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

May 5-6, 2011
Rockville, MD

Summary

INTRODUCTION

A panel of 16 scientific and lay experts from across the United States, with expertise relevant to type 1 diabetes and its complications, convened in Rockville, Maryland on May 5-6, 2011. The goals of the 2-day workshop were to obtain input from panel members on draft concepts, put forth by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC), for research initiatives that could be pursued with funds from the *Special Statutory Funding Program for Type 1 Diabetes Research* (*Special Diabetes Program*) in Fiscal Year (FY) 2012 and FY 2013. The panel was also invited to provide input on other ideas for new and emerging opportunities for type 1 diabetes research that could be pursued with the Special Funds. Thus, the workshop served as a key source of input to the government for informing future research directions.

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

The *Special Diabetes Program* augments regularly appropriated funds that the NIH receives for diabetes research. Unlike regular appropriations, the Special Funds are limited in time and require renewal in law. In December 2010, the *Program* was extended for 2 years (FY 12-13) at a level of $150 million per year. The *Program* will have provided funds in the amount of $1.89 billion for FY 1998-2013 (see Figure 1) 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.

Overview of Program Planning: To ensure the most scientifically productive use of the *Special Diabetes Program* funds, the NIDDK has instituted a collaborative planning process that

involves the participation of most NIH Institutes and Centers; members of the DMICC; and the two major diabetes voluntary organizations: the JDRF and the American Diabetes Association (ADA).

Also critical to the planning process is scientific input that the NIH has garnered from type 1 diabetes researchers, the broad research community, and the public. Sources of input include a variety of scientific workshops and conferences, diabetes research strategic planning processes, and a series of planning and evaluation meetings to assess current research and future opportunities. The planning and evaluation meetings have convened panels of experts external to the NIH to provide input on research supported by the Special Funds. The meetings have been critically important to informing program planning.

Figure 1: Legislative History of the *Special Statutory Funding Program for Type 1 Diabetes Research* (FY 1998-2013)

Special funding for type 1 diabetes research was initially provided by the Balanced Budget Act of 1997, Public Law (P.L.) 105-33 (now Section 330B of the Public Health Service Act). This funding was later extended and augmented by Section 931 of the 2001 Consolidated Appropriations Act (P.L. 106-554) and by the Public Health Service Act Amendment for Diabetes (P.L. 107-360). In December 2007, the funding was extended by the Medicare, Medicaid, and SCHIP Extension Act of 2007 (P.L. 110-173) through FY 2009. The Medicare Improvements for Patients and Providers Act of 2008 (P.L. 110-275) extended the funding for 2 years through FY 2011 at a level of $150 million per year. Most recently, the Medicare and Medicaid Extenders Act of 2010 extended the Program through FY 2013 at a level of $150 million per year (P.L. 111-309).
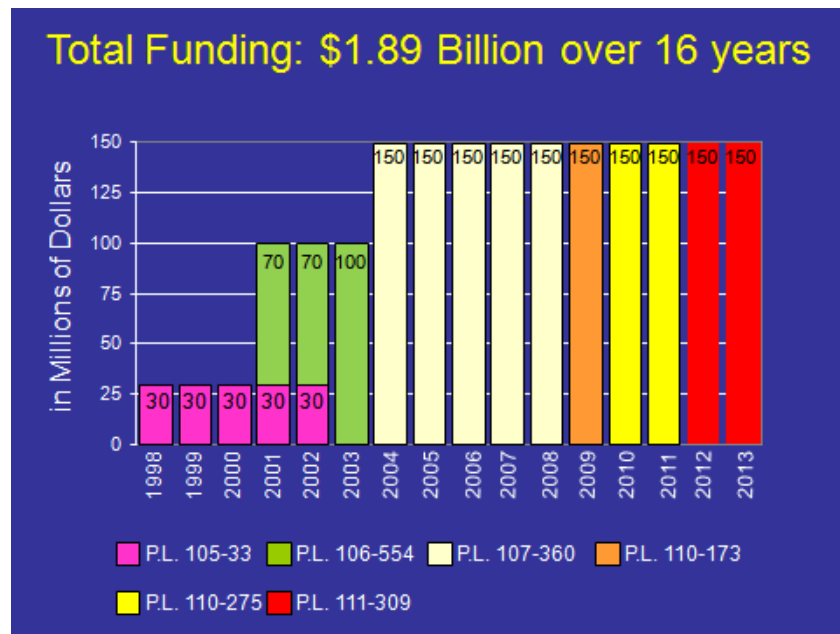
Background on Workshop: In December 2010, the *Special Diabetes Program* was extended for 2 years through FY13. The 2-year extension provides an opportunity to support new and emerging research in type 1 diabetes and its complications. To inform decisions about how best

to use the new funds, the NIDDK convened a panel of external experts to solicit input on future research directions. The Institute asked DMICC members to suggest names of possible panel members. With input from DMICC members, the NIDDK invited 16 scientific and lay experts to serve on the panel. The 15 scientists had expertise in a variety of areas, including type 1 diabetes, type 2 diabetes, diabetes complications, genetics, immunology, beta cell biology, behavioral research, neuroendocrinology, chemical engineering, drug development, clinical trial design, epidemiology, and islet transplantation. A lay panel member with broad expertise in type 1 diabetes was also invited to provide important input from the patient perspective.

Because the *Special Diabetes Program* is a trans-HHS program, the NIDDK initiated a call for proposals to other DMICC member organizations for ideas for research that could be pursued in FY12-13. Specifically, the NIDDK requested:
1. New concepts for basic, pre-clinical, or clinical research that could advance understanding of type 1 diabetes or its complications; or
2. Continuations or expansions of ongoing programs supported by the *Special Diabetes Program*. This included programs that were requesting funds to support a new funding cycle, or programs that were seeking additional funds to support new activities in the current funding cycle (e.g., launch of new clinical trials).

Twenty-eight proposals, submitted by 5 NIH Institutes and Centers and the CDC, were presented to the panel: 15 new initiatives and 13 continuations or expansions of ongoing programs. Write-ups of the 28 proposals were provided to the panel members prior to the workshop.

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

The workshop was then organized around six broad topics related to type 1 diabetes research:
- Autoimmune Etiology and Epidemiology
- Clinical Management
- Resources
- Artificial Pancreas
- Beta Cell Replacement
- Diabetes Complications

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

At the conclusion of the workshop, there was a closing discussion during which panel members were asked to comment on any gaps in the overall *Special Diabetes Program* research portfolio

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

OPENING REMARKS

Griffin P. Rodgers, M.D., M.A.C.P., Director, NIDDK, welcomed the panel and thanked them for attending this important workshop. He emphasized that the *Special Diabetes Program* is extremely important to the NIDDK, and the Institute takes the task of administering the funds and maximizing their value very seriously. He stated that the purpose of the workshop was to discuss how best to use new funds from the recent extension of the *Special Diabetes Program* to support research to combat type 1 diabetes and its complications. Therefore, the input provided by the panel will be critically important to the government in its planning efforts.

Overview of the *Special Diabetes Program*: Judith Fradkin, M.D., Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK, thanked the panel members for participating in the workshop, and provided them with an overview of the *Special Diabetes Program*. The *Program* has been used to support large-scale, high-risk, collaborative research consortia and clinical trials networks. The funding supplements, but does not supplant, research supported by regular NIH appropriations. It is a time-limited funding stream requiring renewal in law, with the funds currently slated to end in FY13.

Dr. Fradkin noted that this workshop is one of a series of planning and evaluation meetings that the NIDDK has convened to obtain external input on research supported by the *Special Diabetes Program*. For example, today's workshop is similar to a meeting held in 2000, in which government agencies were invited to submit proposals for new research initiatives that could be undertaken with the Special Funds. Input from that meeting was instrumental in informing research directions that were supported when the Special Funds were extended and substantially increased in 2001. The NIDDK expects that input from today's workshop will be similarly important for informing decisions about future research. In addition to planning and evaluation meetings, two strategic plans are serving as important guideposts for type 1 diabetes research: a Type 1 Diabetes Strategic Plan (2006) and a Diabetes Research Strategic Plan (2011). These Plans were developed under the auspices of the DMICC with broad input from the scientific community, patient advocacy groups, and the public.

Dr. Fradkin explained that, because the *Special Diabetes Program* is time-limited, the NIDDK has employed different management strategies for the *Program* than it uses for regular appropriations. For example, since 2009, the Program has been extended in increments of 1-2 years (see Figure 1), but most typical research grants are 5 years in duration. Therefore, the NIH cannot fund traditional 5-year research grants with short-term funds because of the uncertainty of out-year funding. To address the challenge of supporting new, multi-year research projects with short-term funding, the NIDDK has made use of special types of grants, such as the Type 1 Diabetes Targeted Research Award. The NIDDK expects that special types of grants will also be used to support research in FY12-13 because of the uncertainty of funding beyond FY13.

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 website on the [Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs](#)). Dr. Fradkin asked the panel members to consider opportunities to utilize those funds.

Dr. Fradkin closed her presentation by describing the workshop agenda. She also provided the panel with a series of questions to help guide discussion throughout the 2-day workshop.

DISCUSSION OF PROPOSALS

The workshop focused on discussion of 28 proposals, submitted by the NIH and CDC, for initiative concepts that could be pursued with Special Funds in FY12-13. The panel members had enthusiasm for 23 of the proposals—either as presented or with enhancements—and also suggested one additional concept that should be pursued, for a total of 24 proposals that were thought to be of high scientific priority. Those 24 proposals are described below, grouped under the relevant topic area.

TOPIC 1: AUTOIMMUNE ETIOLOGY AND EPIDEMIOLOGY

Function of Genes for Type 1 Diabetes
Primary discussant: Dr. Peter Gregersen

Type 1 diabetes has a strong genetic basis that is modified by environmental factors. The disease is "polygenic," meaning that it arises from the interaction of variations in multiple genes. The human leukocyte antigen (HLA) class II genes have long been known to contribute as much as 40-50 percent of the genetic risk for type 1 diabetes. Candidate gene studies also identified four non-HLA genes for type 1 diabetes risk: *INS*, *CTLA4*, *PTPN22*, and *IL2RA*. In recent years, technological advances in genetics research have helped researchers find more than 40 additional genes or gene regions that significantly affect the risk of type 1 diabetes. In total, over 70 percent of the type 1 diabetes heritability has been identified. Despite this tremendous progress in identifying genetic risk factors for type 1 diabetes, little is known about the mechanisms by which these genes predispose people to beta cell destruction and, ultimately, type 1 diabetes.

This new initiative is intended to support research to determine the function of HLA and non-HLA genes conferring type 1 diabetes risk and to further refine the gene regions that are involved in the disease process. Understanding how changes in the function or regulation of these genes alter type 1 diabetes risk is likely to provide new insight into disease pathogenesis.

The expert panel thought that support for this initiative was well justified by the need to better understand the wealth of information emerging from genetic studies of type 1 diabetes. This important and under-studied area will require broad input from geneticists, immunologists, and other functional biologists. Although focused on analysis of human genes, some panel members felt that this line of research would benefit from complementary studies on novel mouse models, including humanized models, in addition to research on human cells. The panel noted that it will also be important to study the function of diabetes susceptibility genes in non-diabetic individuals.

Ancillary Studies to Clinical Trials in Type 1 Diabetes
Primary discussant: Dr. R. John Looney

NIH has invested considerable resources in large prospective epidemiological studies and interventional trials. These studies have identified participants, collected and reposited samples for many years, and in some cases continue to recruit new participants or are in intensive follow-up of participants already enrolled. Among these, Type 1 Diabetes TrialNet screens over 15,000 relatives of people with type 1 diabetes per year to identify persons at risk for the disease and enroll them in trials for disease prevention. However, only a few clinical trials are ongoing at any given time, and many participants do not qualify or choose not to participate in such trials. TrialNet follows some at-risk people and collects samples for mechanistic studies, but opportunities exist for additional collections or other types of studies utilizing the network infrastructure.

The goal of this new initiative is to gain a better understanding of type 1 diabetes in humans and to promote the prevention or cure of the disease by supporting research on biomarkers of disease progression, susceptibility to complications, and response to therapy. Two opportunities for ancillary studies to existing clinical trials are proposed. One component of this initiative would support research using well-developed laboratory assays on non-renewable samples collected in type 1 diabetes clinical trials and studies. Another component would create a "living biobank" of participants in the TrialNet Natural History Study who have been identified as being at risk for type 1 diabetes but who are not enrolled in current TrialNet clinical trials. Investigators would have an opportunity to recruit those people for the collection of new types of samples or the performance of additional measurements that are not currently supported by TrialNet.

The panel was enthusiastic about supporting ancillary studies to type 1 diabetes clinical trials, especially with respect to establishing a living biobank of non-diabetic first degree relatives who had been screened by TrialNet. Such a resource represents an important opportunity to open up the TrialNet infrastructure to the broader research community to address novel scientific hypotheses in the diabetes-vulnerable population. The panel emphasized the importance of widely disseminating information on the availability of clinical resources and biosamples. NIDDK could consider convening a small working group to identify scientifically important questions that could be addressed with a living biobank. Finally, efforts to educate all persons screened through TrialNet on participation in clinical research will help generate an invaluable cohort of people who are committed to helping type 1 diabetes research over the long term.

New Methods and Technologies for Identification of Individuals at Risk for Type 1 Diabetes
Primary discussant: Dr. Roland Tisch

Early identification of type 1 diabetes risk and the onset of autoimmunity provides the basis for a variety of major ongoing studies and trials to prevent or delay the disease. However, current technology for identification of at-risk individuals is costly, requires participation of research laboratories, and may not be suitable for public health screening that would ensue should effective preventive interventions be established. Methods for more efficient identification of at-risk individuals would include low-cost, high-throughput, accurate, and predictive assays that could be used at the point of care level.

This new initiative proposes to stimulate and support innovative research conducted by small businesses for the development of low-cost novel assays and devices for predictive screening for type 1 diabetes risk and autoimmunity using genetic and immune markers. The development of such technologies would facilitate recruitment for clinical research to identify environmental triggers of type 1 diabetes, type 1 diabetes natural history, and interventions to prevent the disease. It would also aid the clinical implementation of measures that, in the future, may be proven effective in delaying or preventing type 1 diabetes in those at risk. Use of such assays in organ donors could facilitate provision of autoimmune pancreata to researchers.

Panel members noted that the development of portable devices that can be used for screening at points of care could facilitate and greatly reduce the costs of research studies and trials that require screening of thousands of individuals. In the long term, if and when research identifies type 1 diabetes prevention approaches, such technologies could be used for pre-diabetes testing in the general population to identify the people who could benefit from those approaches. The panel suggested that NIDDK identify clear milestones to focus grant applications on specific needs. Applicants could also be required to address the cost reduction potential of their proposed technologies compared to current methods of autoantibody detection. Finally, there may be opportunities to leverage this initiative with other NIH Institutes and Centers that have an interest in autoimmune diseases, such as lupus or rheumatoid arthritis, that could benefit from advanced technologies for the detection of autoimmunity.

Type 1 Diabetes TrialNet
Primary discussants: Dr. R. John Looney, Dr. David Nathan

Type 1 Diabetes TrialNet, which is led by the NIDDK, is an international consortium of clinical research centers focused on the delay and prevention of type 1 diabetes. TrialNet has created an extensive network of experienced sites capable of screening large numbers of relatives of people with type 1 diabetes as a source of participants for prevention trials, currently screening at least 15,000 people per year. In addition, TrialNet has spearheaded several clinical trials for beta cell preservation in new-onset patients. Among its accomplishments, TrialNet has determined that the drug rituximab—which targets B lymphocytes—slows progression of type 1 diabetes in the newly diagnosed. This pivotal study demonstrated the importance of B lymphocytes in the pathogenesis of type 1 diabetes and will encourage further development of effective and safe therapies targeting B lymphocytes. TrialNet also conducts studies to optimize the conduct of type 1 diabetes trials and to gain a mechanistic understanding of interventions in type 1 diabetes.

Maintaining the TrialNet screening infrastructure is critical for conducting prevention and mechanistic studies in at-risk individuals now and in the foreseeable future, as well as for the support of ongoing and planned intervention trials in new-onset patients. The expectation is that basic research will continue to provide promising scientific opportunities for progress toward type 1 diabetes prevention and treatment, and as long as TrialNet can provide an efficient means for testing these new ideas, maintenance of the network is more cost-effective than rebuilding a screening network for each new proposed intervention or study. Thus, this initiative proposes to continue support for the TrialNet Biostatistics Coordinating Center for new and ongoing clinical trials.

The expert panel noted that the ongoing TrialNet screening efforts have generated a cohort with long-term value. By identifying key events associated with the natural history of type 1 diabetes, researchers will be able to rationally develop immunotherapies to prevent or treat the disease. Panel members suggested that TrialNet consider studying the natural history of type 1 diabetes in geographic regions with low rates of the disease; research in such populations might uncover mechanisms that protect from type 1 diabetes. The panel discussed the cost-effectiveness of TrialNet screening efforts relative to the productivity of the network. The panel acknowledged the paucity of new drugs available to test in at-risk and new-onset patients and the ethical and safety concerns of testing interventions in at-risk individuals who have not developed overt diabetes. Nonetheless, continued screening and accrual of at-risk individuals has great value for future prevention trials, functional genetics studies, and other applications.

Immune Tolerance Network
Primary discussants: Dr. R. John Looney, Dr. Peter Gregersen

The Immune Tolerance Network (ITN), which is led by the National Institute of Allergy and Infectious Diseases (NIAID), is an international consortium dedicated to advancement of tolerance-inducing therapies for the treatment of autoimmune diseases, asthma, and allergic diseases, and for the prevention of graft rejection following kidney, liver, and pancreatic islet transplantation. The ITN develops and conducts phase I-III clinical trials of novel tolerance strategies that investigate safety and efficacy, as well as the basic biological features and potential biomarkers of tolerance through mechanistic studies integrated into each trial. Among its accomplishments related to the prevention and treatment of type 1 diabetes, ITN completed the first multicenter clinical trial of islet transplantation, investigating the feasibility and practical concerns in standardizing an islet transplantation protocol across multiple centers. This pivotal proof-of-concept trial paved the way for other islet consortia studies now in progress. In addition, ITN is conducting several trials to advance anti-T cell therapeutics for treatment of new-onset type 1 diabetes.

Ongoing support for the ITN will enable further development of type 1 diabetes-related trials and projects. Planned studies include three new clinical trials of immune therapies in people with new-onset type 1 diabetes, as well as mechanistic studies in two additional clinical trials.

Panel members noted that the ITN has been productive and warrants ongoing support; many different interventions have been or are currently being tested in clinical trials with associated mechanistic studies. The panel also discussed the complementary scientific goals and expertise of the ITN, which is composed primarily of immunology experts and focuses on immune-tolerizing interventions in new-onset patients, and TrialNet, which includes clinical endocrinologists and has the capacity to test interventions in new-onset patients, as well as prevention strategies in at-risk individuals. Logistical cooperation between the ITN and TrialNet for recruiting patients and a shared data and safety monitoring board contribute to cost reduction and increased efficiency.

Cooperative Study Group for Autoimmune Disease Prevention
Primary discussant: Dr. Peter Gregersen

The Cooperative Study Group for Autoimmune Disease Prevention (Prevention Centers), led by NIAID, engages in research to advance knowledge on the prevention and regulation of autoimmune disease. The Prevention Centers' goals include the creation of improved models of disease pathogenesis and therapy to better understand immune mechanisms and develop prevention strategies. Such models serve as validation platforms for testing new tools applicable to human studies. The Prevention Centers also encourage core expertise and collaborative projects designed for rapid translation from animal to human studies, emphasizing the development of surrogate markers for disease progression and/or regulation that can be used in clinical trials.

This proposal would provide support for a third competitive funding cycle of the Prevention Centers. The long-term goal of the program is to develop the knowledge to design interventions for the prevention of autoimmune disease that could be administered efficiently and safely to individuals at risk or to the general population, including infants and children. With that goal in mind, two overarching themes have emerged in the consortium that illustrate the need for continued support. First, the Prevention Centers increasingly rely on high-throughput, advanced genetic technologies to bridge the gap between the non-obese diabetic (NOD) mouse model of type 1 diabetes and human diabetes patients and to facilitate translation of basic genetic and phenotypic observations into addressable mechanisms of disease. These technologies are expensive but scientifically fruitful. Second, the Prevention Centers increasingly emphasize human-based studies, including the development and use of sophisticated humanized mouse models. This shift is justified by the progress to date in *in vitro* and animal systems and necessary for continued progress toward successful prevention strategies applicable to humans.

The panel noted that the Prevention Centers have brought together a talented and productive group of researchers, and panel members were enthusiastic about continuing to support this program. Studying immunobiology in mouse models and creating mice with specific characteristics can reveal important insights into the biological mechanisms of the immune system in type 1 diabetes. The panel suggested that this group of investigators could interact with other researchers devoted to functional studies of human genes related to type 1 diabetes.

The Environmental Determinants of Diabetes in the Young
Primary discussants: Dr. Peter Gregersen, Dr. R. John Looney

The Environmental Determinants of Diabetes in the Young (TEDDY), led by NIDDK, was established to develop and carry out studies to identify environmental triggers of type 1 diabetes, such as infectious agents, dietary factors, and/or psychosocial factors, in genetically susceptible individuals. Identification of such factors will lead to a better understanding of disease etiology and pathogenesis and result in new strategies to prevent, delay, or reverse type 1 diabetes. TEDDY has completed screening of 418,371 newborns from the general population and recruited 7,749 participants. The study also completed screening of 6,417 newborns with first degree relatives with type 1 diabetes and recruited 928 participants from that population. Therefore, in total, over 8,000 children are participating in TEDDY.

This proposal for ongoing support for the TEDDY clinical centers would allow for continued monitoring of study participants for the development of autoimmunity and type 1 diabetes. TEDDY was designed to follow newborns for 15 years to accrue enough participants developing

autoantibodies and diabetes to test specific hypotheses about infectious, dietary, and other triggers. Continued follow-up of this cohort, including ongoing collection of data and biological samples, is needed to yield the requisite number of events to address the study's hypotheses.

The panel expressed enthusiasm for continuing to monitor participants who have been enrolled in TEDDY. The large NIH investment in TEDDY has generated a unique cohort that requires ongoing support for data and biosample collection and analysis to realize the full scientific value of the study.

TOPIC 2: CLINICAL MANAGEMENT

Clinical Trials To Improve Outcome in Type 1 Diabetes
Primary discussants: Dr. David Nathan, Dr. Georgeanna Klingensmith

Diabetes management requires complex balancing of medication dosing, diet, and exercise in order to achieve good glucose control while avoiding hypoglycemia. The constant burden of the disease affects the quality of life of individuals with type 1 diabetes and their families and may be associated with poor adherence to medical regimens. Research clearly demonstrates the efficacy of good glucose control in preventing the long-term complications of type 1 diabetes. Yet, despite efforts of patients to keep their glucose levels as normal as possible, it is nearly impossible for individuals with type 1 diabetes to achieve the precise level of control attained by a healthy pancreas. Therefore, interventions to improve clinical management of type 1 diabetes across the lifespan are needed.

This new initiative will support clinical trials to test interventions designed to increase adherence to therapy, improve glycemic control, and/or treat or reduce diabetes complications. The intent of this initiative is to improve the management and treatment of individuals with type 1 diabetes. If successful, the results of such trials would be of practical importance to clinical management and applicable immediately. This initiative is not intended to validate new technologies or test new therapeutics.

The expert panel agreed on the general need to support research aimed at improving care and disease management for individuals with type 1 diabetes, although it was complicated to fully evaluate the merits of this proposal without knowledge of specific trials that would be pursued. The panel acknowledged that it is challenging, but important, to support inherently long-term clinical trials with short-term funding. This initiative to solicit investigator-initiated ideas could motivate the research community to develop fresh concepts for clinical trials. Finally, the early stages of the initiative could be used to help investigators develop independent ideas that could then be integrated into a single, collaborative trial.

Improving Adherence in Adolescents and Young Adults with Type 1 Diabetes
Primary discussants: Dr. Timothy Wysocki, Dr. Georgeanna Klingensmith

Complex and demanding treatment regimens for diabetes may be especially difficult for adolescents and young adults. Adolescents experience significant pubertal and developmental changes, increased peer influence, and issues related to emerging autonomy and increased

responsibilities for life choices. Young and emerging adults are often faced with significant financial, healthcare, social, and interpersonal transitions that make it more challenging to adhere to a diabetes management regimen. Avoiding blood glucose monitoring and skipping, delaying, or under-dosing insulin can result in extreme high or low blood glucose and life-threatening diabetic ketoacidosis. A finite period of poor metabolic control in adolescence can lead to increased risk of complications over the ensuing decades. The development of new and better interventions to improve the ability and motivation of adolescents and young adults to adhere to prescribed treatment regimens could result in short- and long-term health benefits.

The goal of this new initiative is to support research to develop, refine, and pilot test innovative strategies to improve adherence to medications and medical regimens in adolescents and young adults with type 1 diabetes. Studies to improve adherence and health outcomes may address such topics as: low diabetes health literacy/numeracy in individuals with type 1 diabetes and/or their caregivers; health beliefs that reduce adherence, such as over- and under-prediction of risks; improved support systems for diabetes management, including family, peers, social networks, or technology-based support; barriers to the use of technologies, such as insulin pumps, blood glucose monitors, and continuous glucose monitoring systems; and health care delivery, including collaborative communication with the healthcare team, addressing issues of transitioning to greater autonomy in care, assessment of adherence to the medical regimen, and patient-centered goal setting.

Panel members thought that this initiative addresses a real gap in knowledge regarding adherence to diabetes treatment and represents an important area for expanded focus. The initiative could be broadened to include longitudinal studies of the precursors of poor adherence, as well as the concomitant depression and anxiety seen in this population. NIDDK could also consider supporting studies or interventions that target diabetic pre-adolescents and their parents, including research on preventing the deterioration of adherence and self-management. Other relevant topics include: the use of technologies, such as web-based interventions, social networking, and devices in addition to continuous glucose monitors and insulin pumps, that could resonate with adolescents and young adults; addressing diabetes-specific adherence barriers, particularly those related to neuroendocrine factors; and the issue of risky insulin adjustments to manage weight in adolescent girls with diabetes.

Training for Behavioral Scientists in Type 1 Diabetes
Primary discussant: Dr. Suzanne Craft

The skills and resources required for optimal management of type 1 diabetes change over the life course and are dependent on many factors, such as social and familial support and individual characteristics or states, such as mental health status, health literacy/numeracy, stress management, communication skills, and lifestyle. Thus, the behavioral sciences have much to offer to improve the care and management of people with type 1 diabetes. However, the number of trained behavioral scientists involved in type 1 diabetes research is relatively small. The optimal time for career development specific to type 1 diabetes research is likely the postdoctoral and junior faculty years as the individual is past the more general academic and clinical training required for a degree but is still open to a variety of career paths and research directions.

This proposal for a new behavioral scientist career development program is intended to foster the development of a highly trained workforce of behavioral scientists to assume leadership roles in research on type 1 diabetes. The program will assist behavioral investigators' transition to an independent career in type 1 diabetes. Although there have been considerable advances in the treatment of type 1 diabetes, self-management remains a cornerstone of good glycemic control. Thus, it is imperative to enhance research training and career development opportunities for behavioral scientists focused on developing new approaches to improve self-management, adherence, and quality of care for individuals with type 1 diabetes.

The expert panel felt strongly that this proposed investment in training for behavioral scientists in type 1 diabetes research will likely have a long-term, positive impact. The plan to utilize interdisciplinary mentorship teams, by pairing a diabetologist and a behavioral scientist, is critical for recruiting new, appropriately trained investigators into the career pipeline. The panel suggested expanding the program to include support for postdoctoral training and, possibly, predoctoral summer students. The panel felt that research training was a particularly useful endeavor to support with short-term funding, as it is an investment in scientists who could make lifetime contributions to type 1 diabetes research.

TOPIC 3: RESOURCES

Type 1 Diabetes-Rapid Access to Intervention Development
Primary discussant: Dr. Todd Zion

The Type 1 Diabetes-Rapid Access to Intervention Development (T1D-RAID) program, led by NIDDK, program assists translation from the research bench to the clinic of novel therapeutic interventions for type 1 diabetes and its complications. T1D-RAID helps remove the most common barriers between laboratory discoveries and clinical trials of new molecular entities. This facilitates efficient translation of promising discoveries even in the absence of development capacity or clinical expertise in the organization where the discovery was made. The sponsors of approved requests to T1D-RAID gain access to the pre-clinical drug development resources of the National Cancer Institute (NCI)'s Developmental Therapeutics Program. The output of T1D-RAID activities may include good manufacturing process synthesized material, formulation development, stability studies, assay development, or toxicology studies to support an investigational new drug application. To date, the pre-clinical development of five potential new therapeutics for treatment of type 1 diabetes or its complications has been supported through T1D-RAID.

For molecules with compelling evidence of pre-clinical efficacy, academic investigators or small companies have limited resources to conduct the pre-clinical development work that is required to progress toward studies in humans. T1D-RAID fills that critical need for the type 1 diabetes research community. This proposal would provide continued support for T1D-RAID to ensure that promising new therapeutics can move forward to proof-of-concept studies in humans.

Panel members noted that the T1D-RAID mission is critical for allowing investigators to make the leap from basic discovery into clinical application. With relatively modest funding, this program helps investigators overcome the high costs required for developing new therapeutics for type 1 diabetes. In addition, the T1D-RAID application process is highly interactive,

providing valuable feedback even to applicants whose potential therapeutics are not accepted for development by the program. The panel suggested that NIDDK investigate alternate methods to deliver T1D-RAID resources, such as providing funds directly to investigators for some processes rather than relying exclusively on NCI infrastructure. In addition, NIDDK could consider filling the gap in molecular/chemical screening and high-throughput assay development to assist more investigators in identifying potential drugs for development through T1D-RAID. The panel considered T1D-RAID to be an effective, unique program deserving of ongoing support.

Type 1 Diabetes Mouse Resource
Primary discussant: Dr. Alvin Powers

The objective of the Type 1 Diabetes Mouse Resource (T1DR), led by NIDDK, is to enhance existing investments in animal models for type 1 diabetes research by facilitating the development and sharing of unique mouse resources. Goals are fourfold: (1) to import, curate for nomenclature and phenotypic information, and archive mouse models important for type 1 diabetes research to avoid loss or duplication of investments in strain development and characterization; (2) to provide a systematic and uniform characterization of mouse models to clarify strain genetic composition and its influence on disease phenotypes under standardized husbandry conditions; (3) to provide a user-friendly source for distribution of strains to the investigator community; and (4) to provide support for production, maintenance, distribution, and phenotyping of new mouse models for the NIDDK Animal Models of Diabetic Complications Consortium. To date, the T1DR has acquired and archived over 250 strains and distributed over 10,000 mice to more than 1,800 external investigators.

This proposal for a second continuation phase would allow the T1DR to continue its mission to serve as a central repository and distribution locus for novel mouse models that are important to the national effort to understand, treat, and prevent type 1 diabetes and its complications. Moreover, the goals of the T1DR would expand to include support for production, archiving, distribution, and use of humanized mouse models to support diabetes translational research. These humanized models are critical for studies to: assay human allo- and autoimmunity; validate human pancreatic stem or progenitor cell function; and model end-organ damage and therapies for diabetes complications.

The panel enthusiastically supported the continuation of the T1DR. The program has been highly productive to date and provides an invaluable, widely used, and high-quality resource to the type 1 diabetes research community. The T1DR helps preserve past NIDDK investments in research to generate new mouse models and serves as a foundation for future studies as it continues to evolve with the addition of humanized models.

Integrated Islet Distribution Program
Primary discussant: Dr. Megan Sykes

Human pancreatic islets are a critical resource for advancing islet transplantation and other cell-based therapies for treatment of type 1 diabetes. Recognition of the many regulatory and metabolic disparities between human and rodent islets underscores the requirement for human islet availability in discovery research. NIDDK funds the Integrated Islet Distribution Program

(IIDP) to support a single coordinating center that works with 11 qualified islet isolation facilities to prepare and distribute high-quality cadaveric human islets to the diabetes research community. The IIDP currently has an active roster of 55 investigators requesting human islets for varied research programs.

This initiative proposes to extend the islet distribution program within the research community and also incorporates a parallel JDRF program having an identical coordinating center and islet isolation facilities. To enhance cost effectiveness and minimize the inefficiency of duplicate programs, the NIDDK and JDRF programs will be merged in Fall 2011.

The expert panel found the IIDP to be an important, productive resource essential to many key research projects on human islet biology. In addition, as humanized mouse models improve and become more widely available, the demand for human islets from the IIDP is expected to increase even further. Panel members suggested that the NIDDK enhance efforts to advertise the IIDP and the availability of human islets to the research community. The IIDP could also consider supplying non-islet cells or tissues along with islet preparations so that investigators can better determine HLA and other characteristics of the islet donors. The potential to provide fetal islets for research could also be considered. The panel thought that continued support for the IIDP was well justified by its proven value to the diabetes research community.

TOPIC 4: ARTIFICIAL PANCREAS

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

Even with the availability of increasingly effective treatment modalities, including insulin analogues, continuous glucose monitors, and continuous subcutaneous insulin infusion devices (pumps), it is very difficult for people with type 1 diabetes to achieve adequate glycemic control. Compounding this difficulty is the trade-off between improved glycemic control and an increased risk of hypoglycemia. An artificial pancreas able to mimic normal pancreatic beta cell function could potentially restore normal metabolic balance without causing hypoglycemia. Such a system could have enormous potential benefit for many people with type 1 diabetes.

NIDDK support to academic and small business concerns during the last 2 decades has led to significant advances in the field, including the development of new approved devices for diabetes management that are increasingly used in clinical practice. Nonetheless, the approved devices and current technologies have many limitations, highlighting the need for collaborative research for the development of next generation devices and/or optimization of the operability of current systems. This new initiative is intended to stimulate and support innovative research on technologies that may lead to the development or optimization of a portable, personalized, automated closed loop/artificial pancreas system for more efficient metabolic control of diabetes. Emphasis will be put on attracting bioengineers from academic centers and industry to develop new approaches to create devices with enhanced accuracy and less patient burden.

Panel members noted the scientific importance of supporting research on an artificial pancreas. The panel supported the pursuit of research using a collaborative team approach that encourages cooperation between engineers and clinical physiologists, diabetologists, and other relevant experts. In addition, this field would benefit from research on integration of the closed-loop system so that advances in one area, such as algorithm development, are complementary to and supported by advances on other issues, such as insulin formulation. Finally, the panel suggested that this initiative include research on the formulation of therapeutics to be used in the devices (*e.g.*, insulin, glucagon) in addition to the development of advanced technologies.

Expansion of Support for the Testing of Current and Novel Closed Loop Systems through Clinical, Behavioral, and Physiological Studies
Primary discussant: Dr. Todd Zion

New technologies for monitoring blood glucose are already in clinical use and are steadily improving in terms of ease of use and accuracy. Together with integrated insulin delivery systems, this technology may represent the next generation in type 1 diabetes management. Although completely automated systems are the ultimate goal, people with type 1 diabetes would also benefit from systems providing automated glucose control during sleep or not fully automated, yet integrated, systems that require adjustments in insulin for glucose self-management. Further, telemedicine platforms with remote monitoring capacity through portable miniaturized devices are quickly evolving. These emerging and next generation technologies require translational research to evaluate and improve their safety, accuracy, and efficacy. It is important to stimulate collaborative research on current and new technologies to optimize their operability, taking into consideration patient preferences and behavioral or physiological factors.

This new initiative will build on current technology and ongoing clinical research to address barriers that limit progress toward a closed loop system and specifically to: 1) test and improve the safety, reliability, and utility of these technologies in humans; 2) address behavioral factors that limit use of these systems; and 3) use the technologies as tools to advance understanding of glucose regulation in people with type 1 diabetes. Research goals include improved metabolic control with decreased glycemic excursions and prevention of acute and chronic complications, as well as improved quality of life in people with diabetes.

The panel supported this initiative and identified several key areas of research that could be pursued. An important question to address will be the effect of diabetes technologies on treatment and potential reversal of hypoglycemia unawareness, a condition in which patients are unable to detect when their blood glucose has fallen to dangerously low levels. Studies on the effect of intraperitoneal or intraportal compared to peripheral insulin delivery on vascular reactivity could reveal insights on the potential adverse effects of current insulin delivery practices. In people with new-onset type 1 diabetes, research is needed on whether combining intensive therapy, using continuous glucose monitors and insulin pumps, with drugs such as GLP-1 could improve the response to immunotherapy. Studies of continuous glucose monitoring in individuals with dysglycemia could be conducted to assess the potential effect of hyperglycemia on beta cell loss in people who are at risk of developing type 1 diabetes. The panel thought that projects requiring collaboration between bioengineers and clinical researchers will be critically important for this initiative.

Research Training—Joint Training in Bioengineering and Diabetes

This new initiative was proposed by the panel, due to the critical need to recruit talented young engineers to diabetes research. Newly graduated engineers are at a critical stage of choosing a field of research for future career development, but few have been exposed to the complex issues and opportunities related to the development of diabetes management technologies. To fill this knowledge gap, the panel proposed that a new initiative be developed to support postdoctoral training of engineers in clinical diabetes research. Training programs would be administered by partnerships between diabetologists and engineering schools to provide basic and clinical diabetes mentorship to engineering fellows. Collaboration at early career stages could also be encouraged through cross-disciplinary workshops that bring together established investigators, postdoctoral fellows, and students from the fields of diabetes and engineering for the purpose of discussing research on diabetes technology development. NIDDK Diabetes Centers could be a nexus for organizing regional conferences on this topic to stimulate interest among local bioengineering schools and researchers. NIDDK could also support discussions at national engineering meetings, such as those of the American Institute of Chemical Engineers or the Materials Research Society, to highlight opportunities for investigators in engineering and related fields to apply their expertise to diabetes research.

TOPIC 5: BETA CELL REPLACEMENT

Clinical Islet Transplantation Consortium
Primary discussant: Dr. Megan Sykes

The Clinical Islet Transplantation Consortium, co-led by NIDDK and NIAID, comprises eight clinical centers, four associated clinical sites, and a coordinating center. The purpose of the Consortium is to develop and implement a program of single- and/or multi-center islet transplantation clinical trials accompanied by mechanistic studies, in people with or without prior kidney transplantation, for the treatment of type 1 diabetes. The Consortium has developed and launched seven clinical islet transplantation protocols, including two phase III studies, one involving islet transplantation alone and another involving islet transplantation after kidney transplantation. Results from these phase III studies may support future licensure of an islet product by the U.S. Food and Drug Administration (FDA).

This initiative seeks support for the Consortium to complete two ongoing phase III studies, analyze the data, and submit a final report to the FDA. Thus, the results from these pivotal trials can be used for licensure application by investigators within and external to the Consortium. In addition, this proposal requests support for a new clinical protocol to provide long-term follow-up for people who have received a transplant in the islet alone and islet after kidney protocols. This follow-up study will evaluate long-term safety and efficacy while providing maintenance immunosuppression as needed to people who participated in consortium trials and have sustained islet allograft function.

The expert panel expressed its support for the future directions of the Clinical Islet Transplantation Consortium as outlined. The proposals to complete the phase III studies and to continue long-term follow-up of transplant patients were both well justified. The panel noted that recruitment for the islet after kidney transplantation trial is on track after an initial delay in

launching the study. In addition, the panel urged the Consortium to consider publishing negative trial results or information about trials that had to be stopped early. The panel also acknowledged the need to find creative options for providing immunosuppression drugs to transplant patients after the conclusion of clinical trials, but they also noted that issues related to providing medications to patient volunteers after clinical trials ended was not unique to this Consortium.

Collaborative Islet Transplant Registry
Primary discussant: Dr. Megan Sykes

The NIDDK's Collaborative Islet Transplant Registry (CITR) aims to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on transplants performed in North America. Supplemental funding provided by the JDRF, has provided for expanded data collection that also includes selected European and Australian sites. An internal audit conducted in 2010 indicated that the Registry database contained information on 1,254 islet preparations, 560 allograft recipients, and 247 autograft recipients. This compiled data provides the basis of annual reports containing detailed analyses of: recipient and donor characteristics; function of the donated islets; patients' lab results; and adverse events. This information is widely disseminated throughout the islet transplantation community, the scientific community, and the interested public.

Islet transplantation is a complex procedure with many component factors dictating outcomes. The compilation and analysis of data from transplant centers in North America, Europe, and Australia assists the identification of critical risk factors and key determinants of therapy success. It also provides guidance to transplant centers to develop new protocols and procedural refinements. This proposal seeks to extend the CITR and promote the acquisition of new clinical transplantation activity to the Registry.

The expert panel thought that the CITR has been productive in capturing data on most islet transplants being performed at this time and has regularly published information obtained from their database. The expansion of the Registry to include data on islet autotransplantation has added a worthwhile component to this already unique data set. The panel supported this initiative for continuing the Registry activities and urged NIH to seek additional cost effectiveness.

Nonhuman Primate Transplantation Tolerance Cooperative Study Group
Primary discussants: Dr. Ronald Gill, Dr. Roland Tisch

Nonhuman primate transplantation studies bridge the critical gap between discovery research and the translation of these discoveries to the design of scientifically sound and ethically acceptable clinical trials. The nonhuman primate is the preferred translational model due, in part, to the close approximation of the nonhuman primate immune system and physiology to those of humans. The Nonhuman Primate Transplantation Tolerance Cooperative Study Group (NHPCSG), led by NIAID, is a multi-institution consortium that develops and tests the efficacy of novel donor-specific tolerance induction strategies in nonhuman primate models of islet and

kidney transplantation, in addition to heart and lung transplantation models. NHPCSG studies have provided essential supporting data for the initiation of many transplantation clinical trials of new regimens. For example, the group demonstrated that the drug belatacept prolonged islet allograft survival with insulin independence using a steroid-free immunosuppression protocol. This result led to an islet transplantation trial of belatacept that is under way in the Clinical Islet Transplantation Consortium.

This initiative supports the competitive renewal of the islet and kidney transplantation models portion of the NHPCSG program. In part, this support will allow continuation of an Opportunities Pool, which provides a mechanism to fund high-risk, short-term pilot or feasibility projects and shared resources for rapid testing of novel agents or approaches and/or assays. In the past, this support has provided partial funding for maintenance of the NIAID macaque breeding colonies that are used in the NHPCSG research.

The panel expressed strong enthusiasm for this proposal to continue the islet and kidney transplantation research program in the NHPCSG. The group has a solid track record of supporting pre-clinical research studies that have served as essential precursors to human clinical trials. The NHPCSG also provides substantial scientific support to related NIAID-supported resources for the broader scientific community, including reagents for immune research in nonhuman primates and NHP MHC typing services. One drawback is the lack of a nonhuman primate model of autoimmune disease; nonetheless, the panel found the NHPCSG to be a strategic and important program that has been highly successful to date and warrants ongoing support.

TOPIC 6: DIABETIC COMPLICATIONS

Seeing the Development of Diabetes Complications – Retinal Vessels as Biomarkers
Primary discussant: Dr. Lois Smith

Early, noninvasive biomarkers are needed that would predict diabetes complications and responsiveness to therapy. Blood vessels are the primary site of injury for diabetes complications. Cellular damage from high blood glucose manifests as structural and functional changes in blood vessels and, ultimately, vascular disease. Fundus photography (imaging of the retina, including arteries, veins, and capillaries) is widely used in the clinical care of people with type 1 diabetes to detect diabetic retinopathy and is included in many clinical trial protocols. Research has shown a correlation between retinal vessel phenotypes and diabetic kidney disease, myocardial perfusion, acute lacunar stroke, and cerebral atrophy. Therefore, it is possible that retinal imaging can be used as a biomarker for diabetes complications.

This new initiative aims to bring together expertise in retinal vessel biology, diabetes complications, image analysis, chemistry, biostatistics, and biomarker development to develop and validate biomarkers for systemic diabetes complications using measures of retinal vessels in people with type 1 diabetes. Research projects could: 1) apply or modify techniques currently in clinical use to investigate the extent that the structure and function of retinal vessels correlate with systemic blood vessels and predict complications of type 1 diabetes; or 2) develop new

measures of the retinal vascular response to diabetes using probes with the potential for clinical use.

The panel thought that this initiative represented an excellent opportunity to develop noninvasive biomarkers of complications. Identifying a robust biomarker could cut significantly the costs and time required for clinical trials of new therapeutics for diabetes complications. This line of research also has the potential to reveal new insights into microvascular disease in the brain. In addition, research on automating the interpretation of retinal images could have benefits for both research and clinical practice. The initial stages of this initiative will make use of existing fundus photographs and associated clinical data that have been accrued in NIDDK-sponsored clinical studies. In the future, new and emerging technologies, such as optical coherence tomography and adaptive optics, may allow for studies to correlate structure and function at a very high level of resolution, possibly a single cell, in a small portion of the retina.

Impact Awards for Complications of Type 1 Diabetes
Primary discussants: Dr. Ann Marie Schmidt, Dr. Trevor Orchard

Even with close attention to maintenance of normal blood glucose levels, many people with type 1 diabetes experience significant and life-threatening diabetes-associated complications in major organ systems. This initiative aims to support bold and creative basic, translational, and/or clinical research studies that confront major challenges in type 1 diabetes complications. Research supported under the initiative could include concepts and approaches that are at the forefront of complications research and/or studies that will establish new directions and paradigms for the field. Successful projects will be expected to have a major impact on diabetes complications by providing significant improvements in therapies, diagnostic tools, or preventive strategies.

Panel members were enthusiastic about the core of this new initiative—the support of high-impact, innovative, multidisciplinary approaches to complications research. However, the panel suggested a modification of the initiative, which as proposed would provide long-term support for a small number of projects. The panel suggested that supporting more projects for shorter-term pilot and feasibility research would add more value to the NIH complications research portfolio and would be more effective at catalyzing the community to propose truly high-impact, transformative research projects. The NIH could consider supporting projects for preliminary data collection over a short period of time, followed by an accelerated review process for continued support of successful pilot projects. The panel also suggested adding medicinal chemistry and screening to the list of research topics that could be supported through this initiative.

Diabetic Retinopathy Clinical Research Network
Primary discussants: Dr. Lois Smith, Dr. Peter Gregersen

Even with advances in the diagnosis and management of ocular disease in people with diabetes, eye complications associated with the disease continue to be the leading cause of vision loss and new onset blindness in working-age individuals throughout the United States. The Diabetic Retinopathy Clinical Research Network (DRCR.net), led by the National Eye Institute (NEI), develops and maintains a collaborative network to facilitate multicenter clinical research on

diabetic retinopathy, diabetic macular edema (DME), and associated conditions. The DRCR.net currently consists of approximately 100 active clinical sites spanning 35 states. The network has initiated 16 multicenter studies enrolling 3,758 study participants, as of the end of 2010. Among other accomplishments, the DRCR.net completed a landmark phase III clinical trial demonstrating the comparative effectiveness of ranibizumab combined with laser treatment for reversing vision loss caused by DME compared to laser treatment alone.

The first objective of the proposed initiative is to support a clinical trial to determine if intravitreal bevacizumab is non-inferior with regard to efficacy and safety compared with ranibizumab for the treatment of DME. Bevacizumab is structurally similar to ranibizumab, though less costly. In addition, bevacizumab is already in widespread clinical use for DME despite the lack of FDA approval for this indication. A clinical trial that definitively answered whether bevacizumab can be used as a safe and efficacious alternative to ranibizumab could substantially impact nationwide practice patterns for treatment of DME by either validating the current use of bevacizumab or by demonstrating improved outcomes with ranibizumab. The second objective of this initiative is to support a DRCR.net genetics initiative to collect, store, analyze, and distribute genetic material with accompanying phenotypic information from multiple populations, including the type 1 and type 2 diabetic populations in the United States. This project will provide a resource for investigators to define genetic factors that confer risk for development and progression of diabetic retinopathy and response to therapy.

The panel acknowledged the success of DRCR.net to date as reflected in its strong scientific publication record. As important, the community-based nature of the network has allowed new knowledge to be translated rapidly into ophthalmologic practice. The panel supported this initiative for the clinical activities of the network and the collection of DNA for genetic analyses of diabetic retinopathy. Other biosamples that could be collected include plasma, as well as urine for measurement of microalbuminuria and kidney phenotype data. The collection of RNA was not endorsed. The panel emphasized the potential public health benefits of conducting the proposed clinical trial comparing bevacizumab to ranibizumab.

Epidemiology of Diabetes Interventions and Complications
Primary discussant: Dr. Ann Marie Schmidt

The NIDDK's landmark Diabetes Control and Complications Trial (DCCT, 1983-93) showed that, compared with conventional therapy, intensive insulin therapy resulted in lower average HbA1c level and reduced the development and progression of early stages of long-term complications by 35-76 percent. The relatively young age (mean age of 33 years) and brief duration of diabetes (12 years) of the cohort at the end of the DCCT precluded exploration of the effects of diabetes control on more advanced microvascular disease or on cardiovascular disease. The Epidemiology of Diabetes Interventions and Complications (EDIC) study (1994-present) was launched as an observational follow-up study using the same methods and following 96 percent of the surviving original cohort of the DCCT.   In EDIC, the cohort was no longer randomized to the original DCCT treatment groups; the patients returned to receiving diabetes care through their own physicians. EDIC has demonstrated the enduring effects of a period of intensive glucose control early in the course of type 1 diabetes on lowering microvascular complication risk; this has occurred despite A1c levels becoming similar in the two DCCT treatment groups approximately 5 years after the start of EDIC. In addition, EDIC has shown a

58 percent reduction in major atherosclerotic cardiovascular events in the original DCCT intensive control group compared with the conventional control group.

The full clinical, public health, and economic benefit of better glycemic control remains to be established by EDIC for type 1 diabetes. The cohort is approaching an average age of 50 years with 30 years average duration of diabetes. Nevertheless, the majority of patients remain free of major complications. Over the next decade, a substantial increase in the number of severe outcomes is expected, to a level that would permit reliable descriptions of incidence/prevalence, the long-term effects of metabolic memory on outcomes, and the elucidation of multiple risk factors for progression of diabetic complications. This initiative requests support for a portion of EDIC core activities and analytic support. In addition, ancillary studies are proposed to assess the association of haptoglobin with diabetic complications; residual insulin secretion; the re-reading of coronary artery computerized tomography (CT) scans to measure pericardial fat, liver fat, and other calcium measures of atherosclerosis; and hearing impairment in the EDIC cohort.

The expert panel emphasized the scientific importance of continued support to maintain the unique and valuable DCCT/EDIC cohort. The panel identified continued longitudinal assessment of cognitive function in study participants as a key research issue. Additionally, MRIs or other neuroimaging modalities (*e.g.*, PET, fMRI) could be used to evaluate the effects of long-term treatment and aging on the brain in a subset of the DCCT/EDIC cohort. Panel members suggested that the hearing study could be implemented as a pilot study to reduce costs. Other pilot projects could be solicited to ensure that the long-term EDIC study is utilizing the most state-of-the-art technologies for monitoring the progression of complications in the cohort. It is important to ensure that all DCCT/EDIC studies continue to undergo rigorous peer review to ensure that the cohort and collected samples are being utilized to their highest potential.

Diabetic Complications Consortium
Primary discussant: Dr. Lois Smith

The Animal Models of Diabetic Complications Consortium (AMDCC), led by NIDDK, brought together a diverse set of disciplines and technologies with the primary goal of producing and validating new animal models of diabetic complications for the purpose of studying disease pathogenesis, prevention, and treatment. The consortium partnered with the T1D Mouse Resource and the Mouse Metabolic Phenotyping Centers (MMPCs) to ensure that all interesting models were adequately phenotyped across multiple complications and distributed to the scientific community. One of the greatest strengths of the AMDCC has been its ability to create an environment where communication and collaboration are fostered between investigators who do not typically interact.

Because of the strong evidence that diabetic complications are linked via dysregulation of common pathways, there is a continuing need to facilitate the sharing of ideas, information, and reagents among research communities investigating similar pathologic mechanisms in different organs. Beginning in summer 2011, the AMDCC will transition into the Diabetic Complications Consortium (DCC). This new Consortium will provide a nucleation site for interaction and collaboration among complications researchers. The DCC will organize an annual scientific meeting on emerging topics in diabetic complications and solicit new collaborative activities to enhance basic and/or translational research in diabetic complications. This initiative requests

support for a DCC Pilot and Feasibility program to support investigator-initiated pre-clinical efficacy studies of new therapeutics for diabetes complications. In addition, support for the MMPC is requested for continued phenotyping of animal models of type 1 diabetes for the full duration of diabetes and across all relevant complications.

The panel was highly supportive of pursuing the research proposed in this initiative. They felt that, in addition to the research proposed, the NIH consider adding resources for screening small molecules and identifying lead compounds. Such resources would address a major gap in the pipeline for development of new therapeutics for diabetes complications. Efforts to develop a mouse model of proliferative diabetic retinopathy would also be valuable.

ADDITIONAL DISCUSSION

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

- Certain populations could be particularly valuable in identifying environmental triggers and protective factors. Research on the microbiome and immune system development in populations with low rates of type 1 diabetes could shed light on contributors to autoimmunity. Likewise, some populations have a higher rate of diabetes in individuals who immigrate to the United States compared to those who remain in their country of origin. Studying such populations could reveal environmental triggers of type 1 diabetes.
- Methods are being developed to conduct high-throughput, multiparameter phenotypic analyses from small volumes of blood. Such analyses combined with functional genomics and an accessible database could be performed prospectively on at-risk people who are recruited for the TrialNet Natural History Study. This would create an invaluable resource for identifying factors associated with the development of type 1 diabetes over time. Research is needed to optimize the technology for sample preparation or for the high-throughput analyses so that they can be adapted to a multisite study.
- The role of the innate immune system in the development of type 1 diabetes is an understudied but important area of research.
- Type 1 diabetes is a heterogeneous disease. For example, only half of individuals with an identical twin who has type 1 diabetes will develop the disease, despite having identical genetic risk. Also, type 1 diabetes strikes some people in early childhood while others are adults at disease onset. Research to identify different subsets of type 1 diabetes patients may help answer important questions such as why the age of onset is declining or why type 1 diabetes is now developing in people with genes that were not previously considered to be high risk. Stratifying patient groups could reveal different mechanisms of autoimmunity and identify patients who are more or less likely to benefit from specific therapeutic approaches.
- In the TrialNet Natural History Study, some individuals who have high-risk genetic profiles do not develop autoantibodies or present as autoantibody-positive at one screening then convert to autoantibody-negative at a follow-up screening. Research on these individuals could uncover mechanisms that protect from type 1 diabetes.

- More efforts could be made to link basic and clinical researchers to maximize the information gained from both animal and human studies. For example, medicinal chemistry research to identify new compounds for drug development could benefit from basic-clinical collaboration. Developing infrastructure to foster translational research in type 1 diabetes is important for increasing communication and collaboration between basic and clinical scientists at the local level.
- Xenotransplantation of pancreatic islets was identified as an important area for further research.
- Research is needed on the immunologic outcomes of islet transplantation, particularly with respect to distinguishing alloimmune from autoimmune causes of graft loss.
- Research to better understand islet biology is critical for finding ways to improve islet function immediately after transplantation. Studying non-immune related issues, such as the optimal transplant site and islet vascularization, is also important for making progress in islet/beta cell transplantation.
- Research using nonhuman primate models to study non-immune issues in type 1 diabetes would complement ongoing research on immune modulation in these models. For example, nonhuman primate models could be used to study the relative benefits and risks of peripheral versus portal insulin delivery in the context of the development of an artificial pancreas or to evaluate novel islet transplantation sites other than the liver.
- Developing methods to measure beta cell mass using biomarkers, noninvasive imaging, or other strategies is a critical area with implications for type 1 diabetes research across many topics, including the natural history of the disease and islet transplantation.
- Within a short period of time, technological advances are expected to drastically reduce the costs of whole genome sequencing. This may allow efficient mapping of genes for diabetes complications using DNA collections from studies such as FIND and GoKinD.
- The panel urged NIDDK to increase its efforts to disseminate information on funding opportunities to researchers, such as bioengineers, who do not typically apply for diabetes research funds.

Appendix 1: Panel Members

Suzanne Craft, Ph.D.
Professor of Psychiatry & Behavioral Sciences,
University of Washington School of Medicine
Associate Director, Geriatric Research,
Education & Clinical Center, VA Puget Sound
Health Care System

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

Peter Gregersen, M.D.
Head, Robert S. Boas Center for Genomics &
Human Genetics
The Feinstein Institute for Medical Research

Judy Hunt
NIDDK Council Member

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

R. John Looney, M.D.
Professor of Medicine
University of Rochester

David Nathan, M.D.
Professor of Medicine, Harvard Medical School
Director, Diabetes Center, Massachusetts
General Hospital

**Trevor Orchard, M.B.B.Ch., M.Med.Sci.,
FAHA, FACE**
Professor Epidemiology, Pediatrics and
Medicine
University of Pittsburgh

Alvin Powers, M.D.
Director, Vanderbilt Diabetes Center
Professor of Medicine
Joe C. Davis Professor of Biomedical Science
Professor of Molecular Physiology and
Biophysics
Vanderbilt University

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

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

Lois Smith, M.D., Ph.D.
Professor of Ophthalmology
Children's Hospital Boston

Megan Sykes, M.D.
Professor of Microbiology & Immunology
Columbia University

Roland Tisch, Ph.D.
Professor, Department of Microbiology
and Immunology
University of North Carolina at Chapel Hill

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

Todd Zion, Ph.D.
President, Co-founder & CEO
SmartCells, Inc.

Appendix 2: Participants

Kristin Abraham, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Beena Akolkar, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Michael Appel, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Guillermo Arreaza-Rubín, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Larissa Aviles-Santa, M.D., M.P.H., F.A.C.P., F.A.C.E.
National Heart Lung and Blood Institute

Olivier Blondel, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Kasia Bourcier, Ph.D.
National Institute of Allergy and Infectious Diseases

Nancy Bridges, M.D.
National Institute of Allergy and Infectious Diseases

Art Castle, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Catherine Cowie, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Lisa Cox
American Diabetes Association

Tamara Darsow, Ph.D.
American Diabetes Association

Darlene Deecher, Ph.D.
Juvenile Diabetes Research Foundation International

Linda Duffy, Ph.D.
National Center for Complementary and Alternative Medicine

Thomas Eggerman, M.D., Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Abby Ershow, Ph.D.
National Heart Lung and Blood Institute

Thomas Esch, Ph.D.
National Institute of Allergy and Infectious Diseases

Frederick Ferris, III, M.D.
National Eye Institute

Michael Flessner, M.D., Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Judith Fradkin, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Gilman Grave, M.D.
Eunice Kennedy Shriver National Institute of Child Health and Human Development

Reed Graves, Ph.D.
Center for Scientific Research

Julia Greenstein, Ph.D.
Juvenile Diabetes Research Foundation International

Ji Guo, Ph.D.
Food and Drug Administration

Katrina Gwinn, M.D.
National Institute of Neurological Disorders and Stroke

Carol Haft, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Mary Hanlon, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Jerry Heindel, Ph.D.
National Institute of Environmental Health Sciences

Eleanor Hoff, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Christine Hunter, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

James Hyde, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Giuseppina Imperatore, M.D., Ph.D.
Centers for Disease Control and Prevention

Richard Insel, M.D.
Juvenile Diabetes Research Foundation International

Zafar Iqbal, Ph.D.
Veterans Health Administration

Irada Isayeva, Ph.D.
Food and Drug Administration

Teresa Jones, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Jonathan Kaltman, M.D.
National Heart Lung and Blood Institute

Chris Ketchum, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Sooja Kim, Ph.D.
Center for Scientific Research

Aaron Kowalski, Ph.D.
Juvenile Diabetes Research Foundation International

Kristy Kraemer, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Maren Laughlin, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Ellen Leschek, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Daniel Lewin, Ph.D.
National Heart Lung and Blood Institute

Rongling Li, M.D., Ph.D.
National Human Genome Research Institute

Barbara Linder, M.D., Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Saul Malozowski, M.D., Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

James McNamara, M.D.
National Institute of Allergy and Infectious Diseases

Katherine Nicholson
National Institute of Diabetes and Digestive and Kidney Diseases

Dinesh Patwardhan, Ph.D.
Food and Drug Administration

Aaron Pawlyk, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Tracy Rankin, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Griffin Rodgers, M.D., M.A.C.P.
National Institute of Diabetes and Digestive and Kidney Diseases

Daniel Rosenblum, M.D.
National Center for Research Resources

Daniel Rotrosen, M.D.
National Institute of Allergy and Infectious Diseases

Sharon Saydah, Ph.D.
Centers for Disease Control and Prevention

Sheryl Sato, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Peter Savage, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Salvatore Sechi, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Grace Shen, Ph.D.
National Eye Institute

Philip Smith, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Lisa Spain, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Myrlene Staten, M.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Julie Wallace, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Joan Wasserman, Dr.P.H., R.N.
National Institute of Nursing Research

Amy Wotring
American Diabetes Association

Rita Zeidner
National Institute of Diabetes and Digestive and Kidney Diseases

Appendix 3: Acronyms

Organizations
ADA	American Diabetes Association
CDC	Centers for Disease Control and Prevention
HHS	U.S. Department of Health and Human Services
DMICC	Diabetes Mellitus Interagency Coordinating Committee
FDA	U.S. Food and Drug Administration
NCI	National Cancer Institute
NEI	National Eye Institute
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
AMDCC	Animal Models of Diabetic Complications Consortium
CITR	Collaborative Islet Transplant Program
DCC	Diabetic Complications Consortium
DCCT	Diabetes Control and Complications Trial
DRCR.net	Diabetic Retinopathy Clinical Research Network
EDIC	Epidemiology of Diabetes Interventions and Complications
FIND	Family Investigation of Nephropathy and Diabetes
GoKinD	Genetics of Kidneys in Diabetes
IIDP	Integrated Islet Distribution Program
ITN	Immune Tolerance Network
MMPCs	Mouse Metabolic Phenotyping Centers
NHPCSG	Non-Human Primate Transplantation Tolerance Cooperative Study Group
SBIR	Small Business Innovation Research
STTR	Small Business Technology Transfer
T1DR	Type 1 Diabetes Mouse Resource
T1D-RAID	Type 1 Diabetes-Rapid Access to Intervention Development
TEDDY	The Environmental Determinants of Diabetes in the Young

Other Acronyms
CT	computerized tomography
DME	diabetic macular edema
fMRI	functional magnetic resonance imaging
FY	fiscal year
HLA	human leukocyte antigen
MHC	major histocompatibility complex
NOD	non-obese diabetic
PET	positron emission tomography
PL	Public Law