215th NDDK Advisory Council Meeting
Division of Diabetes and Endocrinology and Metabolic Diseases (DDEMD)
Sub-committee Meeting – Open Session
January 28, 2021

Attendees

DDEMD Sub-Committee Members: Ms. Tracey Brown, Dr. David D'Alessio, Dr. Debra Hair-Joshu, Dr. Barbara Kahn, Dr. Jeffrey Pessin, Dr. Philip Scherer, Dr. Michael Snyder, Ms. Lorraine Stiehl

DDEMD Staff Members: Dr. Kristin Abraham, Dr. Beena Akolkar, Dr. Guillermo Arreaza-Rubin, Dr. Olivier Blondel, Dr. Miranda Broadney, Dr. Henry Burch, Dr. Arthur Castle, Dr. William Cefalu, Dr. Brad Cooke, Dr. Thomas Eggerman, Dr. Somayeh Fahim Nia, Mr. Neal Green, Dr. Carol Haft, Dr. Teresa Jones, Dr. Maren Laughlin, Dr. Jean Lawrence, Dr. Christine Lee, Dr. Ellen Leschek, Dr. Yan Li, Dr. Barbara Linder, Dr. Saul Malozowski, Mr. Louis Martey, Mr. Michael Mensah, Ms. Onyinyeoma Okolo, Mrs. Heidi Otradovec, Dr. Sheryl Sato, Dr. Salvatore Sechi, Dr. Corinne Silva, Dr. Lisa Spain, Dr. Philip Smith, Dr. Karen Teff, Dr. Pamela Thornton, Dr. Xujing Wang, Dr. Ashley Xia, Dr. Norann Zaghloul

NIDDK/NIH Staff: Mr. Terry Barnes, Dr. Najma Begum, Dr. John Connaughton, Mr. Tim Kerns, Dr. Jennie Larkin, Dr. Thomas Tatham, Dr. Kenneth Wilkins

Non-NIH Attendees: Dr. Kathleen Sakamoto, Stanford

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

Dr. Cefalu welcomed Council members to the session and provided an overview of the planned presentations. New DEM staff (Dr. Jean Lawrence) and new Scientific Experts (Dr. Debra Haire-Joshu and Dr. Philipp Scherer) were then welcomed by Dr. Cefalu. Next, Dr. Jeffrey Pessin was thanked for his service to Council and willingness to stay on for this meeting. Dr. Pessin made remarks about his positive experience serving on Council and noted that he is always available for consultation. Dr. Cefalu then recognized the upcoming retirement of Dr. Philip Smith and thanked him for his service and contributions to NIH. Minutes from the last Sub-committee meeting (September 9, 2020) were approved. Dr. Cefalu noted that the Special Diabetes Program (SDP) no year money was recently appropriated ($150M per year for FY21, FY22 and FY23) and that DEM was very excited about getting this extension. Presentations for new and renewal concepts will take place during the May 2021 Council meeting.

DEM Centers and COVID-19 Research Opportunities (DRCs- Dr. Pessin and Dr. Silva & CDTRs- Dr. Haire-Joshu and Dr. Thornton)

Dr. Silva provided background information on DEM funded diabetes centers. There are 2 types of centers- Diabetes Research Centers (DRCs) and Centers for Diabetes Translation Research (CDTRs). Both are supported via P30s. Currently, NIDDK funds 16 DRCs and 8 CDTRs. Budgets (direct costs only) for the DRCs are limited to $1M per year and an additional $250K for national/regional cores. There are three competitions every 5 years. Budgets (direct costs

only) for the CDTRs are limited to $250K per year and an additional $100K for national/regional cores plus $75K for Underserved/Health Disparities cores. The renewal CDTR FOA budget limit is $400K DCs/year with additional opportunities to exceed the budget cap. All the CDTRs are re-competing in 2021.

The structures of the DRCs and CDTRs were then discussed. Dr. Silva noted the DRCs have an Administrative core which includes the Enrichment Program; Biomedical Research cores; Pilot and Feasibility program; and additional optional components. Dr. Thornton indicated that the CDTRs have an Administrative core; Translational Research cores; a Pilot and Feasibility program; an Enrichment program; and Network functions such as monthly meetings and Special Interest Groups which constitute unmandated structure or activities.

Dr. Thornton explained that DEM requested the Centers consider two charges of which they accepted: 1) Scientifically- to identify 3-5 high-priority research directions regarding COVID-19 and diabetes, including potential sustainable approaches for post-acute COVID-19 syndrome and 2) Center Structure- to identify ways to leverage infrastructure, facilities, programs to address COVID-19 and diabetes as well as other co-morbidities that increase severity and mortality. Dr. Kahn asked if there was a difference between DERCs (Diabetes Endocrinology Research Centers) and DRCs (Diabetes Research Centers)? Dr. Silva indicated that the term DERCs is no longer used and these are now called Diabetes Research Centers.

Dr. Haire-Joshu and Dr. Pessin then discussed the 3 phase recommendations for COVID-19 Response- 1) Immediate actions- Phase 1; 2) Intermediate actions- Phase 2; and 3) Longer term actions- Phase 3. There are 8 action items in Phases 1 and 2 that can be worked on to address COVID-19 and disparities:

1. DRC/CDTR sponsored national COVID-19 enrichment program
   Dr. Haire-Joshu mentioned this could include coordinating network-wide activities to enhance and build knowledge, research capacity and competency related to COVID-19 and diabetes.
2. Support Early Stage Investigators (ESIs) and Underrepresented Minorities (URMs) conducting diabesity research
   Dr. Haire-Joshu noted that there is a need for underrepresented mentees to feel/know that they have support. Zoom has opened new opportunities to connect people in new ways that may continue supporting this goal.
3. Recommend core equity measures for use in diabesity research
   Dr. Haire-Joshu noted that the goal is not to “advance” health equity but to “achieve” health equity which calls for different considerations, partnerships, and activities.
4. Establish a national COVID-19 Diabesity Advisory Group
   Dr. Haire-Joshu indicated that partnerships expanding beyond the funded centers have grown over the years and the research centers are now leveraging that work to do real world translations for COVID-19. Community input has also become very important to move things forward and has become an ongoing action.
5. Maintain a COVID-19/Diabesity Information Landing page
   Dr. Pessin indicated that to address the long term chronic COVID-19 complications that will remain endemic, we need to quickly establish a COVID-19/Diabesity landing page for easy and comprehensive access to COVID-19 related information and resources.

6. Disseminate access to the NCATS-supported National COVID Cohort Collaborative (N3C) for EMR data sharing
7. Create access to other databases outside of the N3C initiative
8. Support national pilot and feasibility (P&F) and mini-grant programs
    a. For the national P&F- Dr. Pessin noted this can be done for various studies such as basic, clinical, and population-based research.
    b. Dr. Pessin suggested that applications for the program would be approximately 2 pages in length and awards would allow money to be used for accessing services of a specific core. The research centers support making this national.

Dr. Haire-Joshu then discussed 4 research priorities for the CDTRs:

1. Focusing on NIH-designated U.S. health disparity (HD) populations as these populations have been devastated by COVID-19. In addition, the COVID-19 pandemic has highlighted the issues and problems that researchers already knew were present and made them worse.
2. The science of structural racism and social factors as root causes of diabetes and COVID-19 disparities
3. Multi-sector research addressing community, institutional, provider, and patient factors
4. Research partnerships with under-resourced communities

These priorities lead to 3 questions that could be further studied:

1. How do social determinants of health influence COVID-19 inequities and vaccination outcomes among HD populations with diabetes or prediabetes?
2. Which models of telehealth delivery driven by the COVID-19 pandemic best mitigate inequities in care among HD populations with diabetes or prediabetes?
3. What is the impact of interventions designed to shorten the translation gap from discovery to uptake of COVID-19 vaccinations among HD populations with diabetes or prediabetes?

Dr. Pessin then addressed research priorities for the DRCs:

1. Determining impact of glucose, lipids, and metabolic flux on SARS-CoV-2 infection, replication, transmission, and host responses.
2. Examine the potential role of diabetic drug therapy (i.e., metformin, GLP1, SGLT2i, insulin, statins etc.) to influence the severity of COVID-19 symptoms.
3. Understand the different response to COVID-19 therapies (i.e., high dose steroid, antibody cocktails) on patients with diabetes, obesity, age, diabetic complications.
4. Deep phenotyping and -omic analyses of long term (post-acute) COVID-19 patients.

In addition, research on COVID-19 vaccine effectiveness will focus on 2 priorities:

1. Providing research opportunities on vaccine effectiveness in patients with T1D, T2D and obesity organized through the DRCs.
2. Creating new cohort longitudinal studies at the start of vaccination for observational and interventional evaluations.

Dr. Silva thanked Dr. Haire-Joshu and Dr. Pessin for their presentations. There was then time for questions/discussion for Council members. Dr. Kahn thanked the presenters for their comprehensive presentation and noted that concepts like health equity are really difficult to appraise. Dr. Kahn asked how the research centers plan to approach this issue and if there is interest in partnering with other organizations to address these issues? Dr. Haire-Joshu noted that

the research centers are well-positioned to work with other organizations to come to a common agreement on core measurements to address healthy equity issues. While this process should not take too long to do, cooperation and agreement will be needed between the various organizations. Dr. Haire-Joshu noted that we should lead the effort to determine core competencies that are needed. As a follow-up question, Dr. Kahn asked if this is a research effort or more of a communication/coordination effort? Also, would funding be needed? Dr. Haire-Joshu said that some level of support will be needed to do this right and it would be a missed opportunity if we did not do this particularly since NIDDK has invested in building up these partnerships outside of academia among the CDTRs over the past 10 years. Dr. Kahn noted that it was not clear which are research initiatives, and which require funding. In addition, it was not clear which ideas were currently just at a brainstorming level. Dr. Haire-Joshu noted that some ideas can be done within the current structure (e.g., establishing metrics), but funding will be needed for others (large research efforts mentioned, e.g., peer support studies). Dr. Kahn indicated that she thought the mini-grants were a win-win and national P&Fs were a good idea. Dr. Haire-Joshu and Dr. Pessin noted that all centers are supportive of the ideas.

Dr. Cefalu thanked Dr. Haire-Joshu and Dr. Pessin for putting the presentations together and Dr. Silva and Dr. Thornton for coordinating the programs. During May council, Dr. Cefalu suggested that an update could be provided. Dr. Haft asked any council members with comments to reach out to DEM staff since we are very interested in their thoughts.

Human Pancreas Analysis Program- HPAP (Dr. Blondel)

Dr. Blondel gave a brief overview of what was going to be presented. The rationale for the creation of HPAP was then discussed. In 2016, NIDDK started HPAP as a unique community resource since we still knew very little about the human pancreatic tissue environment and how various cell types contribute to the pathogenesis of both T1D and T2D. The initial focus was on T1D and included a 4-year pilot phase. The primary mission of HPAP is to collect, analyze, and distribute, in real time, high value datasets to the diabetes research community (PANC-DB). Dr. Blondel then discussed how HPAP-T1D works. Tissues are sent to the University of Pennsylvania laboratory for processing using various techniques. After data undergoes quality control, it is shared in real time with the worldwide research community. HPAP does not work in a vacuum and is constantly coordinating with other partner programs such as HiRN and TrialNet. The mission of the Immune Cell Analysis Core is to develop an immune atlas of lymphocyte populations, their phenotype, clonal interconnections, antigenic reactivities and epigenetic and transcriptional signatures. Besides collecting data, the team is working on visualization of the data to help extract information from the images. They are working on the development of various visualization tools.

HPAP work is currently in its fourth year. To date the team has processed and analyzed tissues from 77 donors, including: 16 T1D, 15 Ab+ and 11 T2D. Numerous manuscripts have been published or are under revision covering various topics from analysis of the tissues. Dr. Blondel noted that HPAP and nPOD are complementary efforts. HPAP has an emphasis on data generation, data analysis and data sharing, while nPOD has an emphasis on organ procurement, tissue sharing and community building. Procurement of rare donor tissues is evenly split between HPAP and nPOD.

A second HPAP RFA was issued in 2018 to expand the scope of the effort to include T2D. Two teams were funded that overlapped significantly with the University of Pennsylvania and Vanderbilt, which is advantageous for data comparison. In addition, a supplement to HPAP-T2D (University of Pennsylvania), "Ethnic Differences in Pancreas Biology and Risk of Type 2 Diabetes," has been awarded to recover pancreata from deceased African American and Hispanic organ donors. Future opportunities that may take advantage of the infrastructure already in place for HPAP and collection of cadaveric tissues may include: 1) cardiovascular risk of T1D; 2) cystic fibrosis and diabetes; and 3) impact of COVID19 on pancreas.

Dr. Cefalu thanked Dr. Blondel for the presentation. There was then time for questions and discussion for Council members. Dr. Pessin did not have any questions but commented that HPAP was a terrific program and suggested looking into expanding to liver and adipose tissue. Dr. Snyder echoed Dr. Pessin's comments and suggested that the heart be added to the list of possible tissues to expand to. Dr. Cefalu noted that the funding opportunity mentioned by Dr. Blondel for T1D was in collaboration with NHLBI and that goals for the program proposed that study of cardiac tissues (e.g., coronary arteries, cerebral arteries, large peripheral arteries, etc.) be considered. Dr. Snyder suggested that different types of preservation solutions may be needed, depending on what is planned for the tissues, so the programs should think about this. Dr. Pessin noted that special single cell analysis is being done in the brain now but could also be done in pancreatic tissues. Dr. Snyder echoed the comment of Dr. Pessin. Ms. Stiehl suggested from a patient perspective that HPAP is very exciting. Looking into other organs is a great idea. In addition, Ms. Stiehl was glad to see that the SDP funding was extended. Dr. Snyder asked if analysis of specific subtypes of T cells longitudinally and during disease progression was being considered. Dr. Blondel responded that since the tissue source is from cadaver donors, longitudinal studies can only be undertaken using a pseudo timeline of disease progression. He added that interesting data are emerging on the relative distribution of immune cell subtypes within different tissue compartments in a same donor, which may shed new light on disease initiation processes.

Concluding Remarks (Dr. Cefalu)

Dr. Cefalu again thanked Dr. Philip Smith for his service and contributions to NIH. Dr. Smith then made some comments and noted that he was happy to contribute to NIH over the last 30 years. He plans to be active in the future and felt comfortable that DEM was in good hands.

Dr. Cefalu thanked the sub-committee members and NIH staff for their presentations and comments. He noted that DEM looks forward to hearing more about the progress made on the suggestions and programs discussed today by the DRCs and CDTRs. He noted that there is no better infrastructure to put them together like the two diabetes research centers programs. Dr. Cefalu stated that he was impressed with the collaborations.