222nd NIDDK Advisory Council Meeting
Division of Diabetes and Endocrinology and Metabolic Diseases (DDEMD)
Sub-committee Meeting – Open Session
May 17, 2023

Attendees

DDEMD Sub-committee Members: Dr. Carmella Evans-Molina, Mrs. Karen Jordan, Dr. Debra Haire-Joshu, Ms. Davida Kruger, Dr. Philipp Scherer, Dr. Elizabeth Seaquist, Dr. Michael Snyder

DDEMD Staff Members: Dr. Kristin Abraham, Dr. Beena Akolkar, Dr. Guillermo Arreaza-Rubin, Dr. Shavon Artis Dickerson, Dr. Miranda Broadney, Dr. Henry Burch, Dr. Art Castle, Dr. William Cefalu, Dr. Maureen Monaghan Center, Dr. Brad Cooke, Dr. Rafael Gorospe, Mr. Neal Green, Dr. Carol Haft, Dr. Albert Hwa, Dr. Teresa Jones, Dr. Maggie Liang, Dr. Maren Laughlin, Dr. Jean Lawrence, Dr. Yan Li, Dr. Saul Malozowski, Mr. Louis Martey, Dr. Saira Mehmood, Ms. Mansi Mehta, Mr. Michael Mensah, Mrs. Heidi Otradovec, Dr. Nishadi Rajapakse, Dr. Salvatore Sechi, Dr. Corinne Silva, Dr. Lisa Spain, Dr. Pamela Thornton, Dr. Xujing Wang, Dr. Theresa Woo, Dr. Ashley Xia, Dr. Norann Zaghloul

NIDDK/NIH Staff: Mr. Terry Barnes, Dr. Najma Begum, Dr. Rebecca Cerio, Dr. John Connaughton, Ms. Connie Jenkins, Dr. Ann Jerkins, Dr. Cheryl Nordstrom, Dr. Charlene Repique, Dr. Griffin, Rodgers, Dr. Elena Sandovich, Dr. Thomas Tatham

Non-federal Attendees: Dr. Bhadelia Afsan, Purdue University

Welcome and Approval of January 2023 Sub-committee Minutes (Dr. Cefalu)

Dr. Cefalu welcomed Council members to the meeting. Minutes from the last Sub-committee meeting (January 25, 2023) were approved.

Council Member/Staff Transitions (Dr. Cefalu)

Dr. Cefalu noted that Dr. Michael Snyder's service on Council has been extended for a third time. Two new Subject Matter Experts, Dr. Carmella Evans-Molina and Mrs. Karen Jordan were introduced. A new DEM staff member, Dr. Nishadi Rajapakse was also introduced.

Heterogeneity of T2D Working Group of Council Update (Dr. Cefalu)

Dr. Cefalu started his presentation by providing background information on the working group and its formation. The desired outcome of the working group is for NIDDK to have a research roadmap to address the heterogeneity of diabetes toward the goal of precision medicine. The charge of the working group is to prepare a final report outlining the needs of the field as well as the opportunities available.

Next, the leadership and staff of the working group were reviewed. The expertise of the working group includes genetics of Type 1 and Type 2 diabetes, atypical diabetes, chronic disease epidemiology, data science, pediatrics, physiology, laboratory medicine, social determinants of health, population science, computational biology, and molecular biology. The major work will

be done in the subgroups of the working group which will address specific issues related to heterogeneity, e.g., biomarkers, clinical trials, social determinants of health, etc. NIDDK staff members, community members, academic investigators, and external stakeholders will all be part of the subgroups. The structure and main body of the working group have been developed already. Chairs and Co-chairs of the sub-groups will be part of the steering committee.

There will be a global meeting at the upcoming ADA meeting organized by the Working Group of Council to discuss the heterogeneity of diabetes. The idea is to provide an overview of global programs and hopefully work toward collaborative projects. Presentations will come from both domestic and international groups.

Dr. Cefalu noted that great progress has been made. A timeline for future work is currently being developed. In addition, global experts are now being consulted.

Council members then asked questions and made comments. Dr. Snyder suggested that the topic might be branded as precision diabetes. A Council member asked if the subgroups are already set? Dr. Cefalu said no, there are currently only suggestions for subgroups. Dr. Cefalu expects that 40-50 people will contribute to the total working group effort including the sub-groups. As a follow-up, a member of Council asked how many subgroups there would be? Dr. Cefalu said this will be determined by the working group of council but he would expect a minimum of four, more than likely seven to eight.

Mouse Metabolic Phenotyping Centers Live (MMPCL) (Dr. Laughlin)

Dr. Laughlin began by providing some background information on the MMPC which is now the MMPCL. She then talked about the goals of MMPCL. To support the program, two RFAs went out. Four awards were issued for phenotyping centers and one award was issued for a coordinating unit. Dr. Laughlin noted that there is pretty good distribution across the country. The coordinating unit was necessary to serve the goals of MMPC and now the MMPCL.

The major goals and elements of the new consortium were then discussed. The phenotyping centers serve a national client base. They operate as a consortium to coordinate, reduce overlap, and share business practices. The centers perform complex physiologic, metabolic, and behavior phenotyping of living animals. In addition, consultation services regarding experimental design and data interpretation are also part of their work. Among the centers, there are opportunities for collaborative research and training activities. The coordinating center provides support for consortium activities.

Dr. Laughlin mentioned that the MMPCL will roll out a new program called VIBRANT. Its goal is to enhance diversity in the research workforce. Overall, it is designed to improve the ability to compete for research funding for underrepresented minority (URM) basic researchers and will have a competitive national Pilot and Feasibility funding program and a competitive program for reduced fees for phenotyping services. It will also provide consultation for experimental design and training in phenotyping technologies.

This program is meant to help researchers establish a grant track record, help provide preliminary data, and improve quality of experimental plan in future grant applications. The program website was also reviewed.

A Council member asked what the four center core areas of expertise are? Dr. Laughlin said that Yale and Vanderbilt focus on glucose homeostasis and insulin clamps, plus energy balance measures. The University of Michigan focuses on performing a broader set of experiments, the gnotobiotic core, and metabolic studies. UC Davis focuses on producing animal models, and behavior of obesity and metabolic disease as well as bariatric surgery and metabolic studies.

New Initiative Concept- **Diabetes Centers Resource and Coordinating Center (DCRCC) (Dr. Silva)**

Dr. Silva started by providing background information on the DEM Diabetes Centers. Currently, DEM has a large investment in the Diabetes Centers. These center programs provide support for extramural research, cost-effective collaborations, and shared access to technical resources/expertise. The program is currently seeing an increase of cross-center collaborations. These collaborative programs have been really successful but overseeing them has taken significant effort and time. DEM believes that now is a good time to consider establishing a coordinating center to provide support and infrastructure for the already established trans-Diabetes Centers programs. A coordinating center would also facilitate and coordinate bridges to and programs for diabetes researchers at institutions not supported by a Diabetes Center program, broaden the outreach of the Center Programs to teaching-intensive institutions, HBCUs and under-represented minority serving institutions, and leverage and collaborate with resources in already existing programs within DDEM, NIDDK, and NIH.

Additional information on the role in leveraging and collaborating were then discussed by Dr. Silva. She noted that a coordinating center could potentially increase the interactions and synergy of the Diabetes Centers programs with other DDEM, NIDDK, and NIH-wide programs and facilitate data sharing and analysis between Diabetes Centers and other NIDDK supported clinical consortia.

The coordinating center could also coordinate many programs in DEM including the three P30 Diabetes Centers, dkNET, and other consortia. Dr. Silva then talked about the potential role of the DCRCC. Some responsibilities might include providing researchers within the Centers (e.g., ESIs and URMs) opportunities to access resources, establishing networking meetings and career development workshops for P&F awardees, linking to ongoing programs that support increasing diversity in extramural research community (e.g., VIBRANT), providing logistical support for workshops/conferences on timely topics, and facilitating data sharing and analysis across programs.

Dr. Silva indicated that there is a meeting planned to talk about the future of the DRC P30 program specifically on May 31st. She will report back to January 2024 Council on the discussions from the May meeting.

A member of Council noted that the information presented helps with questions that came up during the presentation earlier in the Council meeting. The Council member suggested that the program be sure to reduce the administrative burden. A Council member asked if this will be a standalone center? Dr. Silva said yes. Another member of Council indicated that defining roles will be very important. Dr. Silva agreed with this comment. Dr. Cefalu mentioned that nothing new is being started in this program and the coordinating center concept is only an idea for now and will need to be discussed as to how well it will fit in the overall structure of the DRCs and

will need initiative funding. However, the goal is to avoid the roadblocks that occur when investigators want to collaborate either with additional supplemental funding from NIDDK to support pilots or collaboration across centers. A member of Council noted that sometimes it feels like investigators are being punished when they try to collaborate. Another member of Council thought this would be a great mechanism to put funds where they are most useful but stressed that the administrative structure should be very clear so that multiple groups don't think they are in charge.

A Council member stressed that the coordinating center needs to listen to the research centers to determine their needs and facilitate coordination. Dr. Silva also noted that along with administrative issues, the program would address the issues that occur when getting P&F awardees together. Another member of Council asked if there is currently a steering committee for the centers? Dr. Cefalu said no. Council members predicated that all scientific drive would come from the centers. Dr. Cefalu agreed but said a mechanism to drive this flow was needed. Dr. Laughlin mentioned that sharing resources outside of the local environment (home institution) can't be done without a coordinating center. Dr. Cefalu indicated that DEM is considering this concept to solve a problem and facilitate interactions among the Centers Program. He stressed that the purpose of having a coordinating center was to facilitate but not dictate. Council members agreed that this is the right message regarding the approach and suggested that more program involvement will push things in the right direction. Dr. Cefalu noted that the funding pool is not getting bigger. The only way to get to the greater good is to leverage resources. If it works, it will work to our advantage but we want to make sure that we don't make the problem worse.

The Environmental Determinants of Diabetes in the Young (TEDDY) Update (Dr. Akolkar)

Dr. Akolkar began her presentation by providing some background information on T1D and TEDDY. She noted that approximately 1.9 million American have T1D. The rates of T1D appear to be increasing globally, especially in the very young. For now, the research suggests there is an environmental component contributed to disease onset. To allow for coordination and a taking a multi-disciplinary approach to the problem, NIDDK started TEDDY in 2002. There were six clinical centers and a coordinating center. The primary goals of TEDDY are to identify environmental factors "triggering" disease in individuals genetically susceptible to T1D (infectious, dietary, psychosocial) and study gene-environment interactions causing pre-diabetes autoimmunity and clinical T1D. Over 425,000 people were screened and followed. The expected completion date is 2025. Primary endpoints of the study include persistent islet autoimmunity and development of clinical diabetes. The TEDDY protocol is very intense and includes many sample collections. Information about the study assessments was also presented. Results of some study findings were also presented. Major findings of TEDDY include: 1) higher vitamin 25[OH] D and vitamin C levels are associated with lower risk of islet autoimmunity, 2) fatty acids and various metabolites are associated with the risk of Islet Autoimmunity and T1D, 3) subtle associations between IA and microbiome taxonomy/function, 4) prolonged shedding of enteroviruses predicts development of IA across all TEDDY centers, and 5) respiratory infections predict islet autoimmunity.

Future directions of TEDDY were then discussed by Dr. Akolkar. These include a second phase of analyses that will relate measures to the development of islet autoimmunity and T1D in

subjects that reached the endpoints at a later age and may represent a different phenotype of disease. The analysis includes inflammatory and dietary biomarkers, metabolomics, stool microbiome, RNA sequencing and whole genome sequencing.

Dr. Snyder asked if VDJ sequencing from the various receptors is being done? Dr. Akolkar said no. Due to limited funds, DEM had to choose what would be done. Investigators within the study can apply for ancillary studies. Also, a RFA was issued for outside groups to study things that the study group is not evaluating. Dr. Seaquist indicated that the data from TEDDY was beautiful. A member of Council asked how the data fit into the new TZL drug knowledge (for those in stage 2 of T1D) and if there was a way to refer patients and how would this be done? Participants are free to enroll in other trials and are made aware of all trials going on. Dr. Carmella Evans-Molina asked if members of the new nested cohort are already in the TEDDY parent study? Dr. Akolkar said yes. Mrs. Karen Jordan asked how will screening findings be developed into guidelines? Dr. Akolkar said they are trying to develop faster and cheaper screening guidelines for the general population. People need to be screened more than one time to try and determine who will get the disease.

Proteins and Peptides Mass Spectrometry-based Assays in Type 1 Diabetes Clinical Science (Dr. Sechi)

Dr. Sechi noted that Mass Spectrometry–based assays are having a significant impact in clinical laboratories. For example, newborns can be routinely screened for 20-40 inherited diseases for a cost in the range of 1 to 4 dollars per disease using Mass Spectrometry-based assays. Dr. Sechi then provided an overview of his presentation. He cited several editorials reporting inconsistent antibody-based assays. He then specifically presented the data from the C-peptide harmonization program where there was substantial variability among commercial assays. The variability was reduced after recalibration with the reference material sent out by the NIDDK funded project. Dr. Sechi emphasized that accurate and precise assays can empower clinical research and future treatments. He reviewed the advantages of targeted proteomics by mass spectrometry assays and then stated that reference materials (calibrators) for harmonizing assays that are already in the community together with more robust assays will help decrease discordance among assays. The challenges for developing a robust and reproducible assay for glucagon were presented. Currently, there is no reference material in the community for a glucagon assay. A novel affinity mass spectrometry- based assay for glucagon was presented. The reference material (primary calibrator) and the hybridomas used in this assay will be made available to the community.

The NIDDK has a small program aimed to develop reference materials and mass spectrometry-based assay for proteins and peptides of interest in Type 1 diabetes besides for C-peptide and glucagon. Dr. Sechi concluded the presentation asking for feedback. Dr. Cefalu said that to increase the rigor and reproducibility of some of the NIDDK funded studies, assays such as those discussed by Dr. Sechi are very important. A Council member asked if SomaLogic is part of the game plan since it gives information at a reasonable price? Dr. Sechi said SomaLogic is currently not used in the program and indicated that SomaLogic as well as other platforms like the Olink can be reasonable alternatives, mostly in discovery projects. The validation and assay quantification of specific analytes of interest, using these alternative platforms, can be challenging. Another Council member said that there is a laundry list of analytes that should be considered. Dr. Carmella Evans-Molina thought this was a critically important project and asked about sharing assays and collaborators. She wanted to know about partnering with the Diabetes

Research Centers and other reference laboratories. Why not make it a fee for service at a place that does it well instead of setting it up at each laboratory? Dr. Sechi indicated that a fee for service could be cost effective. He also added that the assays presented were developed within the University of Washington where there is a Diabetes Center. The C-peptide assay is indeed already routinely used there. However, the plan is that we'll put additional effort for disseminating these assays and reference materials and communicate also with the other Diabetes Centers. Dr. Snyder indicated that this is a very valuable effort and it should be focused on a specific wish list of selected targets.

Dr. Sechi thanked Council members for their input and asked them to send by e-mail any additional feedback or suggested targets to work on.

New Initiative Concept- Reducing Diabetes Health Disparities Leveraging Social Network Analysis (Dr. Wang)

Dr. Wang started by providing background information on social networks and health disparities. She noted that the focus of the initiative is to determine ways to reach, increase uptake, and sustainment of diabetes interventions. She mentioned that this challenge largely had to do with social factors. A system approach has been proposed to study social networks.

Next, Dr. Wang reviewed current research on social networks. Social networks can provide social support for general health issues, especially in rural and marginalized groups. They can be especially helpful during a transition or crisis. The term network interventions were defined in 2012. The use of social network interventions has been studied in some chronic conditions. In diabetes research, there are already interventions labeled social network interventions. However, there are still significant gaps in diabetes research utilizing social network interventions as formal social network analysis rarely is incorporated into projects and most social network intervention strategies are under-explored. Dr. Wang noted that social network analysis is not a hypothesis but rather an approach. It offers a nice framework to study disparities and their effects.

In order to explore opportunities in this field, a workshop was organized last year. This initiative was then developed based on discussion/outcomes from the workshop. The overall objective of the initiative is to improve the reach, uptake, and sustainment of our current diabetes interventions in populations facing disparities. To reach this goal, the initiative will establish the Diabetes Social Health Innovation Center(s) led by multi-discipline team(s). Their goal will be to establish standards, methods, and tools along with disseminating pilot funding to existing diabetes clinical studies.

Dr. Haire-Joshu asked if this is going to be a center and shouldn't all elements of social network research, such as agent-based modeling, be included instead of just focusing on one social network analysis? Dr. Wang said there are a couple of layers, and we need to start somewhere. Building a framework is necessary. We can build a big center to do a lot of things but some of the tools need to be set up first. Dr. Cefalu asked Council members if this approach will be too limited? Council members said yes, the initiative should try to include all methods and approaches in the center since they all contribute to the understanding. A center only on social network analysis and then doing pilots sounded more like a R01 instead of a center. Council members suggested that something seemed to be missing and thought the initiative/center should

be broader. Dr. Wang said that while developing this, the mechanism was debated. The workshop recommendations included a quite extensive list including the need to standardize how the data was collected. The conclusion of the workshop was that it was best to have a center coordinate this instead of doing R01s. Dr. Snyder asked if we could piggy-back off other groups? Dr. Wang said there are efforts to do this via the common fund for nutrition programs such as the use of supplement funds to collect social determinant measurers. Dr. Snyder also suggested that hearing aid users could also be recruited as the equipment can capture data as a part of social network measures. Dr. Wang agreed that this was a good group to target.

DEM Sponsored Workshops and Activities of Interest

Dr. Cefalu presented information on recent and upcoming DEM workshops and activities of interest. A large number of NIDDK funded projects will be highlighted at the upcoming ADA meeting. The NIDDK young investigators symposium will also be featured at the ADA.