Summary of the Diabetes Mellitus Interagency Coordinating Committee Workshop on Research Supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*

November 12, 2024
Hybrid Meeting

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 Bethesda, MD on November 12, 2024. The goal of the 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"; Section 330B of the Public Health Service Act) in Fiscal Years (FY) 2026 and 2027. 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 the workshop is presented here, including descriptions of these initiatives and highlights of the relevant panel discussions.

Background on Workshop: To inform decisions about how best to use funds from a possible extension of the Program in FY 2026 and/or 2027, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a 21-member external panel to solicit input on future research directions. The panel consisted of 19 scientific experts that had expertise in a variety of areas, and two lay panel members who provided patient perspectives informed by their broad expertise in type 1 diabetes.

Because the Special Diabetes Program is a Department-wide program of the U.S. Department of Health and Human Services (HHS), 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 2026 and/or FY 2027. Specifically, NIDDK requested proposals for new concepts for research that could advance understanding and improve outcomes of type 1 diabetes or its complications.

Fifteen proposals, submitted by four Institutes of the National Institutes of Health (NIH) were presented to the panel. Written summaries including background, goals and objectives, and proposed cost and duration for each of the 15 proposals were provided to the panel members prior to the workshop.

Workshop Agenda: The workshop began with an overview of the Special Diabetes Program given by Dr. William Cefalu, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, and included welcoming remarks from Dr. Griffin Rodgers, Director,

NIDDK. This was followed by comments from the lay panel members who gave a short presentation of their perspectives.

For each proposal under discussion at the workshop, an NIH 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. Three panel members were assigned to serve as primary discussants for each proposal and were asked to make initial comments before the floor was opened to other panel members for their questions and comments.

There was also 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 to suggest other new and emerging areas of research that could be pursued to advance type 1 diabetes research.

NIDDK REMARKS

Welcome

Dr. Rodgers welcomed the panelists and thanked them for taking time to attend and participate in the workshop. He thanked NIH staff for their efforts to prepare materials for the workshop and to present the initiatives. He also extended a welcome to attendees from other Federal agencies and from the patient advocacy and professional communities. Dr. Rodgers talked about the importance of the Special Diabetes Program, noting that the Program has supported many scientific advances that have improved the lives of people living with type 1 diabetes, including the tremendous progress in developing artificial pancreas and other glucose management technologies that are helping people today. NIDDK has used the Special Diabetes Program funds to undertake challenges that would have been impossible to address with NIDDK's regularly appropriated funding alone. This included supporting long-term research of the TrialNet program that culminated in the first U.S. Food and Drug Administration (FDA)-approved type 1 diabetes preventive therapy, as well as FDA approval of islet transplantation as the first licensed cellular product to treat type 1 diabetes in some adults. Recent Special Diabetes Program extensions have also enabled the initiation of important new programs, such as those focused on addressing hypoglycemia unawareness in adults—a major complication that can lead to severe, potentially life-threatening hypoglycemic episodes and is associated with increased risk of mortality—and programs evaluating neurocognitive effects of type 1 diabetes in children.

Dr. Rodgers stated that responsibly administering the Special Diabetes Program funds and maximizing their value are among NIDDK's highest priorities, which was why the workshop was convened to solicit input from the panel of scientific and lay experts. He also gratefully acknowledged the recent historic increase in Special Diabetes Program funding to $160 million per year – the first increase since 2004. The Special Diabetes Program is slated to end at the end of the 2024 calendar year. Because of the timing required to effectively plan for and develop new initiatives, NIDDK convened this workshop to discuss how best to use possible future funds in FY 2026 and 2027 to support cutting-edge research on type 1 diabetes prevention, treatment, and cure. Dr. Rodgers concluded by noting that input from previous panels has been critical for informing use of the funds and that NIDDK expected that this panel would provide similarly insightful feedback.

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

The Special Diabetes Program is an HHS-wide program administered by NIDDK that began in FY 1998. The Program augments regularly appropriated funds that the NIH receives for diabetes research, and the funds have been distributed to multiple NIH Institutes and Centers and the Centers for Disease Control and Prevention (CDC). The Special Diabetes Program funds have been used differently from regular NIH appropriations to take on broad challenges in type 1 diabetes research that could not have been addressed otherwise. The Program has been used to support ambitious, large-scale, collaborative research consortia and clinical trials networks that supplement, but do not supplant, research supported with the regular appropriation. Unlike regular appropriations, the funds from the Special Diabetes Program are limited in time and require renewal in law.

Dr. Cefalu noted that Program planning is a collaborative effort with other Institutes and Centers at NIH, the CDC, and other federal agencies and has included the participation of various non-federal organizations, including Breakthrough T1D (formerly JDRF), the American Diabetes Association (ADA), the Endocrine Society, and the Leona M. and Harry B. Helmsley Charitable Trust. The Program is coordinated 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.

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 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.

Dr. Cefalu provided an overview of ongoing research supported by the Special Diabetes Program, to help inform the panel's discussion about the proposals being presented at the meeting as well as gaps in the research portfolio. He noted that historically, the Special Diabetes Program has been organized around the following six major scientific goals:

- Goal 1: Identify the Genetic and Environmental Causes of Type 1 Diabetes
- Goal 2: Prevent or Reverse Type 1 Diabetes
- Goal 3: Develop Cell Replacement Therapy
- Goal 4: Improve Type 1 Diabetes Management and Care
- Goal 5: Prevent or Reduce the Complications of Type 1 Diabetes
- Goal 6: Attract New Talent and Apply New Technologies to Research on Type 1 Diabetes

Under each goal, Dr. Cefalu presented information on the following categories of ongoing research:

- Research Programs/Consortia
- Investigator-Initiated Grants in Response to Notices of Funding Opportunity (NOFOs)
- Recent NOFOs for Additional Investigator-Initiated Research

Information on these ongoing efforts was presented to provide a broad overview of existing and planned research to which the panel could refer when considering the workshop's proposed initiatives.

NIDDK's The Environmental Determinants of Diabetes in the Young (TEDDY) study is the largest ongoing program under Goal 1. TEDDY is identifying environmental factors that protect against or trigger type 1 diabetes onset in genetically susceptible children. The Special Diabetes Program also supports research under NOFOs to elucidate the functions of genes and variants that influence risk for type 1 diabetes, as well as supporting collaborative research using existing biosamples from type 1 diabetes clinical studies.

There are several research programs/consortia under Goal 2, including:

- NIDDK's Standardization of C-peptide and HbA1c Measurements Program, which aims to improve and standardize HbA1c measurements and data interpretation across clinical systems and national harmonization programs, as well as to standardize C-peptide measurements;
- the Immune Tolerance Network, led by the National Institute of Allergy and Infectious Diseases (NIAID), which is a collaborative network for research to accelerate the clinical development of immune tolerance therapies;
- the NIDDK-led Type 1 Diabetes TrialNet, which is an international consortium that offers risk screening for relatives of people with type 1 diabetes and conducts innovative clinical studies testing ways to slow down and prevent disease progression; and
- NIDDK's Type 1 Diabetes in Acute Pancreatitis Consortium, which aims to study the occurrence of new-onset diabetes during an episode of acute pancreatitis or subsequently, with an emphasis on type 1 diabetes.

In addition to these and other ongoing research projects, Dr. Cefalu mentioned that the Special Diabetes Program supports research under NOFOs to develop assays for detection of proteins and peptides important in type 1 diabetes research, to study the function of autoantigens and neoantigens in type 1 diabetes, and to investigate the integrated physiology of the exocrine and endocrine pancreas in type 1 diabetes.

NIDDK-led research programs/consortia under Goal 3 include:

- the Collaborative Islet Transplantation Registry, which compiles and analyzes islet transplantation data with the intent to capture all clinical activity in North America as well as at additional sites in other countries;
- the Integrated Islet Distribution Program, which facilitates the distribution of human islets to biomedical researchers by establishing partnerships with qualified islet isolation facilities; and
- the Human Islet Research Network, which organizes and supports collaborative research related to the loss of functional beta cell mass in type 1 diabetes.

Additionally, Dr. Cefalu described how ongoing investigator-initiated grants are funded by the Special Diabetes Program under NOFOs to develop new technologies and bioengineering solutions for the advancement of cell replacement therapies, to study immune cell engineering approaches toward targeted therapy and disease monitoring, and to characterize islet-derived extracellular vesicles in type 1 diabetes.

NIDDK's Closed Loop and Education for Hypoglycemia Awareness Resolution (CLEAR) study is a major ongoing effort under Goal 4. This consortium seeks to address the problem of impaired awareness of hypoglycemia by identifying factors that can restore awareness of hypoglycemia in adults with type 1 diabetes.

Also under Goal 4, Dr. Cefalu described how the Special Diabetes Program has contributed to significant progress in the development of type 1 diabetes management technologies, including artificial pancreas devices and a ready-to-use glucagon rescue pen. He also presented information about numerous NOFOs that support active research grants related to improving type 1 diabetes management and care, including research on technology development, testing, and adoption; on treating diabetes distress and improving the well-being of those with type 1 diabetes; and on improving community engagement in type 1 diabetes research. Examples of current NOFOs under which additional awards are expected to be made include NOFOs for research on adaptation of diabetes management technologies for older adults, and for integrating social and medical care for type 1 diabetes treatment.

Under Goal 5, Dr. Cefalu noted that a previous expert panel encouraged use of Special Diabetes Program funds to support research on cardiovascular disease and type 1 diabetes. Thus, NIDDK and the National Heart, Lung, and Blood Institute (NHLBI) collaborated to form the Cardiovascular Biorepository for Type 1 Diabetes (CaRe-T1D), which provides samples to investigators seeking to understand how type 1 and type 2 diabetes promote cardiovascular disease. Another major ongoing effort under this Goal is the National Eye Institute (NEI)-led DRCR Retina Network, which supports the identification, design, and implementation of multicenter clinical research initiatives focused on retinal disorders, including diabetic retinopathy. Other ongoing efforts into type 1 diabetes complications include research evaluating neurocognitive complications of type 1 diabetes in children, and the Diabetic Foot Consortium, which is laying the foundation for clinical trials on methods to improve diabetic wound healing and prevent amputations.

Dr. Cefalu also described other ongoing research grants that were funded by the Special Diabetes Program in response to NOFOs, including research on understanding cardiovascular disease (CVD) in type 1 diabetes and on investigating the skeletal effects of the disease. Further awards are expected to be made under current NOFOs on utilizing CaRe-T1D resources to study CVD in type 1 diabetes, on assessing strategies for safe use of sodium-glucose cotransporter-2 inhibitors in type 1 diabetes, and on understanding the effects of sleep deficiency in people with type 1 diabetes.

In discussing Goal 6, which includes ongoing research supported by small businesses, Dr. Cefalu reminded the panelists 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. Dr. Cefalu asked the panel to consider opportunities to utilize those funds. He also described several ongoing efforts supported by the Special Diabetes Program related to attracting new talent to type 1 diabetes research. These efforts include career development programs in diabetes research for pediatric endocrinologists, for physician scientists, and for new investigators embedded within existing large type 1 diabetes research programs and consortia.

PATIENT PERSPECTIVES

Ms. Karen Jordan and Mr. Tom Chapman provided comments from the patient perspective.

Ms. Jordan praised how the Special Diabetes Program has resulted in major improvements in care and accelerated progress toward a cure for type 1 diabetes. She described her background not only as the mother of a person with type 1 diabetes but also as someone who herself was diagnosed with type 1 diabetes as an adult. Her family, Ms. Jordan noted, was an example of the many ways that type 1 diabetes can manifest. She mentioned her appreciation for the Program's focus on understanding the heterogeneity of the disease, especially since the adult manifestations of type 1 diabetes need to be better understood. She also emphasized how understanding the breadth of type 1 diabetes heterogeneity requires studying the disease in populations that are reflective of the varied backgrounds of people living with type 1 diabetes today. Such studies, she said, are needed so that therapies can be developed for and available to all people who have type 1 diabetes.

Ms. Jordan also encouraged continued research collaboration, particularly between type 1 diabetes researchers and those studying other autoimmune diseases. Such collaboration could help understand common mechanisms of disease and help identify treatments for other autoimmune diseases that might be effective in those with type 1 diabetes. Finally, Ms. Jordan emphasized the psychosocial toll of type 1 diabetes on those living with the disease and their caregivers, and she expressed appreciation for the Program's work on addressing this personal burden of type 1 diabetes.

Mr. Tom Chapman discussed his experiences living with type 1 diabetes for 35 years and recognized how the Special Diabetes Program's work has allowed him and others with the disease to live longer, healthier lives. He expressed concern about the many people with type 1 diabetes who do not or cannot meet recommended blood glucose management goals, and he encouraged work toward improving type 1 diabetes outcomes. Mr. Chapman also noted the significant progress in the type 1 diabetes research field in the past few years and applauded the increased focus on personalized treatments and patient involvement in research. He also highlighted several opportunities that he felt had high potential to revolutionize type 1 diabetes treatment, including work on cell replacement therapies and immune tolerance engineering, and the application of artificial intelligence to type 1 diabetes data.

Mr. Chapman concluded by stressing how self-assessment can benefit the type 1 diabetes research community, both at the federal level and among other research-funding organizations. He emphasized that looking holistically at past and current type 1 diabetes research can aid in identifying goals, tracking progress, mapping out research gaps, identifying areas of research opportunity, and minimizing overlap between research funding organizations. Such optimization of research would aid in efficient use of research dollars and help build on the progress already made in improving type 1 diabetes care and, ultimately, in finding a cure.

DISCUSSION OF PROPOSALS

Panel members provided input on the proposals and, in some cases, suggested enhancements. This summary includes proposals which may not be supported for a variety of reasons, may be partially supported, may be supported if contingencies are met and revisions made, may be

supported through mechanisms other than the proposed Notice of Funding Opportunity (NOFO), or may be supported as described.

Consortium on Immune Tolerance Engineering (CITE)
Primary discussants: Dr. Norma Kenyon, Dr. Jeffrey Hubbell, Dr. Maria Redondo

Type 1 diabetes is an autoimmune disease marked by the destruction of beta cells by autoantigen-specific T cells, leading to the loss of insulin production. A suppression of the autoimmune response aimed at restoring beta cell self-tolerance could alter the natural history of the disease, reduce clinical symptoms, and facilitate the replenishment of beta cells, particularly if the immune intervention is used early in the disease process and is combined with therapeutics aimed at protecting or regenerating residual beta cell mass. To date, available immunomodulators provide improvements that are only partial, not specific for islet autoimmunity, and not durable. More efficient and targeted immunomodulators are needed that can leave immune responses to pathogens and cancer largely intact while resulting in a long-term tolerizing effect for people with type 1 diabetes. Recent advances in type 1 diabetes research and other fields offer promising opportunities to develop new types of immunomodulatory and tolerization strategies.

The purpose of this proposal is to build a collaborative research environment (consortium) to support the design, production, and biological validation of novel strategies to restore tolerance or significantly inhibit the autoimmune response in type 1 diabetes. The new Consortium on Immune Tolerance Engineering (CITE) would be embedded in the larger and ongoing Human Islet Research Network (HIRN), which would facilitate fruitful scientific exchanges and collaborations with current HIRN scientists. Research conducted by CITE would focus on the development of proof-of-concept tolerizing and/or immune modulatory strategies specifically targeting human type 1 diabetes autoimmunity that could lead to novel therapeutic interventions in the medium- to long-term. The creation of CITE would benefit HIRN itself by adding a translational aspect to its mission and by deepening existing interactions between immunologists, bioengineers, and islet biologists.

The panel commented that the proposal was novel and addressed a need for new approaches in tolerance induction. The panel suggested broadening the collaborative aspects of this research beyond HIRN by ensuring that the new consortium communicates both with ongoing clinical trial networks (*e.g.*, Type 1 Diabetes TrialNet, Immune Tolerance Network) and with the transplant tolerance community. Additionally, one panel member commented that broadening the proposal beyond immune tolerance to include strategies targeting endoplasmic reticulum (ER) stress and insulin resistance could be beneficial. Other panel members suggested that as bioengineers and immunologists work together, the goal should be immunological memory and the long-term maintenance of tolerance early in type 1 diabetes (stages 1/2), toward a curative therapy. A panel member noted that another possible goal of this research could be to acquire new knowledge that informs how best to do sequential or combination therapies in human type 1 diabetes prevention trials—a current knowledge gap. Additional panel suggestions were to ensure that assay development was included in the research and to collaborate with scientists designing cell therapies. Finally, panel members noted the importance of reviewing the broad research landscape related to this area, not only to avoid redundant efforts, but also to take

advantage of immune cell engineering or tolerizing strategies being developed for other diseases such as cancer and/or various autoimmune diseases.

Identification and Validation of Biomarkers for Defining and Characterizing Type 1 Diabetes Endotypes

Primary discussants: Dr. Richard Oram, Dr. Maria Redondo, Dr. Desmond Schatz

Type 1 diabetes is an autoimmune disease characterized by the destruction of the pancreatic beta cells. Monitoring the initiation, severity, and progression of disease typically relies on a limited number of biomarkers found in blood (*e.g.*, glucose, hemoglobin A1c, and autoantibodies). Several studies have suggested that these markers are not optimal descriptors of the complexity and heterogeneity of type 1 diabetes. Several differences in the epidemiology, etiopathogenesis, clinical course, and responses to intervention have been reported for type 1 diabetes. This heterogeneity makes disease prediction, prevention, and treatment challenging. A better identification and characterization of specific endotypes (disease subtypes that have distinct etiopathogeneses that might be amenable to specific interventions) could help in moving toward precision medicine.

The goal of this proposal is to better characterize type 1 diabetes heterogeneity by supporting research on the validation and identification of biomarkers that can help define specific disease endotypes. The research would leverage the collective experience and sample repositories from both NIDDK and NIAID. For example, the Immune Tolerance Network (NIAID) and Type 1 Diabetes TrialNet (NIDDK) have collected a wealth of knowledge and samples that might be used to better define or validate previously proposed type 1 diabetes endotypes. Additionally, it is expected that interdisciplinary teams would be needed to successfully achieve the proposal's goals, including scientists with expertise in type 1 diabetes, clinical phenotyping, clinical chemistry, electronic health record (EHR) mining, computational biology, and immunology. As a first step, a workshop would be held to bring together representatives from various relevant disciplines and consortia.

The panel stated that the proposal addresses a compelling scientific opportunity and represented an area unlikely to be supported by non-government funders. One panel member commented that it will be important to understand the impact of age and stage of disease when studying endotypes. Panel members also commented on the need to study large number of samples and stressed the importance of engaging the clinical trials community in this effort, as well as researchers from efforts like The Environmental Determinants of Diabetes in the Young (TEDDY). Additionally, it may be helpful to make linkages between this effort and other NIH-supported research on assay validation (*e.g.*, Targeted Mass Spectrometry Assays for Diabetes and Obesity Research [TaMADOR]), as well as to require external validation for biomarkers. A panel member stated the importance of not only thinking about subtypes of type 1 diabetes that require different treatments, but also examining similarities among people with different presentations (*e.g.*, youth-onset versus adult-onset type 1 diabetes) that may lead to similar treatment approaches. Finally, one panel member noted that there is still significant scientific debate about endotypes in type 1 diabetes, and also suggested exploring how to synergize efforts

with the related proposal 7 (Multimodal AI to Accelerate Development of Biomarkers for Type 1 Diabetes Initiation, Progression, and Heterogeneity).

The Role of the Innate Immune System in the Pathogenesis of Type 1 Diabetes
Primary discussants: Dr. Carmella Evans-Molina, Dr. Maria Redondo, Dr. Desmond Schatz

Mounting evidence indicates that innate immune system pathways play a role in type 1 diabetes pathogenesis in genetically susceptible individuals. In the NOD (non-obese diabetic) mouse model, macrophages are among the earliest immune cells found in pancreatic islets during development of spontaneous type 1 diabetes. Other data point to roles for interferon and IL-12 signaling pathways, eicosanoids and other lipid mediators, and complement proteins in type 1 diabetes development. Furthermore, pancreatic beta cells express cytokine receptors and produce pro-inflammatory cytokines and mediators. However, it remains unclear whether the actions of these innate components contribute to beta cell stress, or if beta cell stress contributes to the recruitment of innate cells. Additionally, type 1 diabetes research studies have more often focused on the role of the adaptive immune response, and there is a critical need to better understand how innate immune components participate in the autoimmune response during type 1 diabetes.

The purpose of this proposal is to enhance understanding of the innate immune system's role in the initiation of type 1 diabetes, with a specific goal of determining the timing and mechanisms of immunopathogenic interactions between the islets/pancreatic tissues and the innate immune system during the earliest events of disease pathogenesis. This research would use animal models to engage in deep immune phenotyping and mechanistic studies of the initiating events of type 1 diabetes. These studies could ultimately enhance the early identification of those at greater risk of developing type 1 diabetes and may provide a basis for disease prevention and/or cure.

Multiple panelists agreed that this proposal was unique and novel, noting that the topic of innate immunity is a gap in current knowledge of type 1 diabetes initiation. Several panelists appreciated the proposal's focus on studying the timing and characterization of early events triggering innate immune responses in type 1 diabetes pathogenesis, recognizing that such events may be difficult to study in cross-sectional studies in people. Several panelists also discussed that the proposed use of animal models was appropriate and could provide valuable preclinical data to inform future human studies. Suggestions for the initiative were that more emphasis be placed on translation of the animal studies results into clinical studies in humans and including the role of circulating biomarkers in innate immunity in type 1 diabetes.

Pancreatic Exocrine Dysfunction in Type 1 Diabetes
Primary discussants: Dr. Carmella Evans-Molina, Dr. Richard Oram, Dr. Maria Redondo

Type 1 diabetes is associated with significant loss of exocrine pancreatic mass even before type 1 diabetes onset, and studies have documented pancreatic exocrine dysfunction and insufficiency (PEI) in 39-40 percent of people with type 1 diabetes. Endocrine and exocrine pancreatic disease

has also been linked by the discovery of exocrine genes that participate in diabetes onset and the high coincidence of pancreatitis and diabetes. PEI, if untreated, also results in reduced nutrient absorption, including impaired absorption of fat-soluble vitamins such as vitamin D. As osteoporosis and long bone fractures are increased in people with type 1 diabetes, vitamin D deficiency due to PEI may contribute to this complication. However, despite its prevalence, people with type 1 diabetes are rarely tested or treated for PEI. Therefore, it is unclear if loss of pancreatic mass and function interacts with type 1 diabetes, and it is also unknown if treatment of PEI via pancreatic enzyme replacement treatment (PERT) can improve glucoregulatory status and prevent type 1 diabetes.

The purpose of this proposal is to support a multidisciplinary clinical consortium that would explore the prevalence of PEI in type 1 diabetes and the effect of treating PEI by PERT on glycemic control, type 1 diabetes complications, and quality of life. PERT's effects on circulating vitamin D levels, measures of metabolic bone disease, and/or other malnutrition-related complications of type 1 diabetes could also be tested. Better understanding the relationship between type 1 diabetes and PEI may lead to discovery of prognostic biomarkers for type 1 diabetes and/or to the identification of benefits of treating PEI in those with type 1 diabetes.

Multiple panelists appreciated this proposal's novelty, noting that it addressed an important, understudied topic. Several panelists also discussed the advantage of PEI already having an established treatment, and thus if PERT is shown to have beneficial effects in those with PEI and type 1 diabetes, this proposed research could result in swift improvements in clinical care. One panelist suggested including a well-characterized control population of those without type 1 diabetes to allow comparative study of glycemic responses and beta cell function over time. Another panelist urged including participants with a variety of type 1 diabetes subtypes to aid in understanding the immunological underpinnings of PEI in type 1 diabetes. The panel discussed how this initiative could focus on other promising areas beyond the core questions of PEI's role in type 1 diabetes and the potential benefits of PERT, if resources allowed. Such areas included studying the possible relationship between PEI and various type 1 diabetes nutritional complications and identifying PEI-related biomarkers for type 1 diabetes risk or progression, which could be used to monitor treatment.

Engineering Improved Stem Cell-Derived Islet Cells for Replacement Therapies
Primary discussants: Dr. Carmella Evans-Molina, Dr. Matthias Hebrok, Dr. Norma Kenyon

Clinical islet transplantation can restore glucose regulation in people with type 1 diabetes, but its utility is currently limited due to the scarcity of human islets and the need for chronic immunosuppression. However, it is now possible to use human pluripotent stem cells, including induced pluripotent stem cells (iPSCs) that are created from adult cells, to manufacture large quantities of stem cell-derived beta/islet cells (SC-islets). Generation of SC-islets also offers opportunities to precisely manipulate the islets' molecular makeup and cellular compositions. More research is needed on identifying SC-islet characteristics that correlate with beneficial post-transplantation outcomes, and encouraging bioengineering approaches to improve SC-islets

could reduce the burden of immunosuppression and increase the durability and function of transplanted cells.

This proposal would support research on engineering improved SC-islet products that could offer better cell replacement therapy outcomes. This initiative would aim to stimulate studies on targets and pathways amenable to such engineering approaches and to encourage their preclinical testing and validation. Topics of interest could include evading or withstanding immune destruction after transplantation, improving SC-islet cell composition to yield more durable products, refining platforms to test safety and efficacy of engineered traits in SC-islets, and/or assessing such engineered SC-islet health and cellular environment post-transplant. Such studies could lead to design of a manufactured SC-islet cell product that incorporates beneficial cell traits toward the establishment of a curative type 1 diabetes cell therapy.

The panelists felt that this was a compelling scientific opportunity to aid in development of renewable cell sources for cell replacement therapies for type 1 diabetes. They observed that this proposal was an opportunity to, for a reasonable cost, advance this field and possibly result in a platform technology that could connect and improve existing and future technologies by making them more interactive. Several panelists mentioned that the type 1 diabetes community is excited about this work, since future cell replacement therapies that do not require immunosuppression might benefit most people with longstanding type 1 diabetes. A panelist mentioned that safety should be a key component of work in this area. The panelists also agreed that efforts should focus on innovation and novelty (for instance, on novel molecules not already being studied or novel bioengineering approaches beyond existing gene editing strategies), so that they do not overlap with similar efforts being funded by industry or other funding organizations. An additional possible niche identified for federally funded academic research was to lead development of frameworks and methods to rigorously assess the quality of cell replacement products, which would make assessing, improving, and gaining regulatory approval more efficient. Further suggestions included: considering designing transplantable cells that react (for instance, by secreting beneficial factors) to sustain their own health in the transplant environment, remaining open to supporting research on autologous cell transplants which is not generally funded by industry, and considering synergies between this proposal and the proposal for the Consortium on Immune Tolerance Engineering.

Pilot/Opportunity Support for Generative Pretrained Transformers (GPT) to Accelerate Type 1 Diabetes Pancreas Research: Expansion of the HIRN-PanKbase Program
Primary discussants: Dr. Jake Chen, Dr. Avi Ma'ayan, Dr. Eric Rosenthal

The type 1 diabetes research community has generated a large amount of data and literature about the disease, which is growing exponentially every year. These data sources contain critical, but mostly hidden, information relevant to solving the grand challenges in type 1 diabetes research, such as its etiology and pathophysiology. However, it is still a major challenge to integrate literature and multimodal data, extract information from them, and use the information to guide further studies. The past decade has seen rapid advances in data science, most notably, in generative artificial intelligence (AI) and large language model (LLM) technologies. These technologies offer promising new ways to extract information

from data and scientific text, and to put that information in structured forms that can then be broadly used in other data processing and mining tasks. Additionally, more recent work demonstrated their potential in improving interoperability in biomedical research. Among the generative AI and LLM technologies, the transformer, as used in Generative Pre-trained Transformer (GPT) in Chat-GPT, is a leading one. Despite being a new technology, GPT has already shown great promise and is widely used in many areas of biomedicine. To build upon these advances, it is important to bring together AI and type 1 diabetes experts to advance type 1 diabetes research.

The purpose of this proposal is to leverage the rapid advances in AI and other areas of data science to tackle the challenge of extracting knowledge from type 1 diabetes literature and multimodal data and using that knowledge to guide research. The proposal would support pilot studies through the PanKbase (Type 1 Diabetes Pancreas Knowledgebase) program to recruit and train AI expertise in type 1 diabetes research, to develop foundation models for type 1 diabetes pancreas literature, and to utilize the models in multimodal data integration and AI applications, and in enhancing interoperability of PanKbase with partner programs. These pilot funds would provide opportunities to recruit multidisciplinary teams that include both type 1 diabetes and AI experts.

The panel stated the importance of applying AI and LLM technologies to the study of type 1 diabetes. They noted the potential for generating new types of knowledge, such as by using LLM technologies to analyze data in a broader context than is currently possible. A panel member thought that the proposal was innovative because it does not rely on ChatGPT alone, but also noted that given the limited resources available for this proposal, it would be important to merge findings from pilot studies to develop better models. Another panel member suggested considering the risks related to using GPTs, including possible harms from not using the technologies correctly. A panel member suggested broadening the proposal to include groups outside of PanKbase, such as industry partners, and to include funding an evaluation component—*e.g.*, have scientists design test cases for newly developed models. Other panel comments included: make sure the research is able to adapt to advances in new technologies that will be made in the next few years; ensure that standards include the metadata so there is understanding about origin and quality; consider how best to maintain/refine these technologies over time; and prioritize having a variety of different data types in addition to data quality. The panel also stated that knowledge gained about type 1 diabetes through this effort may be applicable to type 2 diabetes and other diseases.

Multimodal AI to Accelerate Development of Biomarkers for Type 1 Diabetes Initiation, Progression, and Heterogeneity
Primary discussants: Dr. Jake Chen, Dr. Avi Ma'ayan, Dr. Eric Rosenthal

Type 1 diabetes is affected by multiple environmental, behavioral, and genetic factors and involves multiple genes, tissues, and organs. Type 1 diabetes etiology and pathology are also heterogeneous, as are the disease's progression and outcomes. Due to this complexity, the lack of a system-level understanding of these factors has hindered identification of early biomarkers and slowed development of intervention and prevention strategies. The type 1 diabetes research

ecosystem—including data-centric research consortia, reporting systems, and data generation programs—has documented an enormous amount of data that can be leveraged to accelerate type 1 diabetes research. Multimodal artificial intelligence (MAI) has also emerged as a promising technique to generate predictions by analyzing multiple biomedical data types simultaneously, and MAI could unlock new discoveries by leveraging existing type 1 diabetes research data.

This proposal would support multi-disciplinary teams to develop an open-source MAI framework to map type 1 diabetes initiation, progression, and heterogeneity using temporal multimodal data, with the goal of identifying new type 1 diabetes biomarkers. This framework would connect multimodal datasets and the type 1 diabetes literature across multiple organs and components. This initiative would initially use labeled and formatted data from the Human Pancreas Analysis Program (HPAP) and The Environmental Determinants of Diabetes in the Young (TEDDY) study to build and pretrain multi-omics foundation AI models and spatial foundation models. These models would then be used to map a person's type 1 diabetes progression, identify disease tipping points, and predict pancreatic health. Data pipelines would be established to process additional datasets for use with the MAI models. The program would also integrate input from various sources (including research participants and external experts in AI ethics) to ensure privacy, fairness, transparency, and accountability. The proposed project would integrate with the Human Islet Research Network (HIRN) Pancreas Knowledgebase Program (PanKbase).

The panel felt that this was an important proposal to develop a predictive AI model that could utilize large "-omics" (*e.g.*, proteomic, genomic, transcriptomic) datasets to better understand type 1 diabetes and enhance personalized medicine approaches. Panelists noted the advantages of leveraging existing large, publicly available datasets to identify new type 1 diabetes biomarkers. One panelist particularly appreciated the proposal's focus on quality control and formatting of data, with other panelists agreeing that the utility of the developed AI models would be dependent on training them with properly curated data. Additional panel suggestions included: developing interoperative agentic AI systems for type 1 diabetes research, using holdout data to test the resilience and validation of the developed AI models, building "digital twins" of people with type 1 diabetes to enhance personalized medicine, and considering synergies between this proposal and Proposal 2 (Identification and Validation of Biomarkers for Defining and Characterizing Type 1 Diabetes Endotypes). One panelist also suggested expanding the proposal's scope to study the drivers of type 1 diabetes and identify important hormone, cell, and gene interactions. Several panelists emphasized that any developed AI models need to be validated to ensure that they are rigorous, robust, and useful for future downstream applications.

New Generation of Type 1 Diabetes Control Technologies Incorporating Artificial Intelligence/Machine Learning Tools/Strategies
Primary discussants: Dr. Eda Cengiz, Dr. Maria Redondo, Dr. Desmond Schatz

NIDDK and the Special Diabetes Program have long supported development and testing of diabetes management technologies such as continuous glucose monitors, hormone formulations, and delivery systems, as well as integration of these technologies in open- and automated hybrid

closed-loop systems. This work has resulted in new technologies being brought to market, but current methods are still unable to replace the pancreas' dynamic control of blood glucose levels. Improvements are needed to make devices that are less invasive and burdensome to use while improving durability, adaptability, reliability, and accuracy. Innovative opportunities also exist to augment these devices or their components with artificial intelligence (AI)/machine learning (ML) tools, which could accelerate development and optimization and possibly result in systems better able to predict and prevent dangerously low or high blood glucose levels.

The goal of this proposal would be to recruit and support a multi-disciplinary research team to address factors limiting progress toward more effective open- and closed-loop diabetes control systems. Such studies could include research on innovative improvements in sensing of relevant analytes/physiologic signals, automated control systems, formulation and delivery of hormones, and/or AI/ML-driven tools/algorithms to augment decision support. Such advances could improve glycemic control, reduce burden of care, and improve the quality of life of people with type 1 diabetes. This initiative would also promote cutting-edge research into the incorporation of AI/ML and "digital twin" personalized simulation tools to make more adaptable systems, address factors limiting the affordability and user-friendliness of these systems, and accelerate development of fully automated systems with minimal user intervention to reduce burden and improve quality of life.

The panel stated that this proposal was unique, novel, and addressed a compelling scientific opportunity, agreeing that current diabetes management systems are helpful but not always efficient, accessible, or user-friendly. The panel stressed the need for device designs that help enhance quality of life, such as combined devices that are more durable and less irritating to the skin, and devices that can take into account life factors such as stress or menopausal status. The panel felt incorporating AI/ML approaches in these devices could expand their utility in personalized health care, for instance by allowing use of digital twins to model a person's reactions to insulin. Also discussed was the need for research on how best to use these systems alongside other medications, such as teplizumab. Other panel suggestions were to use multi-analyte sensors to address delivery site placement issues and diabetic ketoacidosis, and to investigate long-term physiologic effects of insulin delivery. The panel cautioned that this proposal should ensure it does not overlap with device development efforts in industry, but they also identified unique opportunities for the federal government to support research that industry is unlikely to do (such as comparing device usage in different populations). One panelist noted that the device development work proposed here would also benefit those with other types of diabetes.

Development and Application of New and Existing Digital Health Technologies Including Mobile, Wearable, and Continuous Monitoring Tools for Kidney, Urologic, and Digestive Complications of Type 1 Diabetes Mellitus
Primary discussants: Dr. Rodica Busui, Dr. Eda Cengiz, Dr. Connie Rhee

Digital health technology holds the promise of extending the reach of medical care by collecting varied physiologic and environmental, patient-provided behavioral and clinical monitoring data. Since complications of type 1 diabetes are often chronic and affected by behaviors and

environmental drivers, there is a critical need to enhance application of devices and/or tools that can routinely collect and compile real-time, multimodal data from people with type 1 diabetes. Further integrating technology with health care offers great potential for a more personalized approach to preventing initiation or progression of disease, facilitating shared decision-making, and ultimately decreasing morbidity and improving patient quality of life. There is also a need to assemble and support collaborative teams with varied technical and clinical expertise to further develop, optimize, and apply these technologies for kidney, urologic, and digestive complications of type 1 diabetes.

The goal of this proposal is to support development and application of new digital health mobile technologies and/or enhancement of existing digital health tools/devices to facilitate improved characterization, diagnosis, and/or management of acute and chronic complications of type 1 diabetes. Such tools/devices could provide those with type 1 diabetes useful information on their health that could be used to enhance diabetes self-management regimens. Such technologies also have the potential to reduce health care costs by supporting affordable and cost-effective diagnosis and monitoring of type 1 diabetes complications. Finally, these technologies could benefit clinicians and researchers by allowing patients or research participants to provide comprehensive health data to enhance research and/or facilitate the development of personal precision medicine approaches.

The panel acknowledged the importance of addressing type 1 diabetes complications, and panelists were supportive of research to develop new "wearable" devices and/or apps to enhance early diagnosis and/or monitoring of these complications. Despite the many such technologies already available, multiple panelists stated that it is difficult for clinicians or people with type 1 diabetes to determine which tools are reliable and accurate. Several panelists said that research to develop validated tools/devices would help clinicians aid their patients in choosing an appropriate technology to help them avoid or manage type 1 diabetes complications. One panelist also felt that developing the proposed technologies could aid those who, due to location or other factors, find it difficult to access traditional type 1 diabetes complications screenings. Additionally, several panelists described the need for wearable devices that are user-friendly, easy to learn to use, and accessible at all literacy levels. One panelist also noted that high costs can make new technologies inaccessible and urged further development of low-cost options. Another panelist suggested that research into provider strategies for enhancing device use account for and include allied health care professionals, who often aid in device management in the clinic. Several panelists also encouraged the proposal's focus on developing devices that allow easy data sharing, so that users can share their data in convenient formats with clinicians or researchers.

Shared Decision Making to Improve Type 1 Diabetes Care
*Primary discussants: Dr. Ashley Butler, Dr. Sarah Jaser, Dr. Rozalina **McCoy***

Managing type 1 diabetes is a persistent burden, and persons living with the disease frequently need to make important medical decisions. However, little is known about the decision making process in type 1 diabetes or how it could be improved to enhance clinical care. Shared decision making is a collaborative process that enables and encourages patients to play a significant role

in decisions that impact their health. Shared decision making models focus on elements such as ensuring understanding of options and choices associated with a treatment decision, meaningfully engaging the patient and/or supportive others in the decision making process, and exploring options that reflect the patient's specific goals and priorities. Shared decision making has been associated with improvements in patient care and satisfaction in various settings, but there is a critical need to study shared decision making and type 1 diabetes health outcomes across the lifespan. More information on strategies to implement shared decision making strategies in clinical care is also needed.

The goal of this proposal is to evaluate the impact of shared decision making tools and interventions on health outcomes, including person-reported outcomes, among persons living with type 1 diabetes. Projects supported through this proposal would deliver and evaluate shared decision making interventions using novel or existing strategies or tools among diabetes care clinicians and persons with type 1 diabetes and/or supportive others. A particular focus would be to evaluate shared decision making in populations reflecting the wide variety of people in the type 1 diabetes community, including those for whom engagement may be challenging or who have worse glycemic outcomes. Supported studies could also focus on use of shared decision making across different models of care delivery (such as telehealth or remote care) or on addressing factors that affect preferences and priorities for diabetes care. Cost analyses could also provide data to guide future implementation of shared decision making interventions.

The panelists felt that decision making in diabetes care is an understudied area and that this proposal addressed a compelling opportunity to identify ways to better engage patients and optimize type 1 diabetes care delivery. Multiple panelists felt this proposal could result in sorely needed guidance and tools to aid health care providers in communicating with patients about their type 1 diabetes care (*e.g.*, managing expectations around diabetes management technologies, communicating risks of type 1 diabetes progression). One panelist particularly appreciated the proposal's broad focus, which could encourage needed research on shared decision making at different points of care and at different levels (*e.g.*, patient-provider interactions vs. institutional factors). The panelists discussed opportunities for clinical trials in this area to use innovative designs such as pragmatic, hybrid, or decentralized trial designs to help enroll participants outside of traditional academic medical settings. Other panel suggestions were to leverage implementation science and community engagement approaches to ensure that developed tools work for all people with type 1 diabetes, and to investigate possible collaboration with small businesses.

Role of Neuroimmune Interactions in the Pathogenesis of Diabetic Neuropathy in Type 1 Diabetes

Primary discussants: Dr. Rodica Busui, Dr. Connie Rhee, Dr. Eric Rosenthal

Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of type 1 diabetes and is usually underdiagnosed. DPN damage to enteric nerves, glia, smooth muscle cells, and vasculature impacts gut function. DPN is associated with vagal nerve dysfunction, which likely contributes to the gastrointestinal (GI) manifestations. Furthermore, the immune system plays a critical role in pathogenesis of type 1 diabetes, and there is strong evidence

showing that immune/inflammatory processes contribute to the onset and progression of complications such as DPN. Despite the importance of immune cell cross talk with the nervous system, the role of these neuroimmune interactions in the pathogenesis of DPN of the gut in type 1 diabetes remains relatively unexplored. Additionally, there are still no approved treatments for the prevention or cure of DPN that target nerves or immune cells, and available therapies target only symptomatic pain with variable efficacy.

The goal of this proposal is to accelerate research progress on the mechanisms by which the immune and nervous systems interact in ways that contribute to DPN affecting the GI tract in people with type 1 diabetes. Additionally, this proposal would offer an opportunity for collaboration between investigators in type 1 diabetes with expertise in immunology and in enteric neuroscience. It could also result in identification of biomarkers to better correlate DPN symptoms with pathology in the gut, and/or identification of targets for future therapeutic approaches. The knowledge gained through this research may also be applicable to other organs, particularly those innervated by the vagus nerve.

The panel members were supportive of research related to diabetic neuropathy, given the prevalence in those with type 1 diabetes, the negative impact it has on people's health and quality of life, and the paucity of effective treatments. They thought that the proposal was novel from a symptom science and symptom management standpoint. A panel member stated that while studying the microbiome is of interest, it could be challenging to interrogate the role of changes in the microbiome in type 1 diabetes and the impact on neuroimmune interactions linked to inflammation and abnormal GI function/symptoms. Another panel member suggested that the proposal be expanded to examine neuroimmune interactions that may contribute to type 1 diabetes onset, not just DPN. One panel member also noted that more research is needed on treatments for progressive cardiovascular autonomic neuropathy. Finally, a panel member suggested that future diabetic neuropathy-related research should prioritize advancing therapies that would have direct clinical relevance on nerve loss across the entire body, as well as research that would have the most impact on people's health and quality of life (*e.g.*, on DPN-related pain), given the burden that neuropathy places on people with type 1 diabetes.

Understanding Diabetic Wound Healing in Type 1 Diabetes
Primary discussants: Dr. Jeffrey Hubbell, Dr. George King, Dr. Desmond Schatz

In the United States, about 1.6 million individuals with diabetes will develop a diabetic foot ulcer (DFU) each year, with about 20% undergoing lower extremity amputation. For unknown reasons, people with type 1 diabetes have an up to two-fold greater risk for hospitalization and amputation from a DFU than those with type 2 diabetes. Current therapies for DFUs are often of limited effectiveness and do not take advantage of recent advances in understanding the personalized microbiologic, molecular, and cellular factors involved in wound healing. The NIDDK Diabetic Foot Consortium (DFC) offers a unique opportunity to comprehensively study DFU healing in people with type 1 diabetes, providing infrastructure that facilitates type 1 diabetes participant enrollment, collection of high quality biosamples and data, systematic analysis of data across multiple projects, and vital scientific collaborations to enhance study analysis and design. The DFC is currently enrolling people with diabetes and foot ulcers, with

ongoing collection of medical and social histories, patient-reported outcomes, wound images, and biosamples. Current studies are seeking to identify biomarkers and studying contributing environmental factors, laying the foundation for future intervention trials to test new therapies.

The purpose of this proposal is to understand the biological mechanisms and clinical factors that lead to poor DFU outcomes in people with type 1 diabetes. Using existing DFC infrastructure, this initiative would enhance recruitment of people with type 1 diabetes for longitudinal study, support basic mechanistic and clinical studies using DFC and other NIDDK resources, and develop clinical trials of type 1 diabetes-targeted therapies and biomarkers. These studies could leverage remote monitoring (*i.e.*, continuous glucose monitors and off-loading sensors) as well as advanced bioinformatics and -omics approaches. Clinical and other factors affecting DFU healing could also be studied, as well as comparisons between healing and non-healing wounds and between wounds in people with type 1 and type 2 diabetes. The goal of this research would be to develop therapies targeted to specific DFU phenotypes that could enhance wound healing and reduce amputations.

The panel agreed that this was a novel proposal on an understudied complication that places a large burden on the type 1 diabetes community. Several panelists mentioned that this proposal is a good example of gap-filling research, as other research funders are not focused on this area. The panel suggested working with institutions serving high numbers of people with type 1 diabetes to enhance recruitment, and also recruiting people with other type 1 diabetes comorbidities such as end-stage renal disease. Another suggestion was to recruit people without type 1 diabetes to allow comparison of skin and wound healing with and without the disease, which could further illuminate the causes of impaired wound healing. The panel encouraged focus on wound immunology and the effects of type 1 diabetes autoimmunity on the foot, as they felt this was an understudied area. The panel supported developing clinical trials for DFU treatments and felt that this proposal would provide needed validation of promising approaches that could facilitate such trials.

Reducing Cardiovascular Disease Outcomes in Type 1 Diabetes Mellitus
Primary discussants: Dr. Rodica Busui, Dr. Rozalina McCoy, Dr. Connie Rhee

Accelerated cardiovascular disease (CVD) in people with type 1 diabetes is thought to result from many pathways. Additionally, known risk factors may operate differently in people with type 1 diabetes compared to those with type 2 diabetes. Despite a disease process that starts early on and the very high relative risk for CVD through adulthood for people with type 1 diabetes, there is a paucity of primary prevention trials. Several possible interventions are available for study, ranging from those that focus on well-known CVD risk factors (*e.g.*, lipids, blood pressure) or less well-studied risk factors (*e.g.*, diabetic nephropathy, autoimmunity) to newer agents (*e.g.*, GLP-1 agonists, SGLT2 inhibitors). While a definitive cardiovascular events trial studying one or more of these interventions is likely unfeasible among type 1 diabetes participants who are less than 50 years of age, there is increasing interest in using subclinical CVD measures as a reliable surrogate for cardiovascular events that reflects disease severity and response to treatment interventions.

The purpose of this proposal is to support a clinical trial that will further develop and test screening and interventions to prevent CVD among adults 50 years old or younger with type 1 diabetes. The goal is to further enhance evidence-based CVD primary prevention guidelines for people with type 1 diabetes. Researchers would first develop and test the feasibility of protocols for successful participant screening and enrollment, then determine whether the investigator-proposed intervention(s) are efficacious at reducing the onset or slowing progression of subclinical CVD.

The panel commented that conducting a primary prevention trial of CVD in people with type 1 diabetes was an important goal due to gaps in knowledge related to clinical care and the need to address this leading cause of morbidity and mortality in the type 1 diabetes population. The panel made several suggestions, such as the need to establish efficacy before thinking about effectiveness. They suggested using lessons learned from past and from ongoing large trials (*e.g.*, in cancer, CVD) to optimize trial recruitment, retention, and data collection. Other suggestions include use of surrogate markers, including non-invasive measurements (*e.g.*, imaging), as a way to increase trial recruitment and feasibility; collection of patient-reported outcomes to determine if any long-term benefits of treatment mitigate short-term effects/harms; studying a lifestyle component as part of a trial (*e.g.*, examine dual effects of lifestyle and drugs); including outcomes related to kidney health, eye health, microvascular dysfunction, and heart failure; and conducting trials with agents shown to be cardio- and renoprotective in individuals with type 2 diabetes such as GLP-1 agonists and SGLT2 inhibitors, including consideration of a head-to-head comparison of GLP-1 agonists and SGLT2 inhibitors. These are trials that would not be done by industry but would have important clinical implications.

Addition of Ocular and Other Diabetes Complications Tissue to the Cardiovascular Repository - Type 1 Diabetes (CARE-T1D)
Primary discussants: Dr. David Antonetti, Dr. Amani Fawzi, Dr. George King

Diabetes complications research has shifted over time from explorations of unifying mechanisms of molecular and cellular damage to a strong focus on tissue-specific research. Diabetic pathology differs among the tissues affected by diabetes complications, but common mechanisms are also likely, though they have been difficult to study collaboratively for several reasons, including the lack of a forum to share scientific knowledge on common versus tissue-specific pathways; the tendency for animal models to be developed and characterized for single complications; and the limited resources for human diabetic tissue, in general, as well as few biorepositories having multiple tissues from the same individual. A biorepository with cardiac, kidney, ocular, nerve, peripheral artery, skin, and blood samples from the same donor would greatly facilitate cross-tissue research for pathways common to the development of complications, as well as for pathways that could confer relative resistance to damage in a specific tissue. Also, the clinical severity of specific diabetes complications depends on many factors, such as age, genetics, epigenetics, glycemia, and lipidemia. A biorepository with tissue from many donors with type 1 diabetes and type 2 diabetes would allow explorations of this heterogeneity in disease development.

The purpose of this proposal is to expand the biorepository of the Cardiovascular Biorepository for Type 1 Diabetes Program (CaRe-T1D) consortium to include human ocular tissue and other tissues affected by diabetes complications for a better understanding of tissue-specific, diabetes type-specific, and common pathways involved in the development of diabetes complications. A biorepository with such tissues from donors with type 1 diabetes and type 2 diabetes and without diabetes would support research leading to therapies that are critically needed for early diabetic retinopathy to prevent vision loss and for disease-modifying therapies for diabetic neuropathy and peripheral artery disease to prevent lower extremity amputations.

The panel commented that access to human ocular and complications tissue addresses an important need in the research community, as animal models are not always an adequate substitute; there could be much knowledge gained from studying many different tissue samples from the same individual; and having this new NIDDK resource could empower groups to work together rather than in silos. The panel noted the importance of including well-phenotyped tissue in this effort and of carefully considering the next stages of this research (*i.e.*, how best to study the donated tissues). They also stated that it could be beneficial both to include fresh tissue samples to facilitate studying metabolic changes in the retina, and to ensure that definitions of "normal" across different ages are included in this effort. Finally, the panel discussed the limitation that tissues donated to research are not as high-quality as those used for transplantation and encouraged researchers to consider creative ways to obtain high-quality tissues from control donors (*e.g.*, donors whose tissues may not be offered for transplant).

Identifying Early Visual Function Deficits from Diabetic Retinal Disease in Youth
Primary discussants: Dr. David Antonetti, Dr. Amani Fawzi, Dr. George King

Diabetic retinopathy (DR) presents a significant complication in youth with diabetes, frequently showing no symptoms in its initial phases but potentially evolving into a vision-endangering condition. Risk factors contributing to DR among individuals with type 1 diabetes or type 2 diabetes during their youth include the duration of the disease and the onset of puberty. During the past few years, several clinical practice guidelines have been established for the ophthalmic screening of young individuals with diabetes, however, there are discrepancies among medical professional societies regarding the recommended timing for monitoring. It is vital to understand the progression of DR and the necessity for interventions among youth with type 1 and type 2 diabetes. Specifically, understanding early functional changes in the retinas of youth with diabetes is pivotal to developing innovative approaches aimed at early identification and intervention to stop DR, thereby preventing future substantive vision loss in young individuals with diabetes who may have decades of diabetes still ahead.

The purpose of this proposal is to evaluate and identify early visual function deficits from diabetic retinal disease in youth. The ultimate goal of this proposed study is to determine if early visual functional deficits are predictive and can serve as biomarkers of onset and worsening of DR in youth. A comparison of whether there are differences in the change in visual function in youth with type 1 diabetes and in those with type 2 diabetes could also be assessed. Because early detection is key in preventing irreversible retinal damage and preserving sight, screening youths with either type 1 or type 2 diabetes for DR early in the disease course limits delays in

DR detection and maximizes opportunities to improve glycemic control, thus limiting DR progression.

The panel felt that the proposal was timely and supported not only increasing understanding of the underlying pathology of DR but also identifying mechanisms that may be protective in people who do not develop this complication. Additionally, the panel agreed with the proposed focus on studying early visual defects rather than waiting to do studies once vision declines. A panel member suggested that adding patient-reported outcome measures would strengthen the proposal. The panel members also discussed the pros and cons of using handheld electroretinography (ERG) to detect DR. One concern was that the device was limited in its ability to study DR, so a panel member suggested that the research also include other, more well-established methods to study DR, which would also allow collected data to be compared with other clinical studies. On the other hand, a benefit of the handheld ERG is that it is portable and could be used at the point of care (*e.g.*, in pediatrician's offices), which relates to the ability to translate potential positive findings from this research to clinical practice.

ADDITIONAL DISCUSSION

The expert panel made closing comments on the proposals. Specific input on proposals has been included in relevant sections above; other comments included:

- Promote synergies across proposals: The panel stated that there may be ways to integrate/coordinate research described under the proposals, as many of them have commonalities.
- Foster collaborations with industry and other funders: The panel stressed the importance of maximizing research collaboration with industry and nongovernmental partners to identify and fill research gaps.
- Promote community engagement: The panel encouraged continued and expanded community engagement, given its importance in both the research process and in helping to ensure that research results are used by the people they could benefit.
- Pursue the promise of AI/machine learning: Several proposals focused on AI/machine learning approaches. The panel was enthusiastic about the promise of these new technologies to advance type 1 diabetes research progress and stressed the importance of moving forward with appropriately curated data sets and robust validation.

The expert panel also identified promising 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:

- Ensuring that type 1 diabetes research is applicable to all with the disease: The panel commented on the importance of increasing knowledge about type 1 diabetes heterogeneity to help ensure that all people with type 1 diabetes benefit from Special Diabetes Program-supported research. Suggested approaches included: reach more people who may be eligible for clinical trials by improving point-of-care testing in doctor's offices and making home testing available; study people without known type 1

diabetes autoantibodies who are often excluded from current clinical trials; and understand the increasing rates of adult-onset type 1 diabetes (*e.g.*, conducting an adult TEDDY study).

- Improving clinical trials: To improve clinical trial recruitment, shared-decision making could help increase understanding about why people decide to participate in clinical trials and how the research community can make it easier for people to participate. The panel also encouraged approaches to make clinical trials more efficient to speed up the process of bringing new therapies to market, and to build on the success of teplizumab by continuing to study disease-modifying therapies for type 1 diabetes.
- Enhancing patient care: The panel suggested focusing on research that will improve patient care by studying not only possible new treatments, but also issues that are of highest priority to those with type 1 diabetes, such as managing symptoms, preventing or arresting complications, consolidating devices to improve user friendliness, and providing evidence for possible expansion of medications approved for use in type 2 diabetes into the type 1 diabetes population.
- Collecting real-world data on type 1 diabetes: The panel articulated the need to collect and analyze real-world clinical data on type 1 diabetes to help inform future research directions, such as by integrating continuous glucose monitoring data into electronic health records.
- Understanding type 1 diabetes etiology: The panel noted the importance of understanding the underlying mechanisms leading to type 1 diabetes, which can inform approaches to treat disease and monitor its progression. For example, future research could help determine whether studying the peripheral blood can help elucidate mechanisms leading to type 1 diabetes.
- Addressing possible links between nutrition and type 1 diabetes: One research opportunity identified relates to studying the intersection between nutrition and type 1 diabetes outcomes and complications.
- Improving islet transplantation: Developing imaging and other technologies that provide real-time data on transplanted cells may help address a gap in the islet transplant field related to knowing when and how best to intervene to promote transplant success.
- Addressing research workforce needs: To capitalize on the promise of AI, the panel noted that it is important to have an AI-ready workforce to tackle type 1 diabetes research. One promising approach to address this need is to model a future effort on the Special Diabetes Program-funded New Investigator Gateway Awards for Collaborative Type 1 Diabetes Research program, which has successfully embedded awardees into existing consortia to promote their career development. The panel also stated the need to attract bioengineers to the field that could apply their expertise to developing cell replacement therapies for type 1 diabetes.
- Promoting synergies across diabetes complications: The panel discussed the importance of ensuring that research on diabetes complications was not siloed. Suggestions included: organize a meeting to bring together complications experts to discuss research opportunities; create a consortium focused on therapeutic development for complications; more frequently include people with complications, such as chronic kidney disease, in type 1 diabetes clinical trials; study the genetics of diabetes complications; and collect outcome measures for multiple type 1 diabetes complications during trials, such as including eye-related outcome measures in heart disease trials. Another related

opportunity mentioned was to use modern, high-resolution vasculature and neural retinal imaging technologies to study possible links between retinal biomarkers and the health of other organ systems in the body.

- Addressing neurocognitive complications: The panel noted that there is an emerging need in type 1 diabetes research to study neurocognitive complications in adults, which are becoming more prevalent as people with the disease age.
- Building infrastructure: Infrastructure is critical to expand access to research participation, for example to those living in rural areas; support ongoing data collection, curation, and validation for AI-driven research strategies; and develop infrastructure and career development opportunities to support shared decision-making approaches.
- Assessing factors associated with research success: The panel noted that it would be helpful for future planning to consider ways to define and track meaningful advancements towards the overall goals of type 1 diabetes research.

APPENDIX 1: PANEL MEMBERS

Opportunities for Research Supported by the *Special Statutory Funding Program for Type 1 Diabetes Research*: A Workshop of the DMICC
November 12, 2024

EXPERT PANEL MEMBERS

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APPENDIX 2: ACRONYMS

ADA	American Diabetes Association
AI	artificial intelligence
CaRe-T1D	Cardiovascular Biorepository for Type 1 Diabetes Program
CDC	Centers for Disease Control and Prevention
CITE	Consortium on Immune Tolerance Engineering
CLEAR	Closed Loop and Education for Hypoglycemia Awareness Resolution
CVD	cardiovascular disease
DFC	Diabetic Foot Consortium
DFU	diabetic foot ulcer
DPN	diabetic peripheral neuropathy
DR	diabetic retinopathy
DMICC	Diabetes Mellitus Interagency Coordinating Committee
EHR	electronic health record
ER	endoplasmic reticulum
ERG	electroretinography
FDA	U. S. Food and Drug Administration
FY	fiscal year
GI	gastrointestinal
GPT	Generative Pretrained Transformer
HbA1c	hemoglobin A1c
HHS	U.S. Department of Health and Human Services
HIRN	Human Islet Research Network
HPAP	Human Pancreas Analysis Program
iPSC	induced pluripotent stem cell
LLM	large language model
MAI	multimodal artificial intelligence
ML	machine learning
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NOFO	Notice of Funding Opportunity
PanKbase	Type 1 Diabetes Pancreas Knowledgebase
PEI	pancreatic exocrine dysfunction and insufficiency
PERT	pancreatic enzyme replacement treatment
SC	stem cell
TaMADOR	Targeted Mass Spectrometry Assays for Diabetes and Obesity Research
TEDDY	The Environmental Determinants of Diabetes in the Young