National Diabetes and Digestive and Kidney Diseases Advisory Council
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Department of Health and Human Services

I. CALL TO ORDER
Dr. Rodgers

Dr. Griffin Rodgers, Director, NIDDK, called to order the 207th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m. on May 16, 2018, in Conference Room E1/E2, Natcher Conference Center, Building 45, the NIH Campus, Bethesda, Maryland.

A. COUNCIL MEMBERS PRESENT

Dr. Joseph Bonventre
Dr. Margot Damaser*
Dr. Mark Donowitz
Dr. Joel Elmquist
Dr. Lisa Guay-Woodford
Dr. Caren Heller
Dr. Barbara Kahn*
Dr. Lee Kaplan
Dr. David Klurfeld†
Mr. Richard Knight
Dr. Paul Lange
Mr. Thomas Nealon
Dr. Richard Peek*
Dr. Jeffrey Pessin
Dr. Alan Saltiel
Dr. Ronald Sokol*
Dr. Ian Stewart†
Ms. Lorraine Stiehl*
Ms. Pamela Taylor

Also Present:
Dr. Griffin Rodgers, Director, NIDDK; and Chair of the NIDDK Advisory Council
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. Karl F. Malik, Executive Secretary, NIDDK National Advisory Council

* These members served on an *ad hoc* basis at this meeting
† Ex Officio member

B. NIDDK STAFF AND GUESTS PRESENT

Abbott, Kevin – NIDDK
Abraham, Kristin – NIDDK
Ananthanarayanan, Meena – CSR
Anderson, Dana – NIDDK
Berti-Mattera, Liliana – CSR
Bishop, Terry – NIDDK
Blondel, Olivier – NIDDK
Boerboom, Lawrence – CSR
Bourque, Sharon – NIDDK
Bremer, Andrew – NIDDK
Burch, Henry – NIDDK
Burgess-Beusse, Bonnie – NIDDK
Byrd-Clark, Danita – NIDDK
Castle, Arthur – NIDDK
Cerio, Rebecca – NIDDK
Chang, Heidi – McAllister & Quinn
Chowdhury, Bratati – NIDDK
Connaughton, John – NIDDK
Davila-Bloom, Maria – NIDDK
Dayal, Sandeep – NIDDK
Densmore, Christine – NIDDK
Dirks, Dale – Health & Med. Counsel of Washington
Doherty, Dee – NIDDK
Doo, Edward – NIDDK
Duggan, Emily – NIDDK
Evans, Mary – NIDDK
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gansheroff, Lisa – NIDDK
Garcia, Martha – CSR
Gaughan, Denise – NIDDK
Gossett, Danny – NIDDK
Greenwel, Patricia – NIDDK
Haft, Carol – NIDDK
Hall, Sherry – NIDDK
Hamilton, Frank – NIDDK
Hanlon-Tilghman, Mary – NIDDK

Herzog, Peter – Digestive Disease Natl. Coalition
Hoffert, Jason – NIDDK
Hoofnagle, Jay – NIDDK
Hoshizaki, Deborah – NIDDK
Hu, Jianxin – CSR
Hyde, James – NIDDK
Ivins, Jonathan – CSR
James, Stephen – NIDDK
Jerkins, Ann – NIDDK
Jerkins, Connie – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Kimmel, Paul – NIDDK
Kirkali, Ziya – NIDDK
Kozel, Peter – CSR
Kranzfelder, Kathy – NIDDK
Kuczmarski, Robert– NIDDK
Larkin, Jennie – NIDDK
Laughlin, Maren – NIDDK
Lee, Christine – NIDDK
Leschek, Ellen – NIDDK
Li, Yan – NIDDK
Linder, Barbara – NIDDK
Lynch, Christopher – NIDDK
Malozowski, Saul – NIDDK
Martey, Louis – NIDDK
Maruvada, Padma – NIDDK
Mendley, Susan – NIDDK
Mullins, Christopher – NIDDK
Narva, Andrew – NIDDK
Otradovec, Heidi – NIDDK
Parsa, Afshin – NIDDK
Pawlyk, Aaron – NIDDK
Payne, January – NIDDK
Perrin, Peter – NIDDK
Perry Jones, Aretina – NIDDK
Pileggi, Antonello – CSR
Ramani, Rathna – NIDDK
Rankin, Tracy – NIDDK
Reiter, Amy – NIDDK
Roberts, Tibor – NIDDK
Rosenberg, Mary Kay – NIDDK
Roy, Cindy – NIDDK
Rushing, Paul – NIDDK
Rys-Sikora, Krystyna – NIDDK
Sanovich, Elena – NIDDK
Saslowsky, David – NIDDK
Sato, Sheryl – NIDDK
Sechi, Salvatore – NIDDK
Serrano, Jose – NIDDK
Shepherd, Aliecia – NIDDK
Sierra-Rivera, Elaine – CSR
Singh, Megan – NIDDK
Smith, Jaime – NIDDK
Smith, Philip – NIDDK
Spain, Lisa – NIDDK
Star, Robert – NIDDK
Stoeckel, Luke – NIDDK
Tatham, Thomas – NIDDK
Tenuto, Michael – NIDDK
Tilghman, Robert – NIDDK
Torrance, Rebecca – NIDDK
Tuncer, Diane – NIDDK
Unalp-Arida, Aynur – NIDDK
Wallace, Julie – NIDDK
Weiner, Jeff – NIDDK
Woynarowska, Barbara – NIDDK
Xie, Yining – NIDDK
Yanovski, Susan – NIDDK

C. ANNOUNCEMENTS

Dr. Rodgers

Council Member News

Dr. Rodgers welcomed five new members to the Council. They will be divided among NIDDK's three sub-councils: The Division of Digestive Diseases and Nutrition (DDN) Sub-council, the Division of Diabetes, Endocrinology, and Metabolic Diseases (DEM) Sub-council, and the Division of Kidney, Urologic, and Hematologic Diseases (KUH) Sub-council. The new members attended the May meeting as *ad hoc* members, with the expectation that they all will have regular member status by the September meeting.

Dr. Richard Peek is joining the DDN Sub-council. He is the Director of the Division of Gastroenterology and the Mina Cobb Wallace Professor of Medicine, Cancer Biology, and Pathology, Microbiology, and Immunology in the Department of Medicine at Vanderbilt University. He trained at the University of North Carolina at Chapel Hill, the University of Alabama, and Vanderbilt University. Dr. Peek uses basic and translational approaches to studying host-microbe interactions in the gut of microbial-induced disease. His research focuses on the investigation of the mechanisms through which *H. pylori* can induce chronic gastritis and gastric cancer. Over his career, Dr. Peek has been awarded many NIH awards, primarily from NIDDK and NCI, including two long-running R01s on *H. pylori*, and NIDDK's P30 Center on the molecular and cellular basis for digestive diseases. Dr. Peek is the editor-in-chief of *Gastroenterology*, is a member of the Association of American Physicians and recently served as the chair of the American Gastroenterological Association's Council.

Also new to the DDN Sub-council is *Dr. Ron Sokol*, a Professor of Pediatrics and Vice Chair of Clinical and Translational Research in the Department of Pediatrics at the University of Colorado School of Medicine and the Children's Hospital of Colorado. He is also the Director and Principal Investigator of the Colorado Clinical and Translational Science Institute at the University of Colorado, Denver, and the Section Chief on Pediatric Gastroenterology, Hepatology, and Nutrition at the University of Colorado School of Medicine, and the Digestive Health Institute at Children's Hospital in Colorado. He holds the Arnold Silverman, M.D., Endowed Chair in Digestive Health. He was trained at the University of Chicago, the University of Colorado, and Cincinnati's Children's Hospital. Dr. Sokol's research focuses on investigating basic mechanisms of liver cell death and injury and the pathogenesis of several rare pediatric liver diseases. He was among the first to demonstrate the important role of vitamin E metabolism in cholestatic liver disease and the clinical effects of vitamin E deficiency in humans. An NIH grantee since 1987, Dr. Sokol's service record includes membership on the governing board of the American Association for the Study of Liver Diseases, where he was recently elected as president.

Dr. Barbara Kahn joined the DEM Sub-council. She is the George R. Minnow Professor of Medicine at Harvard University Medical School and the Vice Chair of Research Strategy in the Department of Medicine at Beth Israel Deaconess Medical Center. Dr. Kahn completed her training at Stanford University and at the University of California, Davis. A veteran of the NIDDK Intramural Research Program before joining Harvard, she has made many seminal contributions to understanding the molecular pathogenesis of obesity and type 2 diabetes. Her research has advanced understanding of the mechanisms by which adipocyte signaling regulates systemic insulin

sensitivity. She serves on the editorial boards of four scientific journals and has been a member of many NIH study sections. Dr. Kahn received the 2016 Banting Medal for Scientific Achievement, the highest scientific award of the American Diabetes Association. She is a member of both the National Academy of Medicine and the National Academy of Sciences.

The DEM Sub-council also welcomes ***Ms. Lorraine Stiehl*** as a public member. She is a committed and effective diabetes patient advocate. She is also a healthcare executive with extensive expertise in marketing, health-related causes, nonprofit management, and strategic planning. She has made important and sustained contributions to the Juvenile Diabetes Research Foundation (JDRF) in a variety of capacities that have been recognized by awards and leadership positions. These include National Staff Member of the Year, National Volunteer of the Year, National Advocacy Chair, and then JDRF international Board of Directors. Ms. Stiehl and her husband Chris have been selected as patient advocate coordinators for the California Institute of Regenerative Medicine.

Dr. Margot Page Damaser has joined the KUH Sub-council. Dr. Damaser leads the Urological Biomechanics Laboratory within the Department of Biomedical Engineering and the Glickman Urological and Kidney Institute at the Lerner Research Institute of the Cleveland Clinic and the Cleveland Clinic Lerner College of Medicine. Dr. Damaser earned her Ph.D. in bioengineering from the University of California, Berkeley, and completed postdoctoral fellowship training at the University of Lund in Sweden, and at the University of Pennsylvania. Her laboratory investigates the biomechanical control of the lower urinary tract, along with the development of platform technologies for rehabilitation of lower urinary tract and pelvic floor dysfunction. She has advanced innovative wireless and catheter-free methods of monitoring lower urinary tract function and has forged advances in novel regenerative medicine-based therapeutics for diagnosing and treating urinary incontinence, fecal incontinence, and pelvic organ prolapse. Dr. Damaser has received numerous awards and honors, including a prestigious Presidential Early Career Award for Scientists and Engineers for her research on human urinary bladders using mathematical modeling along with physiologic and neurologic studies.
Additionally, Dr. Rodgers also shared some news about various current and former Council members:
Current NIDDK Council member *Mr. Richard Knight*, the president-elect of the American Association for Kidney Patients (AAKP), has been awarded the American Society of Nephrology's Presidential Medal as part of the AAKP's national leadership team. Mr. Knight also serves on the National Kidney Disease Education Program Health Information Technology Work Group and is a founding member of the End-Stage Renal Disease Health Information Technology Project and the National Renal Administrators Association.

On a sad note, ***Dr. Daniel Foster***, a former member of NIDDK's Advisory Council and NIH's Clinical Center Board of Scientific Counselors, died in January. Dr. Foster was a chairman of the University of Texas Southwestern's Medical Center's Department of Internal Medicine for 16 years. Among his scientific contributions was the discovery of an essential mechanism of metabolism, the malonyl-CoA regulatory system for fatty acid oxidation and ketogenesis with his scientific colleague, Dr. John Dennis McGarry.

Dr. Robert A. Goldstein has also passed away. Dr. Goldstein worked at NIH for nearly 20 years before joining the Juvenile Diabetes Research Foundation (JDRF) as its chief scientific officer.

Later, he became the chief scientific officer of JDRF Canada. He was known as an extremely committed and outstanding scientist, and had recently been working to establish type 1 diabetes research activities in Canada, including the formation of a partnership with the Canadian Institute for Health Research to defeat diabetes.

NIDDK News

Dr. Germino, Deputy Director of NIDDK, announced that NIDDK has created a new entity, the Office of Clinical Research Support. The Office, which operates virtually, is part of NIH's multifaceted effort to improve the oversight of NIH-supported clinical trials throughout their lifecycle, from the application and award processes through the dissemination of research results to the public. The Office brings together specialists in biostatistics, regulatory affairs, clinical trial support, data and bio-specimen repositories, and technology transfer.

Working closely with the leadership of NIDDK's Clinical Studies Working Group, the Office will oversee and coordinate the development of policies and procedures to guide extramural NIDDK-funded clinical studies and clinical trials. The goal is to ensure that this research complies with all NIH and HHS human subjects research policies and that planning for and management of clinical research is consistent and effective across NIDDK's divisions.

The office will also work with NIDDK program staff to address challenges in the design, efficiency, and reporting of all clinical trials. These efforts will harmonize NIDDK's policies, provide resources and support, improve trial management, and eventually improve cost-efficiency.

NIDDK Staff News

Dr. Rodgers reported that two staff members have been chosen to receive notable professional recognitions:

Dr. Catherine Cowie, a Program Director in the Division of Diabetes, Endocrinology, and Metabolic Diseases, will be receiving the Kelly West Award at the American Diabetes Association's (ADA) upcoming Annual Scientific Sessions. This is ADA's highest award in the field of diabetes epidemiology for scientific publications that have elucidated changes in rates of diabetes over several decades and the extent to which diabetes treatment reflects the standard of care. Most recently, Dr. Cowie led the development of the third edition of NIDDK's *Diabetes in America*, a compilation and assessment of epidemiologic public health and clinical trials data on diabetes and its complications in the U.S. The new edition of *Diabetes in America* will be soon published by NIDDK, and nearly all 42 chapters are now available on the NIDDK website.

The National Kidney Foundation (NKF) in April selected ***Dr. Andrew Narva*** to receive its 2018 Public Service Award. The NKF Public Service Award honors those who have dedicated their careers to public service and who have helped shape public policies and government programs to improve the outcome of kidney patients. Dr. Narva is a Program Director in the Division of Kidney, Urologic, and Hematologic Diseases, where he directs the National Kidney Disease Education Program and is a project scientist for the Chronic Renal Insufficiency Cohort Study. He is also a chief clinical consultant in nephrology for the Indian Health Service and cares for patients at Walter Reed National Medical Center, and at the Zuni Pueblo in New Mexico via telemedicine. Prior to joining NIH, Dr. Narva served as the Director of the Kidney Disease Program for the Indian Health Service, where he established effective interventions in reducing the rates of diabetes-related

kidney failure among tribes.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 206th COUNCIL MEETING

Dr. Rodgers

The Council approved, by voice vote, the Summary Minutes of the 206th Council meeting, which had been sent to them in advance for review.

III. FUTURE COUNCIL DATES

2018

September 7 (Friday)
Building 10, Conference Rooms FAES B1C204-09; B1C211

2019

January 16-17 (Wednesday and Thursday)
Building 45, Conference Rooms E1/E2, D and F1/F2

May 8-9 (Wednesday and Thursday)
Porter Neuroscience Research Center (Building 35)
Conference Rooms 610, 620/630, 640

September 11-12 (Wednesday and Thursday)
Building 31, Conference Rooms 10, 6 and 7

2020

January 29-30 (Wednesday and Thursday)
Building 31, Conference Rooms 10, 6 and 7

May 20-21 (Wednesday and Thursday)
Building 31, Conference Rooms 10, 6 and 7

September 9-10 (Wednesday and Thursday)
Building 31, Conference Rooms 10, 6 and 7

Note: The September 2018 meeting will be held on a Friday, rather than the typical Wednesday-Thursday schedule.

Most meetings are expected to be a single day. However, the NIDDK asks Council members to reserve two days for each meeting should a situation arise where a longer meeting is required.

IV. ANNOUNCEMENTS

Dr. Karl Malik

Confidentiality

Dr. Malik reminded the Council Members that material furnished for review purposes and discussion during the closed portion of the meeting is considered confidential. The content of discussions taking place during the closed session may be disclosed only by the staff and only under appropriate circumstances. Any communication from investigators to Council Members regarding actions on an application must be referred to the Institute. Any attempts by Council Members to address questions from applicants could create difficult or embarrassing situations for the Members, the Institute, and/or the investigators.

Conflict of Interest

Dr. Malik reminded the Council Members that advisors and consultants serving as Members of public advisory committees, such as the NIDDK Advisory Council, may not participate in situations in which any violation of conflict of interest laws and regulations may occur. Responsible NIDDK staff shall assist Council Members to help ensure that a Member does not participate in, and is not present during, the review of applications or projects in which, to the Member's knowledge, any of the following has a financial interest: the Member, or his or her spouse, minor child, or partner (including close professional associates), or an organization with which the Member is connected.

To ensure that a Member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. A statement is provided for the signature of the Member, and this statement becomes a part of the meeting file. Dr. Malik directed each Council Member to a statement in his or her meeting folder regarding the conflict of interest in review of applications. He asked each Council Member to read it carefully, sign it, and return it to NIDDK before leaving the meeting.

Dr. Malik pointed out that at Council meetings when applications are reviewed in groups without discussion, also called "*en bloc*" action, all Council Members may be present and may participate. The vote of an individual Member in such instances does not apply to applications for which the Member might be in conflict.

Regarding multi-campus institutions of higher education, Dr. Malik said that an employee at one campus may participate in any particular matter affecting another campus, if the employee's financial interest is solely at one campus and the employee has no multi-campus responsibilities.

V. REPORT FROM THE NIDDK DIRECTOR
Dr. Rodgers

Budget Update

Dr. Rodgers explained that, after years of austerity and relatively flat budgets across the government, Congress approved a budget on March 23, 2018. It provides significant funding increases across both Defense and non-Defense discretionary programs, including the NIH. The President quickly signed the bill into law. The 2018 Omnibus Appropriation Bill provides the most significant funding increase for science programs in recent years.

NIH received a $3 billion, 9-percent increase over 2017. This is the largest single-year increase since 2003, the last year of the five-year effort to double NIH's budget. About 40 percent of that $3 billion NIH increase is allocated for specific programs and disease areas. Many of the areas with increased funding are related to therapies contained in the 21st Century Cures Act of 2016. NIDDK received $1.97 billion, a 5.4 percent increase over 2017.

Congress did not approve the Administration's proposal to move the Agency for Healthcare Research and Quality (AHRQ) to the NIH, nor did they accept the Administration's proposal to eliminate the Fogarty International Center. Congress also chose not to impose a proposed cap on institutional overhead costs associated with NIH awards. Most of the specific funding increases were directed to Alzheimer's disease research, NIH's *All of Us* Research Program, the BRAIN Initiative, and regenerative medicine research. There was also an increase for research on antibiotic resistance, opioid addiction, and the development of a universal flu vaccine.

The Omnibus Appropriation Bill also reauthorized NIDDK's Special Statutory Program for Type 1 Diabetes Research, for which funding had expired on October 1, 2017. The agency had received a portion of the special funds in one of the continuing resolutions that preceded this Omnibus Appropriation, which provides full-year funding for both the current fiscal year, FY 2018, as well as next year, FY 2019. The timing of the reauthorization meant that it would be difficult to effectively issue 17 funding opportunity announcements within a six-month time frame. In the authorizing language, Congress lifted the restriction that we spend these funds specifically in the current fiscal year. Thus, NIDDK will be able to use these funds as needed in fiscal years 2018, 2019, and beyond.

Dr. Rodgers explained that NIDDK is waiting to publish the 2018 Funding Policy on the website pending final details from NIH's Fiscal Policy for Grant Awards. One important change is that, in Fiscal Year 2018, the NIDDK's pay line for most R01 applications requesting direct costs less than $500,000 will be the 13th percentile. As in past years, there will be a more stringent pay line for those R01 applications requesting a direct cost of $500,000 or more. This more stringent pay line has been increased and now is the 8th percentile. But, as publicly announced, NIDDK will not apply this more stringent R01 pay line for therapeutic clinical trials where the total direct costs for five years do not exceed $2.5 million in direct costs, even if the therapeutic clinical trial equals or exceeds $500,000 in some years during that five-year period.

For early stage investigators (ESIs) the FY 2018 pay line for ESI R01s will be the 18th

percentile, 5 percentiles higher than the standard R01 pay line. Additionally, NIDDK remains focused on fostering the stable integration of early stage investigators into the biomedical research workforce and so has set the pay line for a first competitive R01 renewal at the 16th percentile, compared to the 13th percentile for the standard pay line. This year is the fourth consecutive year this policy will be in place.

Dr. Rodgers closed by noting that the starting point for FY 2019 appropriations is the President's Budget Request. It includes $34.8 billion for NIH and nearly $2 billion for NIDDK. In addition to again proposing the incorporation of AHRQ into NIH, the Request also proposes to move two other agencies into NIH. The National Institute for Occupational Safety and Health, with a budget of $255 million, would be transferred from the Centers for Disease Control and Prevention; and the National Institute of Disability, Independent Living, and Rehabilitation Research, would move from the Administration for Community Living, along with its budget of $95 million.

The House held a hearing on the NIH's proposed budget on April 11th, while the Senate budget hearing was to be held the day after the NIDDK Advisory Council's meeting. Both the House and the Senate Appropriations Committees plan to work to complete their work by September.

VI. COUNCIL FORUM: REGENERATIVE MEDICINE

Overview
Dr. Germino

Dr. Rodgers introduced Gregory G. Germino, M.D., Deputy Director of NIDDK. Dr. Rodgers reminded Council members that regenerative medicine seeks to develop functional cells, tissues, and organ substitutes to repair, replace, or enhance a biological function that's been lost as a result of congenital anomalies, injury, disease, or the aging process. He also explained that this meeting marked the second installment of a new year-long initiative, the Council Forum, which will consist of special presentations on regenerative medicine at each of this year's Council meetings with speakers selected by each NIDDK division. The plan is to seek input from the Council at the September 2018 meeting regarding where NIDDK and NIH should focus their resources within the broad area of regenerative medicine.

Dr. Germino began by defining regenerative medicine and placing it in the context of NIH's and NIDDK's mission. The emerging field of regenerative medicine is complex, providing many opportunities and challenges that cut across NIDDK's three divisions. There is a lot of excitement and promise in this field, but also some concern that it won't deliver on its promise and that it carries risk.

The field is attracting widespread interest. The National Academies and Congress have sponsored workshops and publications on the topic. The 21st Century Cures Act contains funding for the Regenerative Medicine Innovation Project.

Dr. Germino said that in FY 2017 (the first year of the project), NIH awarded and issued a total of $2.7 million, divided among eight competitive supplements for projects on six different tissues and

cell types. Of these, two were given to NIDDK investigators, which demonstrates the importance of regenerative medicine to the NIDDK portfolio.

Dr. Germino noted the complex science involved in learning about regenerative medicine, and the need to bring together biologists, engineers, clinicians, surgeons, and patient advocates. Some of the most promising applications of regenerative medicine fall within the NIDDK mission area, leading NIDDK to become the second largest funder of regenerative medicine in the NIH, behind only the National Heart, Lung, and Blood Institute. Promising applications include the development of new beta cells to replace those lost in type 1 diabetes or as a result of pancreatectomies, and the potential ability to manipulate fat cells to treat lipodystrophy or improve weight control. Both renal and gastrointestinal medicine deal with a variety of epithelial cell defects that may be addressed by either cellular or gene replacement therapies, whether it be for the kidney or the liver.

Dr. Germino raised several questions for Council members to consider, both for this meeting's presentation and at the upcoming September Council meeting when they will discuss broad issues relating to regenerative medicine. How can NIDDK:

- build and fund complex multidisciplinary research teams?
- address the many ensuing scientific, technical, and operational challenges?
- position itself to help foster both clinical and regulatory advances?

Dr. Germino concluded by asking Council members to determine what other information they need from staff to prepare for the comprehensive discussion on regenerative medicine in September.

Part One: Harnessing Insights into Beta Cell Plasticity for Regenerative Therapies
Dr. Maike Sander

Dr. Sheryl Sato, a program director in the Division of Diabetes, Endocrinology and Metabolic Diseases, introduced Dr. Maike Sander of the University of California at San Diego (UCSD). She is Director of the Pediatric Diabetes Research Center, and Co-Director of the Center on Diabetes in the Institute of Engineering in Medicine. Dr. Sander also is a Professor in the Departments of Pediatrics and Cellular and Molecular Medicine at UCS and is part of the Stanford Consortium for Regenerative Medicine. Dr. Sander holds two R01 grants, as well as a UC4 grant and has participated in various ongoing NIH projects, including the Beta Cell Biology Consortium (BCBC) and the Human Islet Research Network (HIRN). Her projects include teaming-up with geneticists, chromatin biologists, and computational biologists to perform functional analyses on cells derived from both type 1 and type 2 diabetic individuals.

Dr. Sander opened her remarks with an overview of regenerative approaches for the treatment of diabetes. Research in this area is currently focused on ways to increase beta cell mass. Approaches include reprogramming pancreatic alpha and acinar cells, and even intestinal cells, to become beta cells; increasing beta cell replication and directed differentiation of human pluripotent stem cells into beta cells or beta cell precursors, for transplantation into people with diabetes. She explained that the biotech firm Viacyte, Inc., has conducted two clinical trials—one culminated and another is underway—in which scientists have generated beta cell precursors and put them into encapsulation devices that allow nutrients in, while protecting them from the patient's immune system. The

results from the first clinical trial were disappointing due to the fibrotic response of the surrounding tissue that affected the long-term viability of the cells. The company is now combining engineering-based and cell-based approaches to develop a better encapsulation device.

Dr. Sander reported on a completed study and two ongoing studies performed in her own lab. The first was a collaboration with Viacyte, supported by the Beta Cell Biology Consortium, to differentiate human pluripotent stem cells into beta cell precursors *in vitro*. Dr. Sander showed that these precursor cells, once allowed to mature in vivo in mice, have many features of native human beta cells. In a second ongoing study, Dr. Sander's lab teamed with genome scientists at UCSD in the context of the NIH's Accelerating Medicines Partnership-Type 2 Diabetes (AMP-T2D) Consortium, and used a similar cell differentiation platform to look at how known genetic variants associated with T2D might affect beta cell development and function, and explained how using CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) technology to correct these T2D variants can restore normal beta cell function.

In the third study, currently performed in the context of HIRN's Consortium on Human Islet Biomimetics (CHIB), Dr. Sander's lab focuses on making highly functional pancreatic organoids in vitro, starting with human pluripotent stem cells and differentiating them into 3D structures that recapitulate some of the features of the human islet. For this project, she is collaborating with bioengineers at the University of California, Irvine, to first create a simulated "natural" environment in a micro-fluidic device composed of endothelial cell-derived blood vessels, then seed human pluripotent stem cell derivatives of the pancreatic islets into these devices to derive long-lived and highly functional pseudo-islets. She reported that her team has succeeded in creating such a vascularized pseudo-islet that can receive nutrient support through this artificial vasculature.

Dr. Sander also reported on her own effort to identify molecular targets for increasing beta cell replication. She pointed out that human beta cell mass has been shown to increase in pregnancy and obesity, and that this plasticity seems primarily driven by beta cell replication. This replication (and therefore regeneration) capacity has also been shown to decline rapidly with age. Dr. Sander's lab is investigating the following questions:

- What are the molecular characteristics of the proliferative beta cell?
- What triggers age-dependent decline in beta cell proliferation?
- Is this decline coupled with functional changes and can we identify a molecular switch in the beta cell that we can target to change beta cell state and beta cell mass?

What makes answering these questions difficult is the fact that even in the neonatal pancreas, only a small percentage of beta cells replicate, and this replication declines dramatically within the first four weeks of a mouse's life or the first year of life for a human. Because ensembleomics analyses performed on thousands of cells dilutes the signal of these rare replicating beta cells, finding out what genes are specifically expressed or repressed during replication is almost impossible. To overcome this problem, Dr. Sander's lab has generated single cell RNA sequencing measurements at five different time points during the postnatal period using a computational methodology that can analyze 500 individual beta cells per experiment. After analyzing the gene signatures specific for proliferative beta cells they could conclude that during the postnatal period, replicating beta cells produce more mitochondrial reactive oxygen species, which was consistent with earlier studies

showing that intracellular metabolism and glucose itself are key drivers of beta cell proliferation.

Dr. Sander's lab then tried to identify molecular targets by which they could manipulate this nutrient-dependent regulation of beta cell proliferation using an unbiased proteomics approach. They collaborated with a team at The Scripps Research Institute, which has developed technology to quantify proteins in vivo, as well as with collaborators specialized in metabolomics, to explore how metabolism is rewired during beta cell maturation and aging. They ended-up identifying sirtuins (and in particular Sirtuin 2) as regulatory proteins that can link external nutrient concentrations to proliferative responses in beta cells. Dr. Sander has now approached several different companies to develop *in vivo* tools to study Sirtuin 2, but noted that she has found it challenging to find organizations interested in exploring regenerative targeting.

She pointed out that her discoveries would not have been possible without outstanding collaborators from different fields, and that working in larger teams and combining expertise from different disciplines is key to making scientific advances.

Council Questions and Discussion

How much of your observations in mice carry over to humans?

In the proteomics screen performed by Dr. Sander's lab, 30 candidates were screened for whether they can increase beta cell proliferation in rodents and in humans. Out of the 30 candidates, seven were effective in the mouse model and three were effective in the human model.

Are there any niche components that help regulate islet cells? Have you figured out which other cell types are influencing the beta cell?

Dr. Sander explained that beta cells function by communicating with other endocrine cells or vascular endothelial cells. These other cell types are critically important. She reported that they have not identified which cell types influence the beta cell because they have not yet analyzed the whole islet, but that the field of "islet niche signaling" is become an important and active area of investigation.

How do you envision macro-fluidics and other technologies facilitating this knowledge transition from the single cell?

Macro-fluidics are essential to build ex vivo models of the entire islet that can mimic the in vivo condition. The next step using these in vitro platforms is to provide some insight into how beta cells are killed and how to prevent that in type 1 diabetes.

Have you looked at spatial orientation differences in the markers of different beta cell subtypes?

Dr. Sanders reported that this would be an interesting investigation that may provide insights into how cells communicate, but that they have not started such studies yet.

Part Two: Balancing Multi-Disciplinary Team Science and Individual Lab Science
Dr. Sato and Dr. Sander

Dr. Sato reported on two large team projects funded through the Special Statutory Program for Type 1 Diabetes Research: the Beta Cell Biology Consortium (BCBC) and the Human Islet Research Network (HIRN).

The BCBC started in the early 2000s, with the goal of enabling the development of cellular replacement therapies for type 1 diabetes by promoting basic research into the developmental biology of the endocrine pancreas using mouse models and combine this knowledge with the latest research in stem cell biology. The ultimate goal of the BCBC was to try to generate a functional beta cell *in vitro*, starting with human pluripotent stem cells, that could be used in the longer term as a cell source for therapy, as well as a means to model and study disease in *vitro.*

The first efforts were focused on developing monoclonal antibodies as a tool for sorting differentiated cells. The BCBC then focused on developing robust protocols to identify factors driving cell differentiation. This effort has still not reached complete maturation, as Dr. Sander's presentation has illustrated.

In 2014, the mission shifted to understanding how beta cells are lost in type 1 diabetes, and to find innovative strategies to protect or replace functional beta cell mass, which led to the launch of the HIRN. The funding structure changed from the BCBC's 16 U01s, to five smaller scientific consortia to take advantage of technology to develop new methods for basic research into type 1 diabetes. Each of these consortia are focusing on a different aspect, including targeting and regeneration; beta cell death and survival; humanized mouse models and modeling autoimmune interactions, and the building of human islet biomimetics.

Dr. Sato reported that the team science approach accelerated the translation of basic research toward the clinic by promoting the application of exciting new technologies and by enabling high risk, high reward discovery-based projects. The efforts helped build a community of investigators who are now invested in regenerative medicine research and helped forge relationships not only across institutes and centers at NIH, but also with the extramural scientific community.

However, she said, these projects can be time consuming for the Program Staff involved. They require a lot of personal effort and frequent interactions with investigators, as well as solving difficult issues of trust around timely data and resource sharing, especially when dealing with unpublished work. Team science can also be very intense due to strong personalities and issues of scientific overlap. On balance, however, the pluses outweigh the minuses.

Dr. Sato then turned back to Dr. Sander, who discussed how to prioritize scientific issues in regenerative therapies for type 1 diabetes, and gave her perspective on team science.

While it is unclear whether regenerative medicine ultimately will result in effective therapies for type 1 diabetes, Dr. Sanders says that she has identified several strengths and hurdles during her time contributing to several consortia and to this field of regenerative medicine. In the area of

promoting beta cell replication, companies seem hesitant to invest in this effort until a beta cell-specific target or protein has been identified, and a small molecule or biologic to target it. However, from what is known about the beta cell proliferation, the same sort of pathways and proteins that regulate these processes are also in other cells, which makes it unlikely that researchers will ever discover a target specific to the beta cell.

In the area of cell replacement, Dr. Sander thinks that this approach will only be effective in the context of an implanted device. Regarding autologous beta cell replacement, where beta cells can be produced from a patient's own skin and re-implanted, Dr. Sander feels that the strategy is probably not going to be cost-effective and would be difficult to pursue from a regulatory point of view. For her, beta cell replacement using encapsulation strategies, which would involve surgery and monitoring, will most likely be useful to and reserved for subgroups of people with diabetes, particularly type 1. However, she sees greater opportunities for the use of pluripotent cell-derived in vitro platforms for drug discovery.

Dr. Sander said she believes that team science is critical to scientific progress because it allows investigators to take new approaches, apply new technologies, and engage in high-risk/high-gain research that is difficult to undertake in the context of a regular R01 mechanism.

She said that teams work best when they bring complementary expertise and team members are completely vested in jointly developing and conducting the science. But this is a different way of doing science that has to be learned.

She explained that the team approach is an important driver for innovation by bringing together different perspectives and providing early access to reagent tools and data. For the next generation of scientists, team science offers broader exposure to different fields that allows them to make connections and build their own interdisciplinary networks. Established investigators in multidisciplinary consortia have opportunities to work on larger-scale efforts and glean from them specific ideas they can explore in more targeted projects in their own labs.

Dr. Sander also raised some potential disadvantages of team science. Multidisciplinary projects require advanced research coordination skills to gather information from different collaborators and combine that information to create agendas. Graduate students and post docs—who often take on these roles in research projects—may not have these advanced skills at that stage of their careers. Team science challenges the usual trajectory for junior investigators, who usually start with their own project with an R01 grant, then move to multi-disciplinary projects. Another issue is the currency of advancement in our academic system, which is still based on publication of research. In a jointly conceived project, there isn't single ownership of the project, which makes it difficult for junior investigators to publish original research. In a consortium structure, senior investigators may hold too much control over who participates in projects, making it difficult for some junior researchers to advance.

Dr. Sander also pointed out that consortia grants often are awarded for four to five years. Tackling difficult, multi-layered questions, however, often requires continued engagement over a longer period, and that is hard to maintain when funds are not available and people go their separate ways. On the other hand, it's good to build some fluidity into the consortium. She pointed to the HIRN, in

which teams join and leave the consortium on a staggered schedule.

Open sharing of data, expertise, and tools works best when team members have different expertise and goals. Dr. Sander encouraged transparency and visibility in the larger scientific community so that the consortium does not become a closed-system or "club."

Clinical translation presents additional challenges because academic investigators working in a team may not progress as efficiently as one investigator working alone. Another issue is how these teams connect to pharmaceutical companies.

Council Questions and Discussion

Olivier Blondel, Ph.D., Program Director, Division of Diabetes, Endocrinology, and Metabolic Diseases, moderated a discussion of the presentations by raising three questions.

Question 1: Should more emphasis be placed on in vivo/in situ tissue regeneration and repair in type 1 and type 2 diabetes or in vitro/ex vivo disease modeling and drug-screening platforms, and cell replacement?

The Council discussed the benefits and potential pitfalls of these different approaches. Deriving mature, functional cells from induced pluripotent stem cells for replacement therapy is being explored in other diseases, but Dr. Sander felt this approach would not work well for diabetes, except maybe for some cases of type 1. She explained that because the cells must be autologous, they must be made for each patient individually, and there may not be a way to do this in a cost-effective way. The estimated cost is about $1 million per patient.

Council members added that a multi-faceted approach that includes basic discovery, disease modeling and in vivo modeling is needed to move discoveries forward and see whether therapies that work in an ex vivo model can also work in the tissue niche following transplantation, in the context of the surrounding cell types. A team science approach may increase the chances of success in problematic lines of research such as encapsulation techniques for immune protection and tolerance. The worldwide prevalence of diabetes may also attract pharmaceutical companies' interest and accelerate progress toward more effective and efficient technologies and lower the per patient price of the therapy.

Question 2: How can we better promote partnerships among bioengineers, cell biologists, and clinicians to accelerate regenerative medicine research?

Previous experience—such as the National Center for Advancing Translational Sciences (NCATS) consortium—has proven that scientists will work together to meet the criteria for funding in grant applications. However, that does not remove the potential challenges involved in carrying out team science. Council members pointed out that it takes different skills to create a team and to maintain a team, and consortia may need support to make that shift. Dr. Blondel brought up that NIH has grant mechanisms for two-step initiatives where the funding in the first two or three years is lower and focused on team-building. Once a team demonstrates true synergy and collaboration, they move on to the second phase.

The Council discussed different approaches to the challenge of evaluating and identifying junior investigators for promotion in a team science environment, including providing a mechanism by which junior investigators can develop their own ideas within the team context. The Stand Up to Cancer Consortium has had a protocol in which junior investigators handle publications and are either the first or last author on journal articles.

Dr. Blondel said that the HIRN has had a good response from holding specific competitions just for Early Stage Investigators (ESIs), which eliminates competition between senior and junior investigators, and provide ESIs with two-year support to develop a research project of their own that can serve as a basis for their first R01 application.

Question 3: What are the opportunities to leverage NIDDK-supported regenerative medicine consortia to advance regenerative medicine relevant to the NIDDK mission and the translation of discoveries to the clinic?

Council members discussed the potential advantages of bringing in different stakeholders—such as pharmaceutical companies, patient advocacy groups and other government agencies—into the research process earlier to create buy-in and work towards partnerships and strategies for more efficient hand-off of research. Suggestions included bringing representatives from industry into the research process to help devise commercialization strategies and move concepts to the clinic. The Beta Cell Biology Consortia brought in industry representatives and now those companies are carrying out clinical trials. Partners from pharmaceutical companies participated in meetings and made presentations as part of the Tissue Chip Consortium initiated by NCATs in 2012. Patient groups and disease-oriented foundations may also help create momentum for research projects. It may also help to involve the FDA because a lot of novel therapeutic approaches don't have a known regulatory pathway, which makes industry cautious about pursuing.

The Council discussed possible mechanisms, including:

- Alternative ways to reactivate funding, other than re-application and peer review
- Public-private partnerships to initiate research consortia
- Maintenance of an advisory role for NIDDK after hand-off to other stakeholders, perhaps through the new Office of Clinical Trials Support
- Investigation of crowdsourcing or other alternative funding structures

Dr. Rodgers thanked the presenters and Council members for their input and wrapped up the conversation, promising to revisit the topic after the third of the three presentations on regenerative medicine.

VII. SUBCOMMITTEE MEETINGS

VIII. REPORTS OF SUBCOMMITTEES CONSIDERATION OF REVIEW OF GRANT APPLICATIONS.

IX. ADJOURNMENT

Dr. Rodgers

Dr. Rodgers expressed appreciation on behalf of the NIDDK to the Council members, presenters, and other participants. He thanked the Council members for their valuable input. There being no other business, the 207th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m.

I hereby certify that, to the best of my knowledge, the foregoing summary minutes are accurate and complete.

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