212th NIDDK Advisory Council Meeting
Division of Diabetes and Endocrinology and Metabolic Diseases (DDEMD)
Sub-council Meeting – OpenSession
January 30, 2020

Attendees:

DDEMD Sub-Council Members: Dr. David D'Alessio, Dr. Barbara Kahn, Dr. Jeffrey Pessin, Dr. Elizabeth Seaquist, Dr. Michael Snyder, Ms. Lorraine Stiehl

DDEMD Staff Members: Dr. Kristin Abraham, Dr. Olivier Blondel, Dr. Henry Burch, Dr. Arthur Castle, Dr. William Cefalu, Dr. Catherine Cowie, Dr. Thomas Eggerman, Dr. Carol Haft, Dr. James Hyde, Ms. Connie Jenkins, Dr. Teresa Jones, Dr. Maren Laughlin, Dr. Christine Lee, Dr. Yan Li, Dr. Barbara Linder, Dr. Saul Malozowski, Mrs. Heidi Otradovec, Dr. Sheryl Sato, Dr. Salvatore Sechi, Dr. Lisa Spain, Dr. Philip Smith, Dr. Karen Teff, Dr. Pamela Thornton, Dr. Xujing Wang, Dr. Ashley Xia

NIDDK/NIH Staff: Dr. Tolulope Abidogun, Dr. Michelle Barnard, Dr. Dianne Camp, Dr. Rebecca Cerio, Mr. Randy Copeland, Mr. Mitch Curling, Ms. Dee Doherty, Dr. Lisa Gansheroff, Dr. Greg Germino, Dr. Mary Hanlon-Tilghman, Dr. Ann Jerkins, Dr. Peter Kozell, Mr. Robert Pike, Dr. Matt Portney, Dr. Heather Reiff, Dr. Charlene Repique, Mrs. Mary K. Rosenburg, Dr. Elena Sandovich, Dr. Katrina Serrano, Dr. Jaime Smith, Ms. Theresa Smith, Mr. Thomas Smith, Dr. Susan Tenney, Dr. Julie Wallace, Dr. Elizabeth Wright

Non-NIH Attendees: Dr. Lisa Cash, Deputy Program Manager at Betah Associates; Dr. Joseph Laasko, Director, Science Policy at Endocrine Society

Diabetes Research Centers' Cores (Dr. Hyde)

In a late-morning start to the DEM sub-council open session, Dr. Hyde described the Diabetes Center research cores, which support extramural research institutions that have an existing base of high-quality, diabetes-related research. Diabetes Research Centers (DRC) consist of administrative cores, P&F programs and enrichment programs which support activities such as courses and seminars. More recently, Centers have had the opportunity to partner with outside institutions through the competitive acquisition of expanded P&F programs, additional research cores at partner institutions, cores that serve a national client base, and support for underserved populations. Currently there are 72 cores in the 16 centers combined that provide a large variety of technologies and specialized measures. In addition to DRCs ($25.5M), DEM also supports Centers for Diabetes Translation Research ($4.5M) and Cystic Fibrosis Research and Translation Centers ($8.5M).

Welcome and Consideration of Minutes from October 2019 Council (Dr. Cefalu)

When the DEM sub-council reconvened after a lunch break, Dr. Cefalu welcomed everyone and moved for approval of the Sub-council minutes from the October 2019 meeting; the minutes were approved. A new staff member, Norann Zaghloul was introduced. She will participate in the Accelerating Medicine's Partnerships in Type 2 Diabetes (AMP T2D) program as well as manage a portfolio focused on genetics and genomics in Type 2 Diabetes that encompasses genetic mechanisms underlying type 1 and type 2 diabetes and how genetic and epigenetic variation influences the metabolism of therapeutics.

Concept Clearances (Dr. Jones)

Dr. Jones presented two initiative concepts in collaboration with NHLBI focused on reducing cardiovascular disease (CVD) in Type 1 Diabetes (T1D). NHLBI is the lead institute for both concepts. Although CVD risk overall has fallen in recent years, people with T1D, when compared to individuals without diabetes, still have considerably elevated incidence of CV events referred to as "residual risk". The first concept, "Understanding and Reducing Cardiovascular Disease in Type 1 Diabetes Mellitus", would seek to support elements such as investigator-initiated human subject studies across the life-span to provide a better understanding of the pathophysiology of this important complication. It would take advantage of well-characterized longitudinally studied T1D cohorts and propose new drugs, imaging, monitoring and bioinformatics tools. Studies could be designed to refine CVD risk estimation, be mechanistic studies to better understand atherosclerosis, cardiomyopathy and cardiac autonomic neuropathy, or they could test therapies or strategies to improve adherence to current guidelines. The second concept is "Cardiovascular Disease in Type 1 Diabetes - Biorepository and Human Tissue Research". There are no adequate animal models for CVD in T1D, and so there is a great need for access to high-quality human tissues, and therefore a carefully curated biorepository of human tissue specimens from T1D patients would be highly valuable to look at the molecular and cellular pathology of vessels, plaque and cardiac tissue. It is expected that tissue recruitment sites would have access to a large T1D population and work with current organ procurement organizations to collect surgical or post-mortem tissues such as whole hearts, coronary or carotid arteries, brain or extremity arteries, serum and urine and other tissues that might be relevant for study of CVD in diabetes (i.e., kidney). These could be used for histopathological analysis using a range of modern approaches to provide useful information regarding the pathophysiology of CVD in T1D.

Discussion revealed high enthusiasm for these concepts. There is potential to understand more about atherosclerotic plaque in T1D—is it the abundance of plaque or is there something unique about the nature of plaque in T1D that increases risk for CV events? The question was asked about whether these concepts could proceed if special T1D funds are limited in the future, and Dr. Jones noted that NHLBI will be the lead institute and will make decisions regarding any initiatives that arise from these concepts.

DEM FY2019 Funding Summary (Dr. Haft)

Dr. Haft presented a broad overview of funding mechanisms, policies and approaches used for award decisions for applications assigned to DEM. For fiscal year 2019, there were 1021 R01 applications from 975 investigators, from 204 organizations submitted in areas of interest to DEM/NIDDK. Roughly 11% were clinical studies with the bulk of the rest being basic research. Pay lines were 13% for established PI R01 applications, 18% for early stage investigators (ESI) applications and 16% for first renewal applications of ESI grants. The success rate varied from a low of 7% for clinical health disparity research, to 17% for basic and 22% for clinical research. Although most applications submitted were from established PIs, 30% were from new PIs or ESIs, and over 20% of applications submitted had more than one PI. Each year funds are also provided by Dr. Rogers to the three scientific divisions in NIDDK to support applications beyond the pay line or applications which have a priority score assigned but are not percentiled. Specific criteria such as ESI, new PI, minority investigator and clinical studies were used to select 24 applications for FY2019 special funding (SF). In addition, SF supported 7 applications within 5% of the pay line from PIs with limited other support. Six AREA (R15) awards were made in 2019. These are for small original research projects at undergraduate teaching institutions. R21 applications are accepted only to special funding opportunities (FOAs), including for pilot clinical studies or for secondary analysis of extant clinical trial data. Out of 77 submitted, only 16% scored below 30 (where 10 is a perfect score and the lower half are not scored). 3 R21s were awarded for a success rate of 4%. This has prompted NIDDK to consider using a small R01 mechanism rather than an

R21 mechanism for pilot clinical trials. DEM awarded 3 of 7 submitted P01 projects in FY2019, and as this program will be sunsetting, this was the last opportunity for new P01s, although all P01s will be allowed up to a 10-year lifetime via successful competitive renewal. 1 of 6 RC2 "High Impact Interdisciplinary Science" applications was awarded, reflecting the high standards for large grants in DEM.

Staff were asked what fraction of the budget goes to R01 funding. These represent 60-70% of research grants, which receive over 50% of the NIDDK budget. Dr. Pessin asked whether the R56 mechanism is working as hoped to allow investigators to be successful with subsequent applications. NIDDK staff felt that this is difficult to determine, as only grants judged to be of very high likelihood of success are elected for R56 awards. However, staff feels that the mechanism has been very useful to best ensure that outstanding science is competitive for R01 funding. Noting that the budget on the R21 mechanism is too limited to adequately support clinical trial feasibility studies, it was suggested that PI salaries be disallowed when using this mechanism. However, DK staff reported that NIH grant mechanisms are required to cover staff effort for funded projects.

Applying Technology to the Management of Type 1 Diabetes (Dr. Eggerman)

Dr. Eggerman presented the remarkable recent progress in the use of artificial pancreas technology to treat diabetes. These consist of continuous glucose monitoring devises combined with insulin pumps and algorithms that adjust basal insulin delivery in response to glucose readings. Progress has proceeded over many stages and many years, and NIDDK funded projects have supported several currently successful commercial products as well as the clinical trials that have led to FDA approval. While diabetes technology has vastly improved the ability to control glycemia, patient burden combined with significant risks of hypoglycemia and post-prandial hyperglycemia persist. There are now 50 active projects in the DEM portfolio focused on improving technology or testing it in different patient populations. About half of these are focused on improving the algorithms that enable the control of hormone delivered in response to glucose sensing, and about one third of them are awards to small businesses. Other current research efforts are focused on making technology more reliable and less invasive, on employing multiple sensors and additional hormones to better mimic normal control of glycemia, and on providing better patient support for using these devices. An example is a collaboration between NIDDK-funded small business and several universities to develop and test an intra-peritoneal closed loop platform to more closely mimic physiologic glycemic control. Ultimately it is envisioned that similar systems will be employed outside Type 1 Diabetes for cystic fibrosis-related and gestational diabetes, and to deliver glucagon for congenital and post-bariatric surgery hypoglycemia.

Dr. Kahn remarked that this incredibly important technology does need improvement as patients come to rely more on technology. A fully closed loop system that can provide automatic bolus for meals is desired and the pumps need to be less intrusive and require less patient attention, because many people who try them give up. Dr. Pessin remarked that more resources for development may come from other non-diabetes funding sources as these sensor devices are applied to other disease populations besides T1D. Another suggestion was for calcium ion sensing, which may be useful for bone and thyroid diseases. Dr. Snyder asked about sensors for microbiome and nutrition research, and the need to monitor multiple physiologic signals and biomarkers.

Recent Workshops (Dr. Laughlin)

Strategies for Clinical Imaging in Diabetes
Imaging the Pancreas in Diabetes and Benign and Malignant Exocrine Pancreatic Disease

Dr. Laughlin presented outcomes from two recent workshops held on January 13-15, 2020, organized by the DEM and DDN divisions of NIDDK and focused on the use of imaging in pancreatic diseases including pancreatitis, pancreatic cancer and diabetes. Evidence has been mounting that diabetes, like other pancreatic diseases, is accompanied by changes in pancreas size and fat content. Diabetes and pancreatitis often occur together, and both are risk factors for malignant pancreatic diseases. The first workshop, "Imaging the Pancreas in Diabetes and Benign and Malignant Exocrine Pancreatic Disease" showcased the use of imaging to explore the pathophysiology and outcomes of pancreatic diseases of all types. It focused on exocrine diseases and pancreatic physiology on the first day and islet biology and diabetes on the second day. The second workshop, "Strategies for Clinical Imaging in Diabetes", focused on progress toward the use of in vivo imaging to measure beta cell mass and disease processes in diabetic patients. Outcomes included the idea that detailed imaging exams of the entire pancreas, currently used to stage pancreatic diseases, may also be highly informative to monitor diabetes progression in order to gauge whole pancreas involvement. Imaging can provide measures sensitive to a variety of changes, such as size, fat content, blood flow, edema, inflammation and fibrosis. Several reagents useful for PET detection of beta cell mass are in development, and at least one is in early stage observational clinical studies of type 1 diabetes in Europe. Early work indicates high variability of beta cell mass in healthy people, but also in patients with T1D and T2D. These need to be further developed and validated in clinical populations so that they can be used to study heterogeneity of beta cell mass during onset and progression of diabetes.

Council members felt both that there should be increased emphasis on bringing exocrine and endocrine pancreas researchers together to uncover shared pathophysiology in pancreas diseases, and that imaging is an exciting direction for diabetes research. They felt that other tools should be combined with imaging, such as omics analyses, to increase interpretability.

New Initiative Topics (Staff/Council)

Recent progress from TrialNet in delaying T1D was discussed, and DEM was asked for a future council forum, featuring TrialNet investigators, on prevention or reversal of T1D and strategies to protect against islet cell loss in the setting of ongoing inflammation.

Council members would also like to see presentations on efforts to identify biomarkers for diabetes and its complications such as kidney disease.

The recent NIDDK workshops on pancreas diseases and liver diseases were discussed, and council members remarked on the importance of providing opportunities for people from the organ disease communities supported by DDN and the diabetes and metabolic diseases researchers supported by DEM to meet and work on projects together. They felt that NIDDK is missing opportunities for productive synergies between metabolic and organ-specific disease researchers that would greatly benefit people who suffer from these diseases.

Dr. Pessin reminded council of the recent NIH-wide initiatives aimed at providing more support for younger investigators and suggested that an R35-like mechanism to support highly productive established investigators might reduce the number of project-based R01s from these competitive and successful people in the R01 pool, freeing up resources for younger people. Longer awards, such as 7 years, that support individual senior PIs and replace multiple R01-funded projects might both free up these highly productive senior investigators to do more innovative projects, and also encourage them to retire at the end of the award period. Staff discussed the use of this award at other institutes, and noted that there have been unintended consequences; many awardees are mid- rather than late-career scientists who are reluctant to depend on a single source of funding and

attempt to fit new projects into the interests of other institutes in order to raise more funding through R01s anyway. DEM staff propose that NIDDK continue to monitor the outcomes of experiments with this funding mechanism at other institutes. It was noted that NIDDK has been actively investing in R01 support for early stage investigators such that the number of ESI applicants had become stable, and even showed a recent decline.

Concluding Remarks

Dr. Cefalu thanked the sub-council members for their participation and looked forward to productive council meetings in the future.