214th NIDDK Advisory Council Meeting
Division of Diabetes and Endocrinology and Metabolic Diseases (DDEMD)
Sub-committee Meeting – Open Session
September 9, 2020

Attendees

DDEMD Sub-committee Members: Ms. Tracey Brown, Dr. David D'Alessio, Dr. Barbara Kahn, Dr. Rudy Liebel, Dr. Jeffrey Pessin, 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, Mr. Neal Green, Dr. Carol Haft, Dr. James Hyde, Dr. Teresa Jones, Dr. Maren Laughlin, Dr. Christine Lee, Dr. Ellen Leschek, Dr. Yan Li, Dr. Saul Malozowski, Mr. Louis Martey, Mr. Michael Mensah, Mrs. Heidi Otradovec, Dr. Sheryl Sato, Dr. Salvatore Sechi, Dr. Lisa Spain, Dr. Somayeh Fahim Nia, Dr. Philip Smith, Dr. Karen Teff, Dr. Pamela Thornton, Dr. Xujing Wang, Dr. Ashley Xia, Dr. Norann Zaghloul

NIDDK/NIH Staff: Dr. Lawrence Agodoa, Dr. Michelle Barnard, Dr. Najma Begum, Dr. Dianne Camp, Dr. John Connaughton, Ms. Dee Doherty, Dr. Ann Jerkins, Dr. Peter Kozell, Dr. Charlene Repique, Mrs. Mary K. Rosenburg, Dr. Elena Sandovich, Dr. Thomas Tatham

Welcome (Dr. Cefalu)

Dr. Cefalu provided an overview of the planned presentations for the open session. The presentations included an update on Type 1 Diabetes TrialNet, a presentation of RFA-DK-20-021- Mechanistic Studies of SARS-CoV-2/COVID-19 in NIDDK Diseases and Organ Systems followed by a discussion of research opportunities for COVID 19 in areas of interest for NIDDK/DEM, and a review of the Exerkines in Health, Resilience and Diseases workshop.

Type 1 Diabetes (T1D) TrialNet (Dr. Spain)

Dr. Spain presented a summary of the progress and plans of T1D TrialNet in response to Dr. Kahn's prior request. The mission of TrialNet is to prevent T1D and to stop disease progression by preserving insulin production before and after diagnosis. The results of decades of research by TrialNet and others show that T1D is a predictable disease and that prevention is possible. Most TrialNet trials so far have tested agents that intervene with the autoimmune process, consistent with what is known about mechanisms of pathogenesis. T1D is an autoimmune disease that progresses in three stages. In stage 1, individuals test positive for two or more diabetes-related autoantibodies, identified by TrialNet T1D risk screening but have normal glucose tolerance. In stage 2, individuals have two or more diabetes-related autoantibodies, but now have blood sugar levels that have become abnormal, but not diagnostic of T1D. In stage 3, T1D symptoms are present due to significant beta cell loss and the glucose levels with testing are above the threshold for diagnosing T1D. The TrialNet model is to test drugs first in participants with newly diagnosed T1D (Stage 3), and if there is efficacy as assessed with slowed progression of disease

(e.g. preservation of C-peptide secretion), they are then tested at earlier stages (Stages 2 and 1) when there is more beta cell function.

TrialNet, with help from partners like the Immune Tolerance Network, showed that five different therapies (alefacept, abatacept, low dose anti-thymocyte globulin (ATG), rituximab, and teplizumab) preserved insulin secretion in Stage 3 participants with T1D. So far, one agent, teplizumab has been tested in earlier stages and the data showed that teplizumab significantly delayed the onset of T1D symptoms. Two other studies are underway during Stage 1 for earlier prevention, one trial testing abatacept and the other trial testing hydroxychloroquine for prevention of progression to Stage 2.

TrialNet also seeks to understand the mechanisms of T1D pathogenesis and uses mechanistic data to design new trials. TrialNet investigators are engaging with partners to answer 7 key questions about mechanisms of progression from stages 1 to 3. Three new trials are ready to go or in development for launch within the next year, and these were presented in a series of slides. Dr. Spain emphasized that with the validation of TrialNet's scientific approach, and the availability of numerous therapeutic options, TrialNet is well-positioned to continue to make progress towards a more durable delay of T1D for more participants, which could ultimately lead to a way to prevent T1D.

Dr. Spain paused to allow sub-committee members to ask questions. Dr. Kahn noted that most interventions were only tried once (instead of again 3 months later, especially if there was an initial response) and asked if there were dynamics of the immune system, logistics of the trial, or costs which influenced this plan? Dr. Spain responded that some drugs like abatacept are given over time and teplizumab was studied in repeated dosing in new onset studies. This issue has been on the radar of TrialNet but there are some logistical concerns. The thought is that for most of these interventions, repeated dosing is likely to be necessary.

Dr. Spain then discussed challenges that TrialNet faces to accomplish its mission. The challenges fell into 3 general categories- effects of the COVID-19 pandemic on study conduct and procedures, recruitment of under-served populations, and the need for general population screening because relative-only screening will miss 80% of those likely to benefit. With a positive result for prevention, it is urgent that all those who can potentially benefit from treatment be included in trials. Due to COVID-19 clinic shutdowns, reduced compliance with visits was observed. Online screenings also were down but have seen a robust rebound recently. Costs have also increased as the demand for hydroxychloroquine and PPE have increased. In addition, there was discussion of additional costs required to conduct COVID-19 testing, particularly to determine what effects the infection may have on disease progression or onset. Infectious disease experts have always been involved in TrialNet and are providing recommendations based on new information in this rapidly evolving area. At the current time, their recommendation is to avoid use of immune-depleting agents in combination until more is known. Dr. Spain thanked TrialNet participants, researchers, and partners.

Ms. Stiehl commented that she recruits through UCSF for TrialNet and agreed that COVID-19 had a negative influence on the studies, but she was pleased to see families stepping-up to use online screening, capillary screening, and the use of Quest. These extra efforts allowed for

continued progress on recruitment. Ms. Stiehl was very impressed with TrialNet leadership during the COVID-19 pandemic. Dr. Snyder agreed that the efforts were impressive.

Dr. Cefalu thanked Dr. Spain for her presentation and said this highlighted the special issues in TrialNet and impact on research due to COVID-19.

RFA-DK-20-021- Mechanistic Studies of SARS-CoV-2/COVID-19 in NIDDK Diseases and Organ Systems (Dr. Laughlin) and Council Discussion on COVID-19 Research Opportunities

Dr. Cefalu introduced this topic as a follow-up to prior COVID-19 discussions earlier in Council. Dr. Laughlin presented an overview of the new mechanistic R01, RFA-DK-20-021. Some background on the reason for the RFA include the fact that obesity, older age, and male sex are all associated with poor COVID-19 outcomes. Furthermore, diseases, including diabetes (odds ratio 1.48, 16 studies) and chronic kidney disease (odds ratio 3.25, 9 studies) are associated with a significantly greater risk of mortality from COVID-19. Minority and disadvantaged populations are particularly adversely affected by COVID-19, with elevated incidence, severity and mortality. Using this background information, the RFA was proposed to foster studies to generate information leading to treatment and prevention of severe outcomes in COVID-19 patients with NIDDK diseases or in tissues of interest to NIDDK. The RFA also serves as a mechanistic corollary to the NOSI discussed earlier in Council by Dr. Lee. The intent of the RFA is to support new basic and clinical mechanistic research on SARS-CoV-2 and COVID-19 within NIDDK's interests including diabetes and other metabolic diseases, obesity, and endocrine, digestive, liver, pancreas, kidney, urological, and hematologic tissues and diseases. Another goal is to identify biological mechanisms surrounding the role of pre-existing NIDDK diseases in increased susceptibility to COVID-19 and greater morbidity and mortality from COVID-19. In addition, research is needed to understand adverse acute or chronic outcomes in NIDDK tissues/diseases resulting from COVID-19 infection, including new onset of disease, new routes of infection, and understanding the course of disease. The RFA provides for $250,000 DC/year for 3 years and NIDDK aims to make 11-13 awards. This will support studies with minimal preliminary data to do both human subjects or studies in model organisms using isolated tissues, cells or *in vivo* approaches. Very broad research is allowed under the RFA in the hopes of attracting a variety of topics. The RFA was issued on July 10, 2020 and applications are due on December 16, 2020. Given the very recent appearance of COVID-19 and the fact that many labs were on hiatus for several months, there has been little time to acquire substantial preliminary data. RFA DK-20-021 will fund modest 3-year grants with a reduced emphasis on preliminary data, in order to initiate exciting and high yield projects. Larger projects based on substantial preliminary data can be submitted to the normal R01 competition.

Given the 4 supplement projects funded with the NIDDK COVID-19 NOSI and projects solicited with the mechanistic RFA, Dr. Cefalu requested input from Council on other opportunities that DEM should focus on to address the COVID-19 pandemic. Dr. D'Alessio remarked that there has been a tremendous amount of activity on COVID-19 with already 1,800+ publications on COVID-19 and diabetes and *Diabetes Care* publishing a special issue dedicated to COVID-19 and diabetes in July. Most of the information is observational so these mechanistic study opportunities fit the need to study COVID-19 more definitively and in depth. He noted that

while COVID-19 was originally thought to be a pulmonary infections disease, there is an interesting overlap with other NIDDK diseases. Dr. D'Alessio found 2 parts of the RFA to be very interesting- the very broad scope (since we don't know much about COVID-19, there are a variety of avenues to study) and the short/small application time/funding (since this gives the RFA nimbleness and large funding amounts are not committed to one hypotheses when many mechanisms are still unknown). Dr. D'Alessio also noted that COVID-19 allows researchers to study health disparities and the process for this can be used as a model in the future.

Dr. Leibel raised another point that was not explicitly mentioned in the RFA which is how NIDDK tended to emphasize phenotype to phenotype interactions. Diabetes and COVID-19 combined lead to bad outcomes for example. But there is the possibility that perhaps susceptibility of people with diabetes to adverse outcomes could be due to genetic pleiotropy. The genes that predispose to these conditions may also predispose to adverse interactions with the virus. Perhaps gene x phenotype interactions should be explored. One area of particular interest that serves as an example of this possibility is the role of cilia in human disease, notably obesity and diabetes. The structural components of cilia are encoded by a large number of genes and some of those lead to diabetes and obesity and airway problems, so some susceptibility to adverse outcomes could be due to the genes. It is well known that T1D is an immune-mediated disease and those with T1D may have greater adverse outcomes than T2D, so it is possible that some of the immunologic basis for T1D may interact with the virus that may exacerbate outcomes of COVID-19. There now have been substantial collections of data and clinical histories that can allow for this sort of investigation. Dr. Cefalu thanked Dr. D'Alessio and Dr. Leibel for their comments and asked if other Council members had comments.

Dr. Snyder remarked that he liked the new RFA and that it would be acceptable to fund work that later turns out to be wrong. Dr. D'Alessio suggested that connecting the funded investigators would be a good idea since there may be some synergies between the projects and to facilitate the fast-moving research needs -- perhaps use the Diabetes Research Centers (DRCs) or Nutrition Obesity Research Centers (NORCS) to do COVID-19 P&Fs. Dr. Leibel agreed that leveraging the DRCs and NORCs could be deployed to help with the rapid research efforts for pathfinding for a more dedicated RFA or larger grants. Dr. Pessin asked if it makes sense to be proactive about other infections that might come down in the future. Dr. Pessin also asked if there would be an RFA to look at interactions between other infections and diabetes. Dr. Cefalu answered that the current pressing need is COVID-19 given the significant adverse outcomes seen in individuals with co-morbidities of interest to NIDDK (i.e. diabetes, obesity, kidney disease, etc.). The COVID-19 NOSI limits what can currently be done. What we learn from the COVID NOSI and the COVID-19 mechanistic RFA may be applicable to future considerations. Dr. Cefalu further noted that there are enough unique things about COVID-19 that we should focus on that for now rather than generalizing to other viruses. Dr. Snyder agreed that Dr. Pessin made a good point about developing a general knowledge-base, having platforms for more rapid response to future virus outbreaks would be good, and the development of technologies that come out of this would be broadly applicable. Dr. Cefalu mentioned that the RADxUP program, funded by NIH, is helping with testing so there are huge efforts by NIH to create those platforms. Dr. Thornton noted that RADxUP is an NIH effort to ramp up testing in underserved populations- there will be 4 awards and a NIDDK consortium will be involved. The idea is to accelerate dissemination of rapid testing and use that knowledge for rapid dissemination of

vaccines when available. There is also a COVID-19 NOSI that focuses on social, ethical and behavioral implications which could have widespread impact on health disparities. Funding decisions will be made in the next 2 weeks.

Dr. Kahn remarked that these all sound good. One concern is whether funding the COVID-19 studies will take away from the payline funded R01s and Ks? Dr. Kahn is in support of these initiatives and agree we need to fund risky things because all of this is so new. Dr. Cefalu said for the new RFA non-pay line funds will be used but anticipates COVID-19 grants will also be submitted for regular grant cycles. Dr. Smith noted that there is very little we know about inflammation and metabolic disease, so perhaps those working on non-COVID-19 research can delve into the inflammatory process and may help with our main efforts to understand diabetes. Dr. Cefalu encouraged other opportunities and directions on this from Council members to be submitted to NIDDK. Dr. Kahn remarked that she thinks there are not any studies suggesting that T1D can be triggered by COVID-19. Dr. Cefalu noted that there is currently a paucity of data on this area, but there is interest in this topic and an international group trying to collect these cases via a registry (CoviDiab Registry). Dr. D'Alessio mentioned a paper in *Lancet* about this topic and said the funding opportunities are broad enough to get at this. Dr. Kahn said we may get at the immune dynamics contributing to T1D development if we can leverage these samples and cohorts. Dr. Cefalu liked the idea of leveraging the DRCs for COVID-19.

Exerkines in Health, Resilience and Diseases Workshop (Dr. Xia)

Dr. Xia discussed the recent Exerkines in Health, Resilience and Diseases workshop, sponsored by NHLBI and NIDDK. Five hundred thirty-five people attended the workshop, held via Zoom. Twenty-one experts in exerkines research presented on four main topics: 1) Current State of Science of Exerkines in Health and Resilience, 2) Mechanisms Linking Exerkines to Inter-Organ Crosstalk, 3) How to Leverage Exerkines for Therapeutic Purposes, and 4) Gaps and Opportunities in Exerkines Research and How to Stimulate Collaborations. The following two key findings were identified from the workshop – 1) Many molecules have been implicated as exerkines with more to be discovered. These exerkines act locally and/or systemically and have impacts on every system in human body (metabolic, cardiovascular, brain, etc.) and 2) Human responses to exercise are heterogeneous and highly varied by the dose, types and timing of exercise, timing of sample collection in relation to exercise, health and disease states, diets/medications (including dietary supplements), and genetic variations. Some gaps identified during the workshop include: 1) Discovery of exerkines is only the beginning and how the molecules discovered thus far work is largely unknown, 2) Improvement is needed in phenotypic measures and biomarkers for resilience in health and disease states, and 3) Lack of epidemiological data on normal, subnormal and disease conditions of resilience measures in human population throughout the lifespan. Opportunities to fill the gaps identified in this area include wearable devices, minimum invasive detection technologies, and AI applications. Dr. Snyder, one of the workshop Chairs, commented that the workshop was very well done.

Concluding Remarks (Dr. Cefalu)

Dr. Cefalu asked Council members if they had any additional questions or comments. Dr. Snyder suggested that NIDDK consider looking at post-COVID-19 affects. This is important for all NIH

institutes, so hopefully enough samples are being collected to allow all topics to be studied. Dr. Pessin remarked that the use of matching funds for DRC P&Fs could be used to study COVID-19 and diabetes-related topics. These funds have been used for topics such as Alzheimer's and physician scientists for P&Fs at the centers. Dr. Snyder also suggested that data on COVID-19 be collected in a unified way across all institutes and that common data repositories be used. Dr. Leibel emphasized that it is important to make it clear that studies done for COVID-19 are very likely, if properly designed, to shed light on the underlying diseases as well. This may not necessarily be "COVID-19 and" but can be "COVID-19 with." And it may be relevant to diseases outside of this epidemic. For example, if we know that the virus attacks beta-cells, it is important to understand the mechanism for T1D outside of the context of COVID-19 and how this may relate to understanding of other viral assaults in the future. Dr. Leibel further suggested that it is important to emphasize COVID-19-related but not COVID-19-specific issues.

Dr. Cefalu thanked the sub-committee members and NIH staff for their attendance and comments.