

*Primary discussants: Dr. Michael German, Dr. Vincent Poitout*

Knowledge of the exact identity of the numerous cell types and cell subtypes that constitute the human islet environment, the contribution of non-endocrine components and neighboring tissues to islet function and dysfunction, how these cells and components communicate, and the molecular composition and physical/functional properties of pancreatic tissue architecture remain largely unknown. A higher-resolution description of the cellular, molecular, and functional organization of the human pancreatic environment could improve understanding of disease pathogenesis toward prevention, development of highly specific therapeutic strategies, and design and engineering of highly functioning islet biomimetics for cell replacement, disease modeling, drug discovery, and exploration of tissue crosstalk *in vitro*.

This initiative would support detailed and functional characterization of specific components of the human pancreatic tissue environment through the use of technologies with single-cell resolution that can explore tissue architecture with unprecedented granularity and functional assays that can record cell-cell interactions in live human pancreatic tissue or tissue slices.

The panel was extremely enthusiastic about this proposal, calling it an incredibly important question, very doable, and timely. They felt that encouraging investigators to do this research in human samples will not only generate critical information, but will also enable translation of advances into development of human cell-based therapies. Several panelists noted that this research could be incorporated into, or collaborate with, HIRN, and investigators could work with JDRF's Network for Pancreatic Organ Donors with Diabetes (nPOD). One panelist encouraged an emphasis on multi-disciplinary teams with experience in translational science to achieve the biggest impact. Another noted that there are models in the field for this—for combining fine-mapping imaging and molecular characterization of cells—including the Allen Brain Atlas (<http://www.brain-map.org/>).

### ***Overview of the Human Islet Research Network (HIRN)***

The NIDDK-led HIRN was funded in September 2014 to support research to understand how beta cells are lost in human type 1 diabetes and to find innovative strategies to protect/replenish functional beta cell mass in people with the disease. The Network was structured as a modular ensemble of small- to medium-sized research consortia, each focused on a set of specific biological or technological goals. To date, HIRN comprises 34 awards—including cooperative agreements and Opportunity Pool projects—and over 80 investigators in five consortia, a Coordinating Center and a Bioinformatics Center.

The five HIRN consortia are the: Consortium on Targeting and Regeneration, Consortium on Human Islet Biomimetics, Consortium on Modeling Autoimmune Interactions, Consortium on Beta Cell Death and Survival (CBDS), and the Human Pancreas Analysis Program (HPAP). These are organized around an Administrative Hub composed of a Bioinformatics Center and a Coordinating Center, which organizes annual meetings, webinars, working groups, oversees the

HIRN website and manages the HIRN Opportunity Pool. Several components of HIRN were discussed at the meeting and are described below because they will soon be at the end of their project period and up for competitive renewal.

HIRN also operates as a flexible research structure that, pending availability of funds, allows for new initiatives to be issued in any given year to complement ongoing research efforts or to take advantage of emerging technological or scientific opportunities. For example, in 2015, a new CBDS initiative was issued to support the application of state-of-the-art “omics” technologies with single-cell resolution to the exploration of human pancreata. Additionally, in 2016, HPAP was founded as a data-generation resource with a mission to perform systematic, standardized, and deep phenotyping of the human endocrine pancreas and its interaction with the immune system to better understand the cellular and molecular events that precede and lead to beta cell loss in type 1 diabetes.

To maximize resources and coordinate efforts, HIRN has also established multiple interactions with partner programs, including clinical studies (Type 1 Diabetes TrialNet, The Environmental Determinants of Diabetes in the Young), organ and tissue procurement efforts (JDRF’s Network for Pancreatic Organ Donors with Diabetes, NIDDK’s Integrative Islet Distribution Program, and NIDDK and NIAID’s Clinical Islet Transplantation Consortium), and funding partners (JDRF and the Helmsley Charitable Trust).

### ***HIRN Consortium on Human Islet Biomimetics (CHIB)***

*Primary discussants: Dr. Jonathan Himmelfarb, Dr. Vincent Poitout*

CHIB was established to generate a bioengineered human islet microphysiological system that closely mimics a functional human islet. A human islet microdevice could have utility to: 1) study human islet biology by recreating features of the niche (a combination of islet subtypes, 3D cytoarchitecture, extracellular matrix, vasculature, and neural components), 2) understand metabolic tissue cross-talk via integration with other emerging tissue chip platforms, and 3) test new drugs or therapies to protect or restore beta cells. Although CHIB projects have only been active for 2.5 years, the four current teams have made significant progress, including developing ways to maintain functional cadaveric islets in the laboratory for 2-4 weeks; developing novel biomaterials to maintain long-term survival and sensitive, quantitative assays to measure islet function; and creating working prototype devices with patents pending.

This initiative would support CHIB for a second period of funding. In this second phase, CHIB would build on advances made in the first project period to focus on *in vitro* modeling of interactions between human beta cells and the immune system to study, directly, beta cell dysfunction leading to destruction, and enable understanding of the temporal nature and key events involved in the disease process. Because type 1 diabetes is prevalent in children under 10 years of age, CHIB would, using information emerging from other HIRN projects, develop a human juvenile islet chip with which to integrate the immune elements.

The panel was very supportive of this program, feeling that it is extremely important and has great potential to produce a human islet model in which to study the immunology of type 1 diabetes. Members encouraged CHIB to solidify and strengthen the current efforts before

delving into adding the immune system component. CHIB was also encouraged to continue pursuing collaborations with the National Center for Advancing Translational Sciences' Tissue Chip Program (<https://ncats.nih.gov/tissuechip>), which has been using microfluidics and microphysiological systems to make human organ biomimetics for disease modeling and drug discovery. Because the Tissue Chip Program does not include pancreas, panelists felt CHIB fills a critical gap in this very exciting area of research.

### ***HIRN Consortium on Targeting and Regeneration (CTAR)***

*Primary discussants: Dr. Michael German, Dr. Vincent Poitout*

CTAR aims to understand the potential of the human endocrine pancreas to regenerate, as well as to develop innovative therapeutic strategies to replenish human beta cell mass *in vivo* as an alternative to cell replacement therapy through the control of adult beta cell replication and islet cell plasticity or the reprogramming of adult non-beta cells into beta-like cells. In the 2.5 years of CTAR's existence, CTAR investigators have contributed significantly to our understanding of human islet cell diversity, have learned to control islet cell plasticity to make more beta cells, and have identified molecules that promote human adult beta cell division. Current efforts in CTAR are also developing the means to deliver regulatory cargos to the islet compartment.

This initiative would support CTAR for a second period of funding. In phase 2, CTAR would build on the advances made in the first project period and leverage new discoveries in pursuit of its goals. The initiative would emphasize areas of research not currently pursued by CTAR, including strategies for the reprogramming of adult non-beta cells outside of the pancreatic islet compartment, and *in vivo* strategies to reinforce protective pathways and organizational features in and around human islets. Strategies could also include efforts to engineer beta cells to express immune evasion proteins or to engineer immune cells for specific homing to the islet compartment for delivery of immunomodulatory factors.

The panel was highly supportive of this initiative, citing it as a very important effort in islet biology that should be continued. They were impressed with the progress achieved thus far, not only in terms of the number of publications in the best journals, but in the importance of the results. One panelist remarked that the advances made by CTAR, in a short period of time, have made seminal contributions to the field. It was also noted that there are many important research opportunities in this field that could be pursued. An emphasis on *in vivo* approaches was encouraged.

### ***HIRN Human Pancreas Analysis Program (HPAP)***

*Primary discussants: Dr. Michael German, Dr. Rudolph Leibel*

HPAP was established with the rationale that systematic and high-resolution information about the cellular and molecular events leading to the development of type 1 diabetes could be garnered from comprehensive molecular profiling, in unprecedented detail, of the pancreatic islet environment using pancreatic specimens from cadaveric donors recently diagnosed with or at risk for type 1 diabetes. This information could help identify new biomarkers to detect early type 1 diabetes, develop approaches to stimulate the regenerative capacity of the pancreas, and

design therapeutic strategies to stop or delay progression of the disease. The core mission of HPAP is to accumulate, analyze, and distribute high-value, human pancreas-derived, type 1 diabetes-relevant datasets to the diabetes research community. Specifically, in the initial 3-year pilot phase that started September 2016, HPAP investigators were tasked with the following objectives: 1) assemble and process a diverse collection of human pancreata, 2) perform a systematic and deep phenotyping of each tissue, 3) develop an open-access database (PANC DB) for real-time sharing of all collected data with the community, and 4) distribute residual cells and tissues for additional experiments. HPAP is a collaborative effort, building on the strengths of each of the two participating teams, and is expected to be hypothesis-generating for the broad scientific community.

The proposed initiative would support a second period of funding for HPAP with similar goals and objectives. After 3 years of tissue procurement and processing, the HPAP collection of deeply phenotyped pancreatic specimens will likely be significant. Therefore, during the second phase, it is expected that there will be a greater emphasis on facilitating the distribution of stored residual tissues to the research community for further analyses and on development of strategies and computational tools to link PANC DB, in meaningful ways, to other relevant databases. Applicants would likely be asked to develop a strong outreach program to encourage investigators with unique skill sets, technologies, or scientific interests to enrich and expand on the data being collected by HPAP. The specific activities of the second phase would be determined after review by an External Scientific Panel and analysis of the performance of the HPAP pilot by NIDDK staff.

The panel was very supportive of this initiative, calling it an important effort that will generate critical resources. They discussed several issues with this type of effort, including concerns over generation of confounders from procurement and storage, the lack of accompanying clinical data, and incorrect diagnoses (*e.g.*, patients with maturity onset diabetes of the young (MODY) versus type 1 diabetes). One panelist suggested that HPAP be more selective in the types of pancreata that the program procures, due to the limited number of tissues that can be processed. Another encouraged exome sequencing on all samples to obtain valuable genetic data.

***Discovery of Early Type 1 Diabetes Disease Biomarkers in the Human Pancreas (HIRN Consortium on Beta Cell Death and Survival [CBDS])***

*Primary discussants: Dr. Michael German, Dr. Jonathan Himmelfarb*

Since 2014, HIRN-CBDS has supported the development of technologies and approaches to interrogate human pancreatic tissues and islets to discover biomarkers of cell injury in asymptomatic type 1 diabetes, identify cellular and molecular events associated with type 1 diabetes pathogenesis, and develop strategies to stop beta cell destruction early in the disease process in at-risk individuals. CBDS investigators have made progress in several areas, such as development of assays that measure beta cell-specific methylated DNA in blood, allowing more reliable quantification of beta cell death in people with and without diabetes; identification of protein biomarkers that can report on different aspects of beta cell stress, disease initiation, or disease stage; and discovery of cellular and molecular events associated with type 1 diabetes pathogenesis.

This initiative proposes to build on the progress made by CBDS investigators and others and to refine and broaden the goals of the consortium, specifically to support the exploration of the human pancreatic tissue for discovery of biomarkers of human type 1 diabetes pathogenesis. For this initiative, a “biomarker” is defined as a biomolecule (secreted or not) or a cell subtype that can be detected in the human islet or pancreatic compartment in early type 1 diabetes, and can shed light on disease initiation. The initiative would also support the use of these biomarkers for the development of clinical diagnostic tools for the early detection, staging, and subclassification of type 1 diabetes, and the identification of therapeutic targets for preventative or early treatment strategies.

The panel had high enthusiasm for this initiative, citing the importance of the studies and the impressive progress made thus far. They agreed with refocusing the next project period on biomarkers of beta cell death, as developing assays that measure beta cell death would be valuable both in studying the pathogenesis of the disease and in clinical assays. Clinical assays that detect beta cell death have tremendous potential, especially in transplant situations to identify failing grafts.

### ***HIRN Data Coordinating Center (DCC)***

*Primary discussants: Dr. Mark Espeland, Dr. Rudolph Leibel*

Activities within HIRN consortia and across the network are coordinated through the activities of two administrative units—the HIRN Coordinating Center and the Bioinformatics Center (BC). The primary goal of the BC is to assist in rapidly deploying information about HIRN resources within and between HIRN consortia and to enhance sharing of network resources with the external scientific community. In the past 2 years, the BC has begun efforts to: 1) identify and assemble network resources; 2) create a pipeline for providing HIRN resource authentication and research resource identifiers, supporting NIH standards for rigor and reproducibility; 3) enable resource development and sharing across HIRN; and 4) facilitate collaborations with outside communities and programs. The role of the BC is not to duplicate or supersede existing data science efforts within projects, but instead to provide the support needed to integrate and foster collaborations between projects and consortia, and/or to provide support where local expertise is lacking.

The initiative would support HIRN data coordinating efforts for a second period of funding, transitioning the Bioinformatics Center to the Data Coordinating Center (DCC). The DCC would continue to build on progress made in promoting sharing, management, and long-term maintenance of HIRN data and resources. As part of the maturation of the network, the need to coordinate sharing, interoperability, and reuse or repurposing of HIRN data and resources is expected to increase dramatically. In phase 2, the DCC would focus on expanding and expediting data sharing; increasing access, interoperability, and retention of key datasets and resources; and providing ancillary informatics or statistical support to HIRN investigative teams.

The panel was supportive of this initiative, noting that it is a critical and important component of HIRN, providing coordination, integration, and communication. Panelists agreed with the current work scope, in that the majority of bioinformatics should be done in the individual projects and consortia, rather than provided by the DCC. They encouraged that the work scope

of the DCC match the needs of HIRN, as HIRN moves into the next phase. The panel also suggested that the investigators of the DCC provide intellectual input into HIRN, perhaps by pursuing some of the bioinformatics issues as their own research projects.

### **TOPIC 3: DIABETES COMPLICATIONS**

#### ***Current Efforts in Diabetes Complications***

Dr. Fradkin provided an overview of the current research portfolio related to diabetes complications, including discussion of ongoing programs in which funding decisions have already been made, such as the Diabetic Complications Consortium and the Preventing Early Renal Loss in Diabetes clinical trial. She also noted that ongoing investigator-initiated grants supported by the *Program* include seven Type 1 Diabetes IMPACT awards (RFA-DK-14-017), one award made under “Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies” (PAR-14-257); one award made under “Research Using Subjects from Selected Type 1 Diabetes Clinical Studies (Living Biobank)” (PAR-14-258); two awards made under “Research Using Biosamples and Subjects from Type 1 Diabetes Clinical Studies—Complications” (RFA-DK-15-019); and one award made under “Small Business Innovation Research (SBIR) to Develop New Diagnostic, Monitoring, and Therapeutics Technologies for the Complications of Type 1 Diabetes” (PA-14-058). Additionally, new awards are expected to be made in Fiscal Year 2017 under “Neurocognitive Effects of Glycemic Dysregulation in Type 1 Diabetes” (RFA-DK-16-007).

#### ***The Impact of Type 1 Diabetes Mellitus on the Skeleton***

*Primary discussants: Dr. John Buse, Dr. Elizabeth Seaquist*

Metabolic and immune diseases, such as type 1 diabetes, that affect people during a critical window of bone development and maintenance have a significant impact on skeletal health, as has been established by the presence of an increased risk for fractures in people with type 1 diabetes. Low mineral bone density accompanies these events, but the underlying mechanisms affecting bone mass and architecture are not clear. While cross-sectional studies suggest that glycemic control and adequate insulin utilization may decrease the risk of developing diabetic bone disease in type 1 diabetes, the triggering mediators and mechanisms contributing to this complication are largely unknown. Confounding this uncertainty is the fact that available animal models are not adequate to query these issues and their value is questionable. Moreover, additional information is needed about diabetic bone disease toward determining what therapies are safe and effective in people with type 1 diabetes. As life expectancy increases in people with type 1 diabetes, the clinical impact of bone disease will likely increase.

This proposal seeks to support basic, pre-clinical, clinical, and translational research to address the knowledge void at the intersection of type 1 diabetes and bone. There are a number of possible research opportunities to pursue, such as building on longitudinal cohort studies to determine the onset and progression of diabetic bone disease in people with type 1 diabetes to define predictors of bone disease development, determining the best available techniques and measures to ascertain the onset and progression of diabetic bone disease in type 1 diabetes, and

determining what risk factors are modifiable to prevent diabetic bone disease and/or improve fracture risk in type 1 diabetes.

The panel was enthusiastic about pursuing research in this area because they thought that bone health is a very important clinical issue that is understudied as it relates to type 1 diabetes. They commented that there is insufficient information to inform clinical management of bone disease in this population. Some panel members felt that before undertaking clinical research in this area, it was important to understand epidemiology by studying existing cohorts of patients and/or data from health care systems. For example, one suggestion was to utilize the T1D Exchange (<https://t1dexchange.org/pages/>) to study adults with new-onset type 1 diabetes. This type of approach could shed light on fracture risk, as future clinical trials would likely have to be powered for fracture risk; it could also help determine whether having celiac disease or other autoimmune diseases along with type 1 diabetes affects risk for bone disease. Other panel members felt that it would be possible to conduct simple trials now, before having epidemiologic data in hand, to address pressing clinical/treatment questions. Because the panel felt that the next steps were not entirely clear, they suggested that the NIDDK call on relevant experts to define a path forward. Once next steps are identified, the panel cautioned against diluting funds into studying many different areas, but rather suggested focusing on one or two compelling topics.

***Continuation of Diabetic Retinopathy Clinical Research Network (DRCR.net)***

*Primary discussants: Dr. John Buse, Dr. Robert Eckel*

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 next phase of DRCR.net support 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 medical and public health issues of the day 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 continue support for seven studies that will be ongoing in Fiscal Year (FY) 2018, six of which will continue through at least FY 2019. They are also considering new studies, such as a randomized trial to determine if fenofibrate is safe and effective at preventing diabetic retinopathy worsening in participants with mild to moderately-severe non-proliferative diabetic retinopathy (NPDR) at baseline. Two major clinical studies have shown that oral fenofibrate can reduce the risk of diabetic retinopathy worsening in eyes with NPDR; however, a definitive clinical trial specifically in eyes with baseline NPDR that are at higher risk for progression is necessary to confirm these results. The Network would also plan to examine correlations between spectral domain optical coherence tomography parameters and visual acuity outcomes, and conduct a comparative study across multiple software applications to assess their performance to reliably detect diabetic retinopathy.

The panel was highly enthusiastic about continuing to support the overall Network, calling it an incredibly successful and high-impact program. Most of the discussion focused on the proposed fenofibrate trial. The panel noted that fenofibrate has a low side effect profile and has been shown in other studies to reduce the risk for retinopathy, but physicians have not been prescribing fenofibrate to their patients for this purpose. Thus, the panel thought that the proposed trial, if positive, could help increase uptake of this therapy. One panel member noted that there are some data suggesting that fenofibrate may slow the progression of kidney disease. One suggestion was that if this trial was conducted, it could be enhanced, at a low cost, by adding markers for kidney disease and examining fenofibrate's effect on kidney function. Another panel member suggested that data from NIH's Action to Control Cardiovascular Risk in Diabetes study (<https://www.nhlbi.nih.gov/health-pro/resources/heart/accord-trial>) could first be analyzed to examine this question.

***Establishing a Cohort to Clarify Risk and Protective Factors for Neurocognitive Complications of Pediatric and Adolescent Type 1 Diabetes***

*Primary discussants: Dr. Mark Espeland, Dr. Trevor Orchard, Dr. Elizabeth Seaquist*

There is growing evidence that there are neurocognitive complications of type 1 diabetes. However, there are limited data from adequately powered, longitudinal studies on neurocognition, especially in pediatric type 1 diabetes. Thus, it is unknown how specific parameters associated with type 1 diabetes may lead to changes in brain structure and function and deficits in neurodevelopment and cognition, and how this may impact disease management, clinical course of type 1 diabetes, and other outcomes. Recent advances in neuroimaging, computerized neurocognitive assessment, and continuous glucose monitoring/artificial pancreas technologies could lead to improvements in characterizing brain structure/function, cognition, and clinical aspects of pediatric and adolescent type 1 diabetes. If these approaches could define specific risk or protective factors for adverse or optimal neurocognitive outcomes, treatment protocols could be developed to limit neurocognitive complications associated with type 1 diabetes.

The goal of this proposal would be to elucidate the etiology and pathogenesis of the neurocognitive complications of pediatric and adolescent type 1 diabetes to inform future strategies to mitigate this risk. To achieve this goal, it is estimated that approximately 400-800 children and adolescents with type 1 diabetes would need to be followed. It is possible that the new NIH Adolescent Brain and Cognitive Development (ABCD) study (<https://addictionresearch.nih.gov/abcd-study>) could be leveraged by aiding in study design and providing a control cohort for comparisons with the proposed type 1 diabetes patient cohort. However, before making final decisions about the best approach to pursue, a workshop would first be held with key researchers in the pediatric, adolescent, and adult type 1 diabetes neurocognition fields, and other relevant experts. Input from the workshop would inform the development of a Funding Opportunity Announcement for research to address the highest priority research gaps and opportunities to pursue.

The panel had a high level of enthusiasm to pursue what they felt was a very important area of science. Regarding a potential study, they commented that it would be important to follow the

children for a long period of time and include a control group. They also emphasized the need to include very young children in the study, as there are data suggesting that this population may be the most susceptible to developing neurocognitive complications. However, the ABCD study is enrolling children who are 9-10 years of age so it could not serve as a control group for the youngest children enrolled in a type 1 diabetes cohort. Additionally, in one panel member's experience, psychological and neurocognitive tests are the least popular tests among people with type 1 diabetes, so it is important to consider that aspect when designing the study. Other suggestions included: considering whether any information can be gleaned from studying children enrolled in The Environmental Determinants of Diabetes in the Young (TEDDY) study, and considering how results of a study could affect management/care. The panel agreed that it was critical to first hold a workshop to get input on these and other issues to determine how best to design a study.

#### **TOPIC 4: CLINICAL MANAGEMENT**

##### ***Current Efforts in Clinical Management***

Dr. Fradkin noted that ongoing investigator-initiated grants supported by the *Program* include 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; RFA-DK-14-022), and one award under "Understanding Barriers and Facilitators to Type 1 Diabetes Management in Adults" (RFA-DK-13-023). In addition, new awards are expected to be made in FY17 under the following: "Improving Diabetes Management in Pre-Teens, Adolescents, and/or Young Adults with Type 1 Diabetes" (RFA-DK-16-001) and "Improving Diabetes Management in Children with Type 1 Diabetes" (RFA-DK-16-003).

##### ***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. Korey Hood, Dr. David Marrero, Dr. Deborah Wiebe*

Clinical and observational studies indicate that real-time information on blood glucose levels in people with diabetes being treated with insulin improves self-management of the disease and facilitates a reduction in acute and long-term complications. Continuous glucose monitors also may contribute to improved glycemic control without increasing hypoglycemia, facilitating implementation of personalized treatment regimens. However, older adults with type 1 diabetes may have increased vulnerability to hypoglycemia, cognitive impairment, and/or multiple comorbidities, which may affect the risks and benefits of using certain blood glucose monitoring and control technologies. Clinical studies are needed to determine whether use of these technologies can improve health outcomes and quality of life in this population.

This proposal would solicit applications for clinical studies of the use of current and emerging blood glucose monitoring and insulin administration technologies in older adults with type 1 diabetes, to determine if such interventions can improve their clinical and psychosocial outcomes. Studies testing preference, usability, and acceptability of these technologies in this population also would be a priority. The technologies tested might include novel self-monitoring and decision support systems, continuous glucose monitors and/or combinations of sensing and

pancreatic hormone delivery devices in open- or closed-loop systems, or other adjuvant technologies. The research goals would be to improve health, glucose control, and quality of life and to inform clinical decision-making and public health policies.

The panel was enthusiastic about this proposal and felt that it addressed an important and compelling question. The panel was concerned that unless acceptability issues were addressed, the devices eventually brought to market would not be widely used by older people with type 1 diabetes. They agreed that the proposed studies would need to be pragmatic and emphasize collection of patient usability/acceptability data to inform device design. One panelist felt that this proposal could provide information needed to advance precision medicine, by focusing on which devices work best for which people. Another panelist felt that the interventions tested should be broadened, as lower-tech devices/treatment regimens might be more useful to older adults who may face physical, financial, or other limitations that could interfere with their ability to use highly technological solutions.

### ***Patient-reported Outcomes in Type 1 Diabetes Research and Practice***

*Primary discussants: Dr. Corey Hood, Dr. David Marrero, Dr. Deborah Wiebe*

Patient-reported outcomes (PROs) complement biomedical outcomes by capturing patient experiences of disease management and function that are directly related to health care and self-care decision making. PROs include measures such as patient report of wellness/symptoms, functioning/disability, quality of life, emotional status/mood, social/family functioning, satisfaction with treatment, and treatment regimen tolerability or burn out. Patient, regulatory, and health care provider groups have encouraged routine use of PROs, but diabetes care and research does not currently have standardized approaches to assess PROs, and there is little consensus on ideal PRO measures. Several efforts are underway that may partially fill this gap in PRO outcomes for type 1 diabetes. There is a need to harmonize these efforts and to identify and address the highest priority research gaps in developing PROs for type 1 diabetes.

To accelerate the use of validated, generalizable, and standardized PROs in type 1 diabetes research and care, this proposal aims to first hold a workshop that would include key representatives from the above-mentioned PRO measure efforts, along with other experts in PRO research. The workshop findings would inform a Funding Opportunity Announcement for research to fill the highest priority research gaps and accelerate the use of validated, generalizable, and standardized PRO measures in type 1 diabetes research and practice.

The panel felt that developing consensus PRO measures for type 1 diabetes is very important, particularly as more devices for blood glucose management are developed. Several panelists mentioned that the FDA is very interested in the development of PRO measures and that addressing PROs is a requirement when applying for FDA regulatory approval for a device. Development of PRO measures for type 1 diabetes could also inform trial and device design to enhance and evaluate the usability and acceptability of devices for blood glucose management. The panelists acknowledged that developing PRO measures can be very complex, requiring careful design and analysis to produce a replicable and reliable measure. Additionally, they noted that a lack of harmonized PRO measures has hampered comparison of data sets. Two

panelists said that even a group of knowledgeable experts can have difficulty agreeing on the best choices for PRO measures, highlighting the need for a workshop to address this issue.

***Understanding Needs and Identifying Research Opportunities to Improve Treatment and Self-Management for Adults Living with Type 1 Diabetes***

*Primary discussants: Dr. Korey Hood, Dr. David Marrero, Dr. Deborah Wiebe*

Today, new type 1 diabetes diagnoses in adults are not uncommon, and the majority of individuals living with type 1 diabetes are adults. Also, many individuals with type 1 diabetes are now living into old age. However, most research on optimizing type 1 diabetes treatment and self-management has been conducted in youth and young adults or has been done in mixed samples of individuals with type 1 and type 2 diabetes without adequate power to detect unique type 1 diabetes-related factors. A better understanding of the treatment needs and barriers to good self-management in adults with type 1 diabetes is needed to inform development and testing of personalized treatment approaches.

This proposal aims to support research to improve treatment and self-management of type 1 diabetes in adults. Examples of research gaps and opportunities include, but are not limited to, understanding how specific life issues (*e.g.*, building and caring for a family, establishing and maintaining a career) affect diabetes care and self-management, and understanding how to optimally manage diabetes in the context of age- and diabetes-related changes in health or living situation. Toward supporting research on this topic, a workshop would be held to bring together the various stakeholders (*e.g.*, researchers, non-profit organizations, health care providers, patients) to better understand the state of the science, identify important research gaps, and develop a plan to generate interest in this important topic. The workshop findings could be used to inform a Funding Opportunity Announcement (FOA) to address high-priority research gaps.

The panelists felt that this proposal addressed an important research need that will only become more pertinent as people with type 1 diabetes live longer. Panelists noted that much is still unknown about barriers (and perception of barriers) to daily diabetes management and how those barriers differ depending on factors such as race/ethnicity and socioeconomic status. Data on these issues could give valuable information on how to personalize care and encourage adherence to treatment. Panelists suggested that this proposal might be of particular interest to health disparities researchers, as it would be a good opportunity to examine health disparities in type 1 diabetes treatment and the effects of new technologies on those disparities. Another suggestion was to consider strategies for accessing diverse and representative populations for recruitment into these studies.

## **TOPIC 5: ARTIFICIAL PANCREAS**

### ***Current Efforts in Artificial Pancreas***

Dr. Fradkin noted that in this area, ongoing investigator-initiated grants supported by the *Program* include four awards made under “Diabetes Impact Award—Closed-Loop Technologies: Clinical, Physiological, and Behavioral Approaches to Improve Type 1 Diabetes Outcomes” (RFA-DK-12-020; RFA-DK-14-014); four 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; RFA-DK-14-015); four awards made under “Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes” (RFA-DK-14-024); three awards made under “Impact of the Use of Glucose Monitoring and Control Technologies on Health Outcomes and Quality of Life in Older Adults with Type 1 Diabetes” (RFA-DK-15-028); one award made under “Small Business Innovation Research (SBIR) to Develop New or Improved Closed Loop Automated Technologies for Diabetes Therapy and Monitoring (R43/R44)” (RFA-DK-15-022); and one “Type 1 Diabetes Pathfinder Award” (RFA-DK-15-030). In addition, new awards are expected to be made in FY17 under the following: “Clinical, Behavioral and Physiological Research Testing Current and Novel Closed Loop Systems” (RFA-DK-16-009), “Small Business Innovation Research (SBIR) to Develop New or Improved Closed Loop Automated Technologies for Diabetes Therapy and Monitoring (R43/R44)” (RFA-DK-15-022), and “Development of New Technologies and Bioengineering Solutions for the Advancement of Cell Replacement Therapies for T1D (R43/R44)” (RFA-DK-16-004).

***Advanced Clinical Trials to Test Artificial Pancreas Device Systems in Type 1 Diabetes***  
*Primary discussants: Dr. John Buse, Dr. Joseph Wolfsdorf*

New portable/wearable technologies to measure blood glucose levels and administer insulin and other glucose-regulating hormones through an automated closed-loop artificial pancreas system have been developed recently. Initial in-hospital and outpatient testing has shown very promising results, improving maintenance of near-normal glucose levels with less variability when compared with non-automated open-loop systems. These results are very encouraging, and an effective, wearable, automated system may help reduce diabetic complications and improve quality of life for people with type 1 diabetes. However, there is room for improvement in accuracy, reliability, and burden of the current systems’ devices and algorithms. Also, device successes in current trials may not translate to all people with type 1 diabetes. Thus, it is important to clinically test emerging technologies that could reduce patient burden and enhance acceptability.

This proposal’s aim would be to prove and improve the efficacy, safety, accuracy, and reliability of emerging artificial pancreas technologies. This initiative would encourage investigative teams that have developed and initially tested an artificial pancreas device system with robust, promising results to expand the testing to trials in clinical and outpatient settings. Such trials would be designed to generate data to address regulatory agencies’ safety and efficacy requirements for the approval of a user-friendly, multicomponent artificial pancreas product.

The panel was very supportive of this proposal. Panelists stated that they see a lot of excitement in the type 1 diabetes community about artificial pancreas device trials: participants in past trials often contact study investigators regularly to inquire about and offer to participate in future trials. The panelists noted that safety and efficacy is of paramount importance and that there will be an ongoing need to tweak devices’ insulin-dosing algorithms to avoid hypoglycemia. One panelist suggested that the proposed trials collect detailed information about the participants’ views on device acceptability and usability.

### ***Clinical, Behavioral and Physiological Studies of Closed-loop Systems***

*Primary discussants: Dr. John Buse, Dr. Georgeanna Klingensmith, Dr. Deborah Wiebe*

New technologies for monitoring daily blood glucose patterns are already in clinical use, and ease of use and accuracy are steadily improving. Together with integrated insulin delivery systems, these technologies 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 to human trials. It is therefore important to continue supporting collaborative research to clinically test current and new technologies, taking into consideration patient preferences and behavioral and physiological factors, to optimize their operability and achieve the goal of viable, functionally integrated, closed-loop systems for routine use.

This initiative would expand and extend ongoing research supported by previously released NIDDK Funding Opportunity Announcements, JDRF, Helmsley Charitable Trust, and industry. It would build on current technology and ongoing clinical research to address barriers limiting progress toward a fully automated pancreatic hormone replacement closed-loop system. Specifically, this initiative would support research to: 1) test and improve the safety, reliability, and clinical efficacy of these technologies in humans; 2) address behavioral/psychosocial factors that play a role in the usability and acceptability of these systems and validation of outcomes measures to demonstrate efficacy and benefit; 3) test these technologies in subpopulations not usually included in clinical trials of these technologies but that may benefit most from their use; and 4) use these technologies as tools to advance understanding of glucose regulation in people with type 1 diabetes.

The panelists' feedback on this proposal was positive, and they agreed that these trials (moving in parallel with support of the next generation of technologies) are essential. It was suggested that large trials of devices close to market might best be done by the companies themselves. The panelists supported performing clinical trials in populations usually excluded from clinical trials, such as those who are pregnant or those who have high HbA1c levels. One panelist observed that specific algorithms may be required to use such devices safely in these populations. Several panelists expressed concern that artificial pancreas devices will be so expensive as to limit access, and it was suggested that trials supported by this proposal might include some assessment of cost/benefit or return on investment calculations, to support the coverage of artificial pancreas devices by insurers.

### ***Development and Integration of Novel Components for Open- and Closed-loop Hormone Delivery for Type 1 Diabetes Therapy***

*Primary discussants: Dr. Korey Hood, Dr. David Marrero, Dr. Joseph Wolfsdorf*

While recent technological advances have helped many people with diabetes, recapitulating the dynamic control of blood glucose levels imposed by the pancreatic beta cells is still impossible with current methods. Due to such limitations, there is still a high risk of acute complications when current glucose control regimens and technologies are used. Thus, it is a research priority to develop physiological and adaptable technologies that are more accurate—such as glucose-

sensing and pancreatic hormone delivery (open- or closed-loop) systems/methods—to help people with diabetes achieve and sustain intensive blood glucose management in a personalized fashion. It is also important to support development and optimization of novel self-management system components—including personalized digital insulin dosing decision support systems, linked or unlinked to remote monitoring and telemedicine resources—in parallel to optimization of closed-loop systems and components. Additionally, a new generation of less burdensome and more user-friendly components (such as implantable components) are needed to increase usability and acceptability of these devices.

The goal of this initiative is to address barriers that limit progress toward effective open- and closed-loop glucose control systems. Research supported by this initiative would tackle the most important obstacles at the level of sensing, hormone formulations and delivery, automated controllers, self-management decision support systems, and controllers/algorithms to manage an integrated platform adaptable to remote monitoring and telemedicine when needed.

*(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.)*

***Support for SBIR Research to Develop New Therapeutics and Monitoring Closed-Loop Automated Technologies for Type 1 Diabetes***

*Primary discussants: Dr. Korey Hood, Dr. Robert Sherwin, Dr. Joseph Wolfsdorf*

Despite the availability of increasingly effective treatments, a substantial proportion of people with type 1 diabetes cannot achieve adequate glycemic control and avoid acute complications such as hypoglycemia with current technology. Development of an affordable, automated, artificial pancreas able to mimic normal pancreatic beta cell function—restoring normal metabolic homeostasis without causing hypoglycemia—has enormous potential benefit for people with diabetes. Emphasis is needed on creating next-generation devices that will aid in relieving patients of the burden of diabetes self-management and will help them manage blood glucose levels to prevent acute and chronic complications.

This proposal would stimulate bioengineers, researchers, and designers in academic centers and small businesses to develop new devices with enhanced accuracy and less patient burden to improve the safety and effectiveness of currently available technology. The goal of this proposal is to achieve a clinically viable, functionally integrated closed-loop system with commercial potential and high usability and acceptability to people with type 1 diabetes. Examples of topics that might be explored under this proposal include: interoperability of devices, more effective fault-tolerant control systems algorithms, more durable and reliable hormone infusion systems, next-generation sensors (including non-invasive and long-term implantable devices), improved hormone replacement formulations, glucose-responsive biomaterials, and remote monitoring systems to optimize device performance.

The panel had high enthusiasm for these initiatives, which they felt were needed to push the artificial pancreas field forward. Several panelists remarked that there is high demand for new devices in the type 1 diabetes community. One panelist added that two additional areas to

possibly address were 1) increasing infusion pump reliability and 2) treating or preventing skin irritation at the device's adhesive sites, both of which are concerns with current devices. Current glucose sensors' lag in detecting blood glucose changes was also noted as a limitation in current devices. One panelist highlighted the importance of developing implanted sensors to directly monitor blood glucose levels, which he felt was the only way to finally "close the loop." Additional panel suggestions included supporting biomarker research, supporting software development to take advantage of new advances in artificial intelligence and machine learning, and supporting development of robust safety systems to protect against device failure.

### **PATIENT PERSPECTIVE**

Ms. Ellen Leake provided comments on the proposals from the patient perspective. She emphasized that it is critically important to balance short-term "wins"—research that can lead to advances to help people with type 1 diabetes in the near-term, such as artificial pancreas technologies—with long-term investments, such as clinical studies on type 1 diabetes prevention. She commented that in today's fast-paced world, it is often difficult to appreciate the need for long-term research. She commended the NIH for taking this long-term approach when appropriate, realizing that the fruits of this research will be realized in years to come and can greatly benefit the type 1 diabetes patient community and those at-risk for the disease. She also stressed the need to consider patients' perspectives in the context of supporting research, so she was enthusiastic about the proposals related to developing patient-reported outcomes for type 1 diabetes and to improving treatment and self-management of type 1 diabetes in adults. Additionally, she encouraged the NIH to consider how best to reach underserved populations with type 1 diabetes, such as those who live in areas that are not serviced by doctors or hospitals, to ensure that all people with the disease benefit from research discoveries. She closed her remarks by talking about the resilience of the type 1 diabetes patient community: they do not focus on the tremendous burden of managing their disease, but lead successful, fulfilling lives. They represent hope for the future, as research strives to ultimately cure this disease.

### **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:

- **Examining genetic factors that protect against type 1 diabetes development:** A panel member suggested that the studies studying large numbers of people at high-risk for developing type 1 diabetes (*e.g.*, TEDDY, TrialNet) could be leveraged by aggregating data to examine differences in people who do and do not develop type 1 diabetes when they have the same baseline risk. This could help to tease out the genetic factors that mitigate risk. Another panel member suggested that this could also be addressed by studying people who are known to have genes that are protective against type 1 diabetes but nonetheless develop the disease.
- **Investing in bioinformatics:** Panel members thought that a coherent strategy for data storage, management, analysis, and sharing is necessary, given the large amounts of data being generated by TEDDY, HIRN, and other consortia. The suggestion of two bioinformatics workshops—one for data management and one about making data accessible for the broader scientific community—was met with enthusiasm by the panel.

- Evaluating animal models for studies of hypoglycemia: Panel members commented that people fear getting hypoglycemia as a complication associated with insulin treatment. There has been recent progress in understanding hypoglycemia and the mechanisms involved, but more research is needed, such as to understand how the counter-regulatory response is activated and what changes occur in diabetes. The panel suggested that the NIDDK convene a workshop to discuss research opportunities in this area, specifically focusing on the best animal models to use to conduct these studies, so that results could be translated into human studies.
- Investigating biomarker(s) for hypoglycemia: One panelist suggested supporting discovery of a biomarker for hypoglycemia similar to the HbA1c biomarker for hyperglycemia. The panelist suggested that trials involving intensive monitoring of blood glucose levels—*e.g.*, clinical trials of artificial pancreas devices--would provide a good opportunity to look for such a biomarker.
- Examining cardiovascular disease (CVD) risk in type 1 diabetes: Currently, there are no guidelines for physicians to use to help them determine when to begin their type 1 diabetes patients on statin therapy, or what blood pressure goals to target, to decrease CVD risk. To address this gap in knowledge, there was enthusiasm for studies on CVD involving combined analyses using existing cohorts to develop risk assessment equations specifically for people with type 1 diabetes.
- Continuing follow-up of the Preventing Early Renal Loss in Diabetes (PERL) clinical trial cohort: A panel member suggested continuing to follow the PERL cohort to assess long-term outcomes of this patient population with well-phenotyped kidney function.
- Leveraging the NIDDK's Kidney Precision Medicine Project (KPMP): A panel member commented that it could be useful to add a type 1 diabetes kidney disease component to the NIDDK's new KPMP.
- Exploring blood glucose management device acceptability in diverse populations: The panelists mentioned in several contexts that diabetes treatment noncompliance is high and that some users might take on burdensome devices in exchange for better blood glucose control while others would like simpler devices. Therefore, development of automated devices should consider diverse needs. The panel suggested that proposed blood glucose management device acceptability research include diverse groups of participants to aid in determining which devices work best for different subpopulations of people with type 1 diabetes.
- Supporting and retaining the next generation of clinical and basic researchers: The panelists voiced concern about maintaining a robust pipeline of researchers, particularly physician researchers, in the adult endocrinology field. The panel mentioned that the K12 career development program in diabetes research for pediatric endocrinologists ([RFA-15-006](#)) had been very successful and suggested a similar program for adult endocrinology training. Another suggested that a similar program could be developed in partnership with the Clinical and Translational Science Awards Program administered by the NIH's National Center for Advancing Translational Sciences. A third panelist mentioned that targeted support for the K award to R01 grant support transition might help retain early stage investigators.
- Supporting use of clinical trial biosamples in induced pluripotent stem cell (IPSC) research: One panelist noted that there is increasing research interest in using IPSCs made from patients' own cells for therapy development and disease modeling. The panelist encouraged

NIDDK to support opportunities for the research community to use biosamples from clinical trials (particularly large cohort trials) for such studies.

## APPENDIX 1: PANEL MEMBERS

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## APPENDIX 2: ACRONYMS

### Organizations

ADA	American Diabetes Association
DMICC	Diabetes Mellitus Interagency Coordinating Committee
FDA	U.S. Food and Drug Administration
HHS	U.S. Department of Health and Human Services
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health

### Research Programs

ABCD	NIH Adolescent Brain and Cognitive Development study
DIYA	Incidence of Type 1 Diabetes Among Young Adults: Diabetes in Young Adults Study
DRCR.net	Diabetic Retinopathy Clinical Research Network
IEDB	Immune Epitope Database and Analysis Resource
ITN	Immune Tolerance Network
KPMP	Kidney Precision Medicine Project
nPOD	Network for Pancreatic Organ Donors with Diabetes
SBIR	Small Business Innovation Research
TEDDY	The Environmental Determinants of Diabetes in the Young

### Other Acronyms

CVD	cardiovascular disease
DAA	diabetes autoantibodies
EHR	electronic health record
FOA	Funding Opportunity Announcement
FY	fiscal year
IPSC	induced pluripotent stem cell
MS	mass spectrometry
NPDR	non-proliferative diabetic retinopathy
PRO	patient-reported outcome
RFA	Request for Applications
RFI	Request for Information