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 208th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m. on September 7, 2018, in Building 31, C-Wing, 6th Floor Conference Center, Conference Rooms 10, the NIH Campus, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Joseph Bonventre
Dr. David D'Alessio†
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†
Dr. Paul H. Lange
Dr. Richard Peek
Dr. Jeffrey Pessin
Dr. Alan Saltiel
Dr. Ronald Sokol
Ms. Lorraine Stiehl
Ms. Pamela Taylor
Dr. Beverly Torok-Storb

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

Also, Present:

Dr. Griffin Rodgers, Director, NIDDK
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. Karl Malik, Executive Secretary, NIDDK Advisory Council

B. NIDDK STAFF AND GUESTS

Abbott, Kevin – NIDDK
Abraham, Kristin – NIDDK
Ajose, Aricia – NIDDK
Akolkar, Beena – NIDDK
Anderson, Dana – NIDDK
Arreaza-Rubin, Guillermo – NIDDK
Barnard, Michele – NIDDK
Barthold, Julia – CSR
Begum, Najma – NIDDK
Bekirov, Iddil – NIDDK
Berti-Mattera, Liliana – CSR
Best, Caroline – Am. Urol. Assoc.
Bishop, Terry – NIDDK
Blondel, Olivier – NIDDK
Boerboom, Lawrence – CSR
Bourque, Sharon – NIDDK
Burch, Henry – NIDDK
Burgess-Beusse, Bonnie – NIDDK
Camp, Dianne – NIDDK
Castle, Arthur – NIDDK
Chowdhury, Bratati – NIDDK
Connaughton, John – NIDDK
Curling, Michell – NIDDK
Dayal, Sandeep – NIDDK
Densmore, Christine – NIDDK
Dirks, Dale – Health & Med. Counsel of Washington
Doherty, Dee – NIDDK

Donohue, Patrick – NIDDK
Doo, Edward – NIDDK
Drew, Devon – NIDDK
Duggan, Emily – NIDDK
Evans, Mary – NIDDK
Fleischhacker, Sheila – NIDDK
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gansheroff, Lisa – NIDDK
Garcia, Martha – CSR
Gonzales, Ryan – NIDDK
Gossett, Daniel – NIDDK
Greenwel, Patricia– NIDDK
Guo, Xiaodu – NIDDK
Haft, Carol – NIDDK
Hall, Sherry – NIDDK
Hanlon-Tilghman, Mary – NIDDK
Hansen, Dani – NIDDK
Hong, Julie – NCI
Hoofnagle, Jay – NIDDK
Hoover, Camille – NIDDK
Hoshizaki, Deborah – NIDDK
Hyde, James – NIDDK
Ivins, Jonathan – CSR
James, Stephen – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Ketchum, Christian – NIDDK
Kimmel, Paul – NIDDK
Kirkali, Ziya – NIDDK
Kozel, Peter – 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
Morris, Ryan – NIDDK
Mullins, Christopher – NIDDK
Narva, Andrew – NIDDK
Nguyen, Thuthuy – NIDDK
Norton, Jenna – NIDDK
Olumi, Aria – AUA/Mass General Hospital
Otradovec, Heidi – NIDDK
Parsa, Afshin – NIDDK
Pawlyk, Aaron – NIDDK
Payne, January – NIDDK
Perrin, Peter – NIDDK
Perry Jones, Aretina – NIDDK
Pike, Robert – NIDDK
Pileggi, Antonella – CSR
Portnoy, Matthew – OD
Repique, Charlene – NIDDK
Roberts, Tibor – NIDDK
Rojas, Raul – CSR
Rosenberg, Mary Kay – NIDDK
Roy, Cindy – NIDDK
Sanovich, Elena – NIDDK
Sato, Sheryl – NIDDK
Shepherd, Aliecia – NIDDK
Sherker, Averell – NIDDK
Sierra-Rivera, Elaine – CSR
Silva, Corinne – NIDDK
Singh, Megan – NIDDK
Smith, Jaime – NIDDK
Smith, Philip – NIDDK
Spain, Lisa – NIDDK
Spruance, Victoria – NIDDK
Star, Robert – NIDDK
Stoeckel, Luke – NIDDK
Tatham, Thomas– NIDDK
Teff, Karen – NIDDK
Thornton, Pamela – NIDDK
Tilghman, Robert – NIDDK
Tong, Betty – NIDDK
Torrance, Rebecca – NIDDK
Tuncer, Diane – NIDDK
Unalp-Arida, Aynur – NIDDK
Voss, Alyssa – NIDDK
Wallace, Julie – NIDDK
Wang, Xujing – NIDDK
Wilkins, Kenneth – NIDDK
Williams, Keyera – NIDDK
Yang, Jian – NIDDK
Yanovski, Susan – NIDDK

A. ANNOUNCEMENTS

Dr. Rodgers

Council Member News

Dr. Rodgers opened the meeting by recognizing five members who were concluding their Advisory Council service with the September meeting: ***Dr. Mark Donowitz*** and ***Dr. Lee Kaplan*** served on the Council's Digestive Diseases and Nutrition Sub-Council. ***Dr. Alan Saltiel*** and ***Ms. Pamela Taylor*** served on the Council's Diabetes, Endocrinology, and Metabolic Diseases Sub-Council. Finally, ***Dr. Joseph Bonventre*** served on the Council's Kidney, Urology, and Hematology Sub-Council.

The retiring Council members had been honored at a special dinner the previous evening, Dr. Rodgers said, and had also received two certificates of appreciation, one signed by U.S. Secretary of Health and Human Services Alex Azar and another by Dr. Rodgers and NIH Director Dr. Francis Collins. Since Dr. Kaplan had been unable to attend the recognition dinner, Dr. Rodgers summarized the many contributions he has made to the Council, NIDDK, NIDDK's Clinical Obesity Research Panel, and to the Obesity Society, where he will now serve as its President-Elect.

Additionally, Dr. Rodgers also shared some news about various current and former Council members:

Former Council member and longtime NIDDK grantee ***Dr. Jeffrey Gordon*** has received the 2018 Copley Medal from the Royal Society in Great Britain for "his contribution to understanding the role of gut microbial communities to human health and disease." The Copley Medal was first awarded in 1731 and is the Society's oldest and most prestigious award. Other notable winners include Benjamin Franklin, Charles Darwin, Albert Einstein, and Dorothy Hodgkin. Dr. Gordon is the Robert J. Glasser Distinguished University Professor at Washington University in St. Louis. His work has helped to revolutionize our thinking about the interactions of gut microbial communities and how these microbial communities impact host biology.

Longtime NIDDK grantee ***Dr. Gianrico Farrugia*** has been elected the new President and CEO of the Mayo Clinic. Working in the field of neurogastroenterology and gastroparesis, Dr. Farrugia has published more than 250 articles on genomics and the treatment of disorders of gastrointestinal motility.

Dr. Jennifer A. Lewis, who is subcontracted by the Division of Kidney, Urologic, and Hematologic Diseases (KUH) for work on the ReBuilding a Kidney Initiative, was recently elected into the National Academy of Sciences. Dr. Lewis is the Hansjorg Wyss Professor of Biologically Inspired Engineering at the School of Engineering and Applied Sciences at Harvard University, where her lab participates in the activity involved in 3-D printing of soft functional materials for use in printed electronics, optical materials, lightweight structures, and microvascular architecture for cell culture and tissue engineering.

On a sadder note, former Advisory Council member ***Dr. George Stamatoyannopoulus***, a leading physician/scientist in genetics and hematology, passed away in June at age 84. A native of Greece who spent his career at the University of Washington, he published more than 400 papers that contributed to research advances, including the structure and function of hemoglobinopathies, the genetics of thalassemia syndrome, and the regulation of globin genes. "Dr. Stam", as most people referred to him, led the foundation of the American Society for Gene and Cell Therapy and went on to become its first President in 1996. He was also President in 1992 of the American Society of Hematology.

NIDDK Staff News

Dr. Rodgers reported several staffing changes within NIDDK:

Dr. David Saslowsky has been promoted to Deputy Director for Basic Science in the Division of Digestive Diseases and Nutrition (DDN). When he arrived at NIDDK three years ago, Dr. Saslowsky began by overseeing the career development "K" award portfolio for DDN. Since then he has served as the program official for DDN's intestinal stem cell consortium and is co-representing NIDDK as the program team lead for the Stimulating Peripheral Activity to Relieve Conditions (SPARC) common fund program. As Deputy Director for Basic Science, Dr. Saslowsky will help coordinate the development of basic science initiatives, research priorities, and facilitate overall administrative duties within the division.

Dr. Christine Maric-Bilkan, a former part-time program officer within the Renal Pathophysiology and Acute Kidney Injury Programs in the Division of Kidney, Urologic and Hematologic Diseases (KUH), has rejoined the division as a full-time program officer. Her duties within KUH will include advising the division on topics such as sex differences in biology and renal pathophysiology. Dr. Maric-Bilkan, who received her training from the University of Melbourne in Australia, and University College in London, has received numerous awards, including the American Physiologic Society New Investigator Award and the American Society of Hypertension Young Scholar Award.

Dr. Victoria Spruance has also joined KUH as a fellow in the Presidential Management Fellow Program. She completed her Ph.D. in neurosciences at Drexel University and is interested in science policy and outreach.

KUH scientific program manager ***Dr. Denise Gaughan*** is leaving NIDDK to accept a position at the Centers for Disease Control (CDC) in Atlanta. An epidemiologist, she assisted KUH staff by applying causal inference methods to observational data.

Dr. Charlene Repique joined NIDDK's Scientific Review Branch as a scientific review officer in May 2018. She earned her Ph.D. in biomedical sciences from Northeastern University, and then completed postdoctoral research training at the Food and Drug Administration's Center for Biologic Evaluation and Research. She has also served as a scientific review officer for the Department of Defense Prostate and Breast Cancer Research Programs and was a science manager at the Susan G. Komen Breast Cancer Research Program. Most recently, she worked with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) as a small grants coordinator for the U.S.

Embassy in Zambia in Southern Africa.

Dr. Peter Kozel joined the Scientific Review Branch in June 2018 as a scientific review officer. He earned his doctorate at the University of Cincinnati, and then was selected as a Mirzayan Science and Technology Policy Fellow at the National Academy. Before joining NIDDK, he was at the NIH's Center for Scientific Review in the Healthcare Delivery and Methodologies Integrated Review Group in the Division of AIDS, Behavior, and Population Science. He managed the Biomedical Computing and Health Informatics Study Section, and the review of applications in statistical genetics, health informatics, international development, and mobile health. Before that, he was a scientific review officer at the National Center for Complementary and Integrative Health.

Dr. Rodgers also reported with sadness the death of ***Dr. Francisco Calvo,*** former Chief for Scientific Review Branch for NIDDK. He joined the Institute in 1987 as Director of the Endocrinology Research Program and project officer in the National Hormone and Pituitary Program. He then joined DK's Scientific Review Branch in 1990 and rose to become its chief in 2001. During his long career, he served on several committees, both within NIDDK and NIH-wide, including the NIDDK Awards Committee, the Working Group for Clinical Trials, the Loan Repayment Steering Committee, and the Review Policy Committee.

Dr. Rodgers also made special note of the scheduled December retirement of ***Dr. Judith Fradkin***, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases (DEM). After receiving her medical education at the University of California, San Francisco, and Beth Israel Deaconess Hospital in Boston, she completed fellowship training at the Clinical Endocrinology Branch of NIDDK. She joined the extramural program at NIDDK as the Chief of the Endocrinology and Metabolic Diseases Branch in 1984. Her first challenge in that position was to oversee the termination of the longstanding National Pituitary Distribution Program following the discovery that some patients receiving human pituitary-derived growth hormone had developed Creutzfeldt-Jakob Syndrome. Her leadership legacy in this area endures as the division continues to monitor the thousands of patients who received this human growth hormone during the program's 25 years.

Dr. Fradkin became the Director of DEM in 2000, in which role she quickly became adept at planning and overseeing the unusually tight funding schedules associated with the Special Diabetes Program, as Congress has often voted on authorization and funding for this key program late in the fiscal year. She has also served as an ambassador for NIDDK and NIH to other agencies within the government, patient advocacy organizations, and scientific societies. Her work has won prestigious awards from the American Diabetes Association, the Juvenile Diabetes Research Foundation, and the American Association for Clinical Endocrinologists.

The final NIDDK staff announcements concerned Dr. Rodgers. Deputy Director Dr. Gregory Germino announced that ***Dr. Griffin Rodgers*** has received several notable recognitions lately. He was selected by the National Medical Association in conjunction with the Harlem Fine Arts Show to receive the prestigious Harlem Fine Arts Show Lifetime Achievement Award during its inaugural salute to African Americans in medicine. Dr. Rodgers was honored at an event in Washington, D.C., in June for his outstanding contribution to the medical field, and his impact particularly on the African American community.

In July, Dr. Rodgers was elected and formally instated as a fellow of the Royal College of Physicians in London. In addition, the Association of American Medical Colleges (AAMC) has announced that Dr. Rodgers will receive the 2018 Herbert W. Nickens Award in November. The AAMC established the Herbert W. Nickens Memorial Fund to continue advancing Dr. Nickens's concerns about the educational, societal, and healthcare needs of minorities. The award notes that Dr. Rogers has dedicated his career to eliminating racially based health disparities while creating opportunities for underrepresented minorities within the biomedical workforce.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 207th COUNCIL MEETING

Dr. Rodgers

The Council approved, by voice vote, the Summary Minutes of the 207th Council meeting, which had been sent to them in advance for review.

III. FUTURE COUNCIL DATES

2019

January 16-17 (Wednesday and Thursday)
Natcher Conference Center, Building 45

May 8-9 (Wednesday and Thursday)
Porter Neuroscience Building, Building 35

September 11-12 (Wednesday and Thursday)
Natcher Conference Center, Building 45r

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

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 handle 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 reminded the Council that the 2019 budget process started with the release of the President's proposal that cut the National Institutes of Health budget, including $6 million less for NIDDK. The budget request also proposed merging three agencies into the NIH: the Agency for Healthcare Research and Quality (AHRQ), the National Institute of Occupational Safety and Health (NIOSH), and the National Institute of Disability, Independent Living, and Rehabilitation Research (NIDILRR). The President's proposal included full funding for the Fogarty Center and did not contain a provision to reduce indirect costs and grants. When the House and Senate appropriations committees considered the proposal, they did not include the provisions to consolidate those agencies within NIH. Dr. Collins testified before the House and Senate Labor-HHS-Education appropriations subcommittees, and the subcommittees released their proposed 2019 funding for NIH.

The House proposal included $38 billion for the NIH, an increase of 3.4 percent over FY 2018. The Senate included $39.084 billion for NIH, an increase of 5.4 percent over FY 2018. NIDDK's share in the House proposal would be $1.994 billion (a 1.17 percent increase); the Senate proposal includes $2.031 billion (a 3.05 percent increase). These proposals do not include the Special Diabetes Program funds. Targeted funding for projects such as those included in the 21st Century Cures Act, the All of Us program, and research into Alzheimer's disease, a universal flu vaccine, and antibiotic resistance accounts for the percentage differences between the increase for NIH as a whole and the individual budgets for Institutes and Centers, such as NIDDK.

The Senate Committee on Appropriations passed its bill on June 29, and the House Committee on Appropriations followed on July 11. The full Senate passed the Labor-HHS-Education bill coupled with the Defense spending bill. This was a bipartisan effort that met the priorities of both parties. Dr. Rodgers noted that this is the fastest an appropriations package has moved through the Senate since 1994. In addition, a House-Senate conference is scheduled on this bill, a good sign that the appropriations bills for Labor-HHS-Education and Defense may be passed before the start of the 2019 fiscal year, October 1, 2018.

VI. UPDATE FROM THE DIRECTOR, NATIONAL CANCER INSTITUTE
Dr. Norman E. Sharpless

Dr. Rodgers introduced Norman ("Ned") Sharpless, Director of the National Cancer Institute. Dr. Sharpless was sworn as the 15th Director of NCI on October 7, 2017. Prior to joining NCI, Dr. Sharpless was Director of the Lineberger Comprehensive Cancer Center at University of North Carolina (UNC) since January 2014. Dr. Sharpless earned his medical degree from the UNC School of Medicine and completed his internal medicine residency at Massachusetts General, followed by a fellowship in hematology/oncology at Dana Farber Partners Cancer Center. Both

are associated with Harvard Medical School in Boston. With the Cancer Moonshot and other initiatives underway, it is an exciting time for NCI.

Dr. Sharpless thanked Dr. Rodgers and Dr. Malik for the opportunity to address the Council. He started by highlighting some of the ways NCI is different from other parts of NIH. This difference, he explained, goes back to the War on Cancer and the National Cancer Act of the 1970s. Unlike other IC directors, the director of NCI is a presidential appointment, which means that the job tends to have a much shorter tenure than other director positions.

According to the provisions of the National Cancer Act of 1971, NCI bypasses the NIH budget process and instead makes its budget request directly to Congress. The National Cancer Act also established the National Cancer Advisory Board of White House-appointed directors (which means that NCI effectively has two advisory councils), and established the NCI Cancer Center Program, the Frederick National Laboratory for Cancer Research, and the Clinical Trials Network. These programs are in addition to NCI's extramural grants program and intramural research programs and the Institute's work at the Clinical Center, where NCI has a large portfolio.

Dr. Sharpless talked in more detail about a few of the programs established by the National Cancer Act:

Frederick National Laboratory
The purpose of establishing the Frederick National Laboratory was to give NCI the ability to start projects rapidly. As a federally funded research-designated center, Frederick National Laboratory is not required to use traditional contracting mechanisms, so it is easier to start projects in response to needs, and then end them if they are no longer needed. Alternatively, projects can be transferred to the intramural or external research community as they become better established. Examples of projects that started at Frederick include The Cancer Genome Atlas and the RAS Initiative. The RAS Initiative, he explained, brings together extramural academic researchers and industry representatives to focus on the structural biology and molecular details of RAS signaling, a mutation implicated in 30 percent of cancers, especially pancreatic and colorectal cancers.

Frederick National Laboratory also includes the following two facilities:

- Nanotechnology Characterization Lab, which works with both academic investigators and biotech partners to develop, characterize and reformulate cancer therapeutics using nanotechnology platforms.
- National Cryo-Electron Microscopy facility, which offers the latest imaging technology as well as help with data analysis.

SEER Program
The National Cancer Act also mandated the creation of a national database of cancer, which has evolved into the Surveillance, Epidemiology, and End Results (SEER) Program. This program, founded by NCI in 1973, supports research on the diagnosis, treatment and outcomes of cancer. By federal and state law, all states have cancer registries. SEER covers 34 percent of the population, with 550,000 incident cases added annually; the remainder of the population is covered by state registry programs, which are administered by the Centers for Disease Control and Prevention.

SEER and state registry programs at the CDC combine to create a national registry of cancer incidence and mortality in all 50 states. He pointed out that, because the SEER database pre-dates and is exempt from requirements of the Health Insurance Portability and Accountability Act of 1996, it contains some of the best epidemiologic information available to health services and cancer researchers to get a sense of what is happening to cancer patients in the real world.

President's Cancer Panel
As part of the National Cancer Act, NCI administers the President's Cancer Panel, an independent body appointed by the President to study topics relevant to cancer. An example of their work is the report on HPV vaccination, which concluded that, based on the evidence, the vaccine is safe and effective for preventing some kinds of cancer. The panel's most recent report, which was released earlier in 2018, covers drug pricing.

NCI-Designated Cancer Center Program
There are currently 70 NCI-designated Cancer Centers. States and medical centers actively seek this designation, and there are probably 100 additional centers that aspire to be NCI-designated. The program gives NCI active ties in communities across the country, including the ability to conduct clinical trials and receive feedback about the national cancer research enterprise. However, he noted, the majority (85 percent) of patients in the United States do not go to NCI-designated cancer centers. To reach these patients, NCI has created the National Community Oncology Research (NCOR) Program with 50 sites and approximately 900 satellites through which patients in all 50 states can enroll in NCI-sponsored clinical trials. Recently NCI launched the MATCH trial that enrolled 6,000 patients nationally two years ahead of schedule through the NCOR program.

Annual Report on the Status of Cancer
The National Cancer Act also requires NCI to produce an annual report to the nation on the status of cancer. The 2018 report is based on data through 2015 and shows that, with wide bipartisan support for cancer research and massive investment on the part of the biopharmaceutical and biotechnology industries, there has been real progress in cancer research and outcomes. Deaths from most cancers are declining at an annual rate of 2 percent. The exceptions to this are pancreatic and liver cancers, the second of which is relevant to NIDDK. Incidence of liver cancer has increased, as has mortality. In the past, most liver cancer was associated with viral hepatitis, but the number of cases associated with alcoholic cirrhosis and obesity are on the rise. NCI is working with other groups to explore how to address this increase.

Dr. Sharpless also pointed to developments in lung cancer, which kills more Americans than breast, colon, and prostate cancers combined. Recent therapeutic advances in lung cancer have led to drugs that put the disease into remission and even cure some cases of metastatic disease.

Looking at NCI's clinical trials portfolio, a focus in the future will be "de-escalation" trials to look at reducing the amount of therapy needed for effective treatment or cure of disease. He pointed to the TAILORx Breast Cancer trial that showed that for most women with early state estrogen-receptor positive breast cancer, hormone therapy alone is effective, sparing them the side effects of chemotherapy. Reducing the need for chemotherapy may lead to savings of up to $1 billion a year, Dr. Sharpless noted.

NCI Intramural Research in Immunotherapy
He also pointed to groundbreaking work on immunotherapy by Dr. Steve Rosenberg in the NCI intramural program. This work has led to development of treatment that cures, or at least achieves very durable remissions, for advanced solid tumors that do not respond to other treatments. The therapy uses patients' own immune cells to attack their own cancers. This highly individualized therapy has led to remarkable results and minimal toxicity, but at a very high cost. The next step is to figure out how to make this therapy available to more patients.

Dr. Sharpless pointed out that NCI has been a leader in immunotherapy since the 1960s when Dr. Michael Potter discovered monoclonal antibodies. The first FDA-approved immunotherapy drug for renal cancer was Interleukin-2, based on work by Dr. Bob Gallo at NCI. Developments in this field continue. In response, NCI is stepping up its ability to make autologous T-cells for use in multisite clinical trials. Similarly, the Clinical Center is also building its own T-cell engineering facilities to increase the availability of engineered T-cells on the NIH campus.

Dr. Sharpless explained that NCI's intramural research program has two parts: the Center for Cancer Research (CCR), which conducts both clinical and basic research; and the Division of Cancer Epidemiology and Genetics (DCEG), which focuses on cancer epidemiology, including incidence and environmental carcinogen risk. He pointed to a study from the DCEG into the mechanism behind checkpoint agents like pembrolizumab and nivolumab. By analyzing data from The Cancer Genomic Atlas, scientists determined which types of tumors were more likely to respond to these agents. This led to a new standard of care by which tumor samples are sent to get a neoantigen score, which indicates whether the tumor is likely to respond to this type of therapy. Since 2014, this method has moved into common usage, with reimbursement from Medicare. Even a subset of breast cancers appears to respond to checkpoint inhibitors.

Cancer Moonshot
The 21st Century Cures Act created the Cancer Moonshot, which provides $1.78 billion to the NCI over seven years. Dr. Sharpless explained that 2019 is the peak year of that funding, at $400 million. The focus of this program is to accelerate clinical translation—not to fund basic science or train scientists. This is "any year funding," which allows NCI to spend money beyond the year in which it is appropriated, for maximum efficiency. A Blue-Ribbon Panel first convened in 2016 to advise NCI on the program on the top 10 priority areas. While it is too soon to point to accomplishments of the Moonshot effort, Dr. Sharpless remains enthusiastic about the potential and vision of the program.

Areas of Future Focus
When Dr. Sharpless became NCI director, he talked to former NCI directors, federal officials, patients, advocates, doctors, scientists and cancer center directors to get input on what NCI does well, what NCI could do differently or better and what problems in cancer research are well suited for NCI to tackle. This process identified three areas of focus:

Clinical Trials: Dr. Sharpless explained that the high cost of clinical trials in cancer is in part related to the fact that each type of cancer—breast cancer, lung cancer—are actually many different

diseases that respond differently to available treatments. This makes clinical trials very challenging. NCI is looking at using smaller trials or pragmatic trial design (without a control arm) to reduce the per-patient cost of cancer clinical trials.

One example of this is the MATCH trial, which is investigating metastatic advanced cancer. With no standard therapy, patients have their tumors sequenced and are allocated to a therapy based on molecular genetics. This trial has 6,000 patients at 1,100 sites across the country, making it the fastest-accruing trial in NCI history. The trial has 700 allowed therapies and 10-15 percent of patients in the trial will have their therapy changed based on the sequencing results. For the second phase of the trial, patients are identified based on mutations found by commercial sequencing labs, resulting in even higher enrollment rates.

Basic science: Dr. Sharpless said he believes basic science is most likely to hold the key to understanding cancer, and the best way to support basic science is through research project grants (RPGs) that fund investigator-initiated science, which often includes creative, change-the-world innovations. The new NCI budget includes a $150 million increase for the RPG pool.

Workforce development: NCI has also started to award R37 grants, which are Merit Awards to Early Stage Investigators. These are 5-year awards that include the same budget as an R01 but also have an option to extend for two years without going through the competitive renewal process, giving junior scientists access to 7-year awards before they receive tenure. Other early stage investigators are continuing to get R01 grants, in effect forming a "control arm" that will allow NCI to evaluate which funding method is most effective.

Big Data: Another goal is to expand the availability and usability of datasets and increase interoperability among datasets to increase understanding of the etiology and progression of disease as well as real-world treatment responses. Strategies include supporting links among existing datasets, maintaining the data ecosystem, creating common data standards and incentives for data sharing and aggregation.

Dr. Sharpless pointed to ways NCI is working with other ICs within the NIH. For example, one study is looking at ways to predict which patients with type 2 diabetes are at increased risk for pancreatic cancer. One percent of people with type 2 diabetes will develop pancreatic cancer within 3 years of diagnosis. This study is supported by NCI, NIDDK and the Pancreatic Cancer Action Network (PanCAN) and holds potential to make an impact on this cancer that currently has limited treatment options.

Council Questions and Discussion

Is there a cap on the number of NCI-designated Cancer Centers nationally?

Dr. Sharpless explained that there is not a fixed set of centers, however, the designation is very time consuming, difficult, and expensive to qualify for.

Cancer enters also go through an extensive reevaluation process. Some centers have three full-time people preparing and administering this activity. Nonetheless, most centers pass with very high

scores and it is very rare for a Cancer Center to lose its status, Dr. Sharpless said. NCI is looking at perhaps extending the period between renewals as well as finding alternatives to the current evaluation process.

I've heard that the mouse is not a great model for a lot of human cancers. Can you comment on that?

Dr. Sharpless explained that there are two kinds of mouse models: genetically engineered mice, and xenograft models. These models play an important role in preclinical research, but each mouse model is only good for one kind of cancer. In addition, both types of models have serious limitations for cancer research purposes, particularly when investigating immunotherapy, the fourth modality used to treat cancer. The lack of reliable methods to validate checkpoint inhibitors and immunotherapy drugs preclinically is a problem for the field, he said. NCI is looking at developing better clinical models for immunotherapy to increase the efficiency of this process.

If the SEER registry is exempt from HIPAA because it predated the law, does that also apply to other registries established before HIPAA?

Dr. Sharpless explained that HIPAA allows the gathering of this data for clinical use, but not for research. SEER does not fit either category—it is a national monitoring system. It's not for specific clinical use at any institution, although the information contained in it can help guide clinical care. He said that state and federal law requires the collection of certain information about deaths from cancer, including demographic information and cause of death. The SEER program, which is administered by outside contractors, takes that primary data and combines it with other data, including claims data, that identifies the patient. The SEER program holds that combined data, but de-identifies it before making it available to the research community.

What are the opportunities for integrating the work of NCI and NIDDK to investigate the relationship between nonalcoholic steatohepatitis (fatty liver disease, also called NASH) and the development of hepatocellular carcinoma (liver cancer)? What do we know about the precision medicine approach to this type of cancer?

Dr. Sharpless explained that hepatocellular cancer is an advanced solid tumor that affects many people but generally does not benefit from somatic sequencing in most patients. However, it is a heterogeneous disease and about 5 percent of patients have microsatellite instable (MSI)-high tumors that may respond to certain drugs. As research on this cancer continues, it is likely that other druggable subtypes will be identified.

Dr. Sharpless said liver cancer is an area in need of additional research investment and a good area for interactions with NIDDK. Dr. Sharpless has been working with Dr. Rodgers on methodologic approaches to enhance nutrition research and increase our understanding of diet and obesity, pointing out that in the near future NASH and alcoholic cirrhosis may replace viral hepatitis as the most common cause of liver cancer.

Has anyone looked at preventing autoimmunity by reverse engineering checkpoint inhibition,

leading to checkpoint activation? This could be important in type 1 diabetes.

Dr. Sharpless said this is an area of research in both cellular immunotherapy—which involves engineering T-cells or expanding a T-cell population—and agent-based immunotherapy using checkpoint inhibitors. For example, CAR T-cells are very effective at eliminating B cells implicated in some autoimmune conditions. Dr. Sharpless felt this was a promising area of research and one of the reasons behind NCI's current push to build on-campus T-cell engineering capabilities.

Why is research training not included in the Cancer Moonshot initiative?

Dr. Sharpless pointed out that the Cancer Moonshot was developed before his tenure as NCI director. However, he said the Moonshot has led to increased interest in cancer research, and as a result, NCI is receiving more applications from a larger pool of scientists from different areas. In addition, NCI has sufficient resources to conduct the Moonshot as envisioned by the Blue-Ribbon Panel while also continuing its work in workforce development.

Checkpoint inhibitors have led to an increase in diarrheal diseases. What is NCI doing to address this?

Dr. Sharpless recognized that immunotherapy is associated with a variety of adverse events, including diarrheal diseases as well as an increase in hypophysitis, which used to be a rare disease. Many of these side effects of immunotherapy do not show up for many years, which can be a diagnostic challenge.

Just as HIV led to new advancements in science, checkpoint inhibitors are leading to new knowledge about immunology, Dr. Sharpless pointed out. The pharmaceutical industry is looking at this, and this may lead to more data sharing among different companies to create a large enough pool of cases for study. NCI can act as a neutral broker for that information through Project Data Sphere.

VII. 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 due to congenital anomalies, injury, disease, or the aging process.

Dr. Germino explained that this meeting marked the third and final installment of a year-long initiative, the Council Forum, which has consisted of special presentations on regenerative medicine at each Council meeting in 2018 with speakers selected by each NIDDK division. The goal of the year-long plan has been to seek input from the Council at this September 2018 meeting regarding how NIDDK and NIH should focus their resources within the broad area of regenerative

medicine.

Dr. Germino noted that NIDDK has an unusually broad research mission and that changes on the research workforce, the need for training, and the increased complexity of issues addressed by the agency mean that the agency must carefully choose where to spend resources. The Council Forum has been an experiment in NIDDK staff seeking input from the Council on a broad but crucial topic.

The emerging field of regenerative medicine is complex and has received increasing attention in recent years. The National Academies have conducted various workshops and meetings and published books on the topic. Congress has appropriated funds for regenerative medicine in both the 21st Century Cures Act and the Regenerative Medicine Innovation Project. Many of the conditions that may benefit from discoveries in regenerative medicine fall within NIDDK's research mission, including type 1 diabetes, epithelial cell defects in the GI tract, end-stage kidney disease, and end-stage liver disease. To date, NIDDK remains the second-largest funder of regenerative medicine in the NIH, behind only the National Heart, Lung, and Blood Institute. In 2017, NIDDK support of regenerative medicine-related projects totaled $95 million.

Dr. Germino reviewed the questions Council members should consider for the post-presentation discussion of regenerative medicine and noted Council feedback so far on each.

1. *What are the major cross-cutting scientific, technical, and operational challenges we must overcome to accelerate progress in the field of regenerative medicine?* Council members had not provided specific feedback prior to the September meeting.
2. *What can be done to improve the transition and translation of these discoveries into something that benefits people? How can we move from preclinical trials to clinical trials and beyond?* In previous meetings, Council members emphasized the importance of pursuing more basic science research and of avoiding the temptation to test new developments clinically before the science supports them. Additionally, NIDDK should seize opportunities for translation when it makes sense for a specific condition or subset of patients. The final piece of feedback on this question is that Council emphasizes that the needs and voices of patients should be considered throughout the scientific process, especially when setting research priorities.

3. *Given the deeply interdisciplinary nature of regenerative medicine, how can NIDDK build, fund and support novel interdisciplinary teams and help them accelerate scientific progress*? Council members have expressed that training young investigators in the required interdisciplinary approaches will be vital. Young investigators should be able to follow training pathways that foster team-based science as the widespread paradigm it is expected to be while also training them to excel in that paradigm. In particular, Council members have stressed the importance of crediting junior investigators appropriately for their scientific contributions, despite the large size of the expected teams, so that reviewers and funders can truly appreciate the value of all participants' contributions. Investigators may also need special training and support to build long-term working partnerships.

Finally, any NIDDK-built programs must be developed with longevity and post-NIDDK funding in mind. To that end, NIDDK should build and sustain partnerships with appropriate advocacy groups, patient-related foundations, and industry.

Kidney Regenerative Medicine
Dr. Drummond

Dr. Deborah Hoshizaki, program director, Division of Kidney, Urologic, and Hematologic Diseases, introduced Dr. Iain Drummond, an associate professor in Medicine and Genetics at Harvard Medical School. Dr. Drummond received his Ph.D. from the University of California, Berkeley, for work on ionic signaling and heat shock response in Drosophila. His postdoctoral work at Northwestern University Medical School and the University of Chicago focused on gene regulation in Dictyostelium and the Wilms tumor suppressor in human cells. In addition to his Harvard Medical School appointment, Dr. Drummond is a biologist at the Massachusetts General Hospital, and a member of the Program in Developmental and Regenerative Biology at Harvard Medical School. Most notably for this presentation, he is Director of the Kidney Group at the Harvard Stem Cell Institute. Dr. Hoshizaki pointed to the fundamental advances strategies in rebuilding kidneys and regenerating kidney tissue over the past five years,

Dr. Drummond opened his remarks by noting that there have been few advances in the last 50 years in treating chronic kidney disease/end-stage renal failure since the invention of dialysis. Transplantation remains the best treatment option, but a shortfall in organ availability means that 13 people die each day waiting for new kidney. "Rebuilding" kidneys or making new kidney tissue may be an answer to this urgent problem.

The goals of the ReBuilding a Kidney (RBK) Consortium, launched by NIDDK in 2015, are to develop and implement strategies for *in* vitro engineering of replacement kidney tissue, and to devise strategies to stimulate regeneration of nephrons in *in situ* to restore failing kidney function. Some of the questions and challenges involved in this research include:

- How do we make kidney cells?
- How do we know we have made the right kidney cells?
- How do we organize them into useful structures?
- How can we show they are useful for functional replacement?
- How do we integrate them into patient tissue to augment or replace renal function?
- How do we promote regeneration of damaged kidney tissue to prevent end-stage renal failure?

Dr. Drummond summarized the work and strategies consortium labs and other active labs to build functional renal cells

The labs of Dr. Ryuji Morizane and Dr. Joseph Bonventre are working with induced pluripotent stem cells (IPSs) and driving them into mesoderm tissue using Wnt and activin signaling, which essentially replicates the environment of an early embryo. About 90 percent of the cells driven through this renal differentiation protocol express Six-2 a cell marker for kidney progenitor cells.

Dr. Leif Oxburgh's lab at the Maine Medical Center Research Institute is working on expanding these cells by replicating an embryonic niche *in vitro*, allowing the creation and expansion of kidney progenitor cells. The capacity of these cells is demonstrated by their ability to differentiate when implanted under the mouse kidney capsule where these cells give rise to many elements of a functional kidney, including segmented tubules, podocytes, and vascular components. Generation of a reliable pool of cells is critical for many bioengineering efforts.

Dr. Drummond noted that the field as a whole continues to grapple with the challenge of integrating the neo-tissues with blood flow to allow generation of functional glomeruli and the interconnection of the nephrons to the host collecting system.

Dr. Drummond also discussed ways to take advantage of induced pluripotent stem (IPS) cells to drive the cells into organs and tissue structures.

Work by Dr. Melissa Little's group has concentrated the cells into small pellets, enhancing their differentiation into organoids. Most of the final differentiation steps under current investigation involve no growth factors; the cells self-organize and differentiate for the most part.

Exploring this mystery and ways to direct that differentiation are important areas for research, Dr. Drummond said. However, the many variables and combinations of possibilities makes this an expensive and time-consuming proposition.

The group led by Dr. Oliver Wessely within the ReBuild a Kidney Consortium has developed a computational approach to understanding which growth factor combinations and concentrations are mostly likely to produce the desired end result—helping to make the research enterprise more efficient and cost-effective. Using this approach, the Wessely group has driven IPS metanephric mesenchyme-like cells from the Morizane lab into podocytyes or podocyte-like cells with a six-growth-factor combination that shows expression of WT1 and MATH-B, both markers for podocytes. Work is ongoing to determine if these cells are capable of performing filtration functions.

The RBK group led by Dr. Thomas Carrol has discovered that kidney stromal cells, once thought to be homogeneous, have different gene expression patterns that define at least 6 zones associated with different segments of the nephron. Nephron development is dependent upon the stromal cells and, thus, it is clear that the spatial patterning and nature of stroma is an important and unstudied area.

Similarly, Dr. Ondine Cleaver's lab is looking at blood vessels in the kidney, where they find the endothelial cells that make up blood vessels exhibit spatial heterogeneity in their gene expression. These differences likely reflect the functional specificity of different blood vessels.

Another line of research is looking at how well the mouse relates to human in their kidney gene expression. The RBK group led by Dr. Andrew McMahon is transcriptionally profiling thousands of single kidney cells to understand how different transcription factors and cell types relate to the

human and mouse kidney. Extrapolating from this knowledge, researchers are looking at overlapping gene expression sets to iteratively build pseudo trajectories of changes in cell transcription profiles, and to understand changes in cell transition states. This type of analysis can be applied to the initiation and progression of injury in mice and in humans to understand where cells have productive repair responses.

Other researchers are looking at how to use this knowledge to build actual three-dimensional organs that could eventually filter blood and function like a kidney. The RBK group led by Dr. David Kaplan is aligning cells and matrices along silk films, allowing them to self-organize into tubules that might eventually perform sequential blood processing.

Another Consortium member, Dr. Jennifer Lewis, is working with 3-D printing of tissue to study the vasculature of the kidney tubule. She plans to use the printed organoids and kidney tissue to build complex three-dimensional structures. The challenge at this point is not the technical aspects of 3-D printing, but rather maintaining cell viability while building a multilayered organ.

Dr. Drummond also summarized his own work using a fish model. Unlike humans, adult fish can regenerate their kidneys from nephrogenic cells. He has found that fish regenerate their kidneys by activating similar growth factors used by humans during nephrogenesis. Looking at how the fish fuses new nephrons with the collecting system can increase understanding of how to build a complex structure and promote tubule interconnection and drainage.

Before engrafting tissue, researchers will need to better understand how it will impact the processing of patient blood and regeneration. No one has yet to perfuse these small organoids. One possibility is to use genetically-encoded fluorescent biosensors to indirectly measure luminal fluid and offer clues about the physiology of the cells. Dr. Jennifer Lewis hopes to design experiments using printed cells.

Another challenge will be to determine, once these organoids are engrafted, whether they are contributing to kidney function. Possibilities for answering this question include implanting into mutant mouse kidneys transgenic organoids that secrete “tagged” molecules that can be measured in the urine to show functional interconnection and urine output. Dr. Lewis’ lab is working on introducing solutes in the lumen of the proximal tubule and measuring the output of the vascular tube or introducing human serum albumin labeled with a fluorescent probe to show how the proximal tubule takes up albumin and transports it back into the vasculature. Physiologist Dr. Lisa Satlin, an expert in single tubule perfusion, is using printed tubes to look at flow rate impact on flux of ions. In a method that marries physiology with developmental biology, Dr. Tom Kleyman is using barium (a non-specific inhibitor of potassium channels) to demonstrate that the organoid can secrete potassium.

Dr. Drummond pointed out that the ideal goal of this research is not necessarily to produce a replacement organ but to develop ways to regenerate or regrow existing kidney tubes and prevent progression to end-stage renal disease. He pointed to the work of Dr. Andrew McMahon’s group using gene expression profiling to address productive and nonproductive repair. Dr. McMahon has identified genes such as SOX9 that seem to activate on injury and recapitulate certain repair events.

This technology could bridge work on kidney regeneration to the kidney precision medicine program to look at how well mouse models replicate human datasets. Another researcher, Dr. Ben Humphreys, is looking at ways to mark injured kidney cells to reveal endpoints and effectors of kidney regeneration. Dr. Humphreys is also proposing to develop an atlas of mouse cell repair at different stages of regeneration.

Dr. Drummond closed the talk by addressing how the Consortium works together. He credited the Consortium's Coordinating Center with facilitating data sharing through the use of a web-based database that is easy to reference and search. The Coordinating Center also provides training to the researchers on how to use the data model, and organizes monthly teleconferences for the research teams, which encourages open and regular communication.

He also pointed out that Consortium members are encouraged to talk about struggles and failures as well as successes. This helps develop and reveal solutions, learning, and fights isolation. The Consortium has led to new collaborations among the different member labs, pushing the work further.

To keep the Consortium nimble and bring in new technologies, Drs. Deborah Hoshizaki and Chris Ketchum actively recruit new researchers to join the Consortium. Dr. Drummond also pointed that buy-in from the entire NIDDK investigator community to public data sharing leads to new capabilities and benefits the wider research community. He pointed to potential spin-offs from the work of the Consortium in modeling polycystic kidney disease and printing tiny organoids for drug screens.

The Consortium works with other groups with similar goals, including the Kidney Health Initiative that started in 2012. Representatives from the Initiative participate in Consortium teleconferences and bring a patient-centered focus that motivates the group.

Lastly, he credited the foresight, wisdom and support of NIDDK and NIDDK staff in initiating and nurturing the program.

Council Questions and Discussion: Drummond Presentation

Does the ReBuilding a Kidney Consortium have a mechanism to provide attribution for the scientists who contribute data to receive recognition, perhaps a unique identifying number?

Dr. Drummond explained that Consortium has created data structures that will permit individuals who contribute to claim credit and those who cite them to be very specific in their attribution.

How much NIDDK funding does the ReBuilding a Kidney Consortium currently receive?

Dr. Hoshizaki noted that the Consortium currently receives approximately $3 million in initiative funding from NIDDK per year.

Is there a single renal stem cell, or do they differ based on the segment?

According to Dr. Drummond, it has been assumed that the SIX2 population of the renal stem cells *in vivo* is homogeneous and gives rise to the entire nephron. Patterning and differentiation probably occur before the nephron elongates. In terms of the IPS cell-derived organoids, the question is more whether it's possible to make a clonal nephron.

How will you deal with the translation of your work from animals to humans, particularly given the human propensity for fibrosis as a response to injury and disease?

Dr. Drummond believes increased research in animals that heal without scarring can be an avenue to understanding how regeneration can be achieved despite fibrosis. Scientists are trying to understand the differences in these models that perhaps can then be engineered into a human using gene therapy or pharmaceuticals. Dr. Drummond's research in fish has shown that regenerating a fish kidney involves the same molecules as a mouse kidney. The main difference is that fish can do it as adults, he said. This leads him to believe he can eventually engineer some of the same niche or growth factor environments in a mammalian kidney that other species use, leading to regeneration, not fibrosis.

What is the status of the kidney regeneration field regarding what scientists are doing in intestinal regenerative medicine, i.e., starting with an individual stem cell and expanding it via the Cleaver method, in addition to using the IPS method?

Dr. Drummond noted that the gut is known to have stem cells, but the human kidney appears not to. The kidney has not been shown to have any adult progenitors that can develop full nephrons. The kidney and other epithelial organs may use more of a tubule regeneration or epithelial expansion model to deal with injury. The entire consortium has shifted to human IPS cells and nephrogenic cells derived from them.

How does the source of cells used to rebuild kidneys affect their long-term usefulness and help them avoid pathological fibrosis?

Dr. Drummond pointed out that roller tube reactors can now produce organoids in the thousands. Smooth muscle actin, a marker of the myofibroblast, can be seen re-expressed in the organoid, raising the question of whether we can model fibrosis in the organoids and then intervene with a drug screen. He added that understanding the durability of any engineered cells will be a priority as they move into use in humans.

Have any researchers yet explored the role of macrophages and other immune components in repairing cellular structures?

Dr. Drummond reported that Dr. Melissa Little has searched for immune cell markers within organoids created in her lab and has found fibrosis. This implies the presence of cytokine signaling, but whether that process requires immune cells within the organoid remains unknown.

Dr. Bonventre added that his lab is conducting experiments to develop organoids in the presence of macrophages, potentially creating different substrates of macrophages or T-cells and trying to introduce the immune response.

What happens if you put the organoids or IPS cells into the liver or another organ? Do they still form structures that look like glomeruli?

Dr. Drummond noted that Dr. Eric Lagasse and Dr. Carl Bates are using the lymph node as a matrix and a microenvironment for growing organs.

Vascularization is a necessary step in getting these systems to work. What research is ReBuilding a Kidney doing in this area?

Dr. Drummond pointed to the work of Dr. Ondine Cleaver, who is looking at the organoids for evidence of endothelial cells. Additionally, both Drs. Jennifer Lewis and Joseph Bonventre are showing that exerting flow on organoids can enhance the incorporation of endothelial cells and vasculature.

Council Questions and Discussion: Regenerative Medicine Forum

Dr. Germino then took the floor to lead a discussion of the year-long Regenerative Medicine Forum by asking the Council members to address the three questions put forth at each session:

Question 1: What are the major cross-cutting scientific, technical, and operational challenges we must overcome to accelerate progress in the field of regenerative medicine?

Council members saw many opportunities for collaboration and knowledge sharing to hasten progress in regenerative medicine. Epigenetics research, for example, might increase understanding of stem cells and how to predict which ones will respond to manipulation. Involving representatives from industry partners at early research stages may help more quickly identify innovative ways to scale up and achieve mass production. Biomedical engineers might focus on the scientific aspects of regeneration and physicists could investigate microsensor materials to allow the generation of

real-time data on organoid function during scale-up efforts. Combining datasets to correlate findings about regional organ/organoid relationships and functions such as gene expression could foster understanding of common features across tissue types.

Dr. Germino said that the improved use and sharing of datasets in the cloud is of great interest at NIDDK. To that end, Dr. Jenny Larkin has been leading an internal NIDDK working group to proactively address ways to use and combine relevant datasets for widespread use to prevent them from becoming sequestered in discipline-specific silos.

Emphasizing sustainability and cross-validating tissue types may also offer new insights. One example would be in looking at fibrosis in the kidney and then similarly in the gut in hopes of overcoming common hurdles to help translate findings into clinical application.

Another idea was the creation of a national service, perhaps led by NIDDK, to make IPSCs and organoids more available to regenerative medicine research programs. NIDDK may also be uniquely situated to provide cross-training to scientists in preparation for creating new regenerative medicine-focused collaborations.

Dr. Drummond said that the Harvard Stem Cell Institute recently initiated a program in which a fellow from, say, an organoid lab, would define a project with a bioprinting lab and then rotate between two labs and reap the benefits of having two mentors. However, reporting to two different labs presents challenges for fellows that also need to be addressed.

Question 2: What can be done to improve the transition and translation of these discoveries into something that benefits people? How can we move from preclinical trials to clinical trials and beyond?

Council members did not have any additional insights to this topic that they have not already shared earlier or at prior meetings.

Question 3: Given the deeply interdisciplinary nature of regenerative medicine, how can NIDDK build, fund, and support novel interdisciplinary teams and help them accelerate scientific progress?

Council members advised NIDDK to encourage efforts to build community among diverse scientific disciplines through interdisciplinary conferences and other efforts to foster communication and scientific progress. Involving diverse disciplines and sectors—including social sciences and the commercial sector—can help increase understanding of effective ways to conduct team science and form productive teams. The profit motive can also drive effective collaborations and lead to funding projects to address NIDDK diseases based on their potential for translation or commercialization. One council member pointed out that the Hematology Branch of KUH has begun taking small steps in this direction via a consortium grant that is funding small pilot studies, but the effort is hampered by a lack of funds. Recipients are typically awarded only about $20,000, and she believes KUH would receive more and better applications if they could provide better funding.

Dr. Germino then took the floor again to solicit Council feedback on the experiment of offering a themed, continuing forum over the course of an entire year. Specifically, he asked Council members about the idea of hearing about NIDDK division perspectives, including the state of science, challenges associated with that field, and ideas about how to move that field forward.

Council members commented positively on the value of the forum approach with the provision that NIDDK take appropriate action based on at least some of Council's input. The hope would be to avoid the frustration of offering input that does not result in needed change.

Dr. Germino noted that, as forum moderator, he was initially concerned about the effectiveness of repeatedly asking Council to consider the same questions at multiple meetings. He has found it encouraging to have seen the answers and discussion grow and evolve over the course of the year and reiterated his hope of continued discussion on themes raised by the forum. He asked Council members to suggest issues or themes across the disciplines that would be appropriate for the year-long forum format.

Dr. Germino closed by thanking the presenters and Council members for their input and promised to continue focusing on where both barriers and opportunities lie in the exciting field of regenerative medicine.

VIII. SUBCOMMITTEE MEETINGS

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

X. 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 208th 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