Meeting Minutes
Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
May 11, 2011

I. CALL TO ORDER

Dr. Germino, Deputy Director, on Behalf of Dr. Rodgers, Director

On behalf of the NIDDK Director, Dr. Griffin Rodgers, the NIDDK Deputy Director, Dr. Gregory Germino, called to order the 186th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m., Wednesday, May 11, 2011, in Building 31, 6th Floor, Conference Room 10. Dr. Germino announced that Dr. Rodgers had been asked to accompany the NIH Director, Dr. Francis Collins, to a Senate Appropriations Committee hearing on the NIH budget that morning, along with Dr. Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID); Dr. Susan Shurin, Director of the National Heart, Lung and Blood Institute (NHLBI); and Dr. Harold Varmus, Director of the National Cancer Institute (NCI). Dr. Germino said that he would chair the meeting that morning for Dr. Rodgers, who extended his regrets to the Council members and attendees. Dr. Rodgers was able to join the meeting in the afternoon.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Domenico Accili*
Dr. David Altshuler
Dr. Nancy Andrews
Ms. LaVarne Burton
Dr. Judy Cho
Dr. Robert Flanigan
Dr. James Freston
Dr. Christopher Glass
Dr. Gregory Gores
Ms. Jane Holt
Ms. Judy Hunt
Dr. Francine Kaufman
Dr. David Klurfeld
Ms. Robin Nwankwo
Dr. Jerry Palmer
Dr. Thomas Robinson
Dr. Anil Rustgi
Dr. John Sedor
Dr. William Steers
Dr. Mark Zeidel

Also Present:
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. Griffin Rodgers, Director, NIDDK*
Dr. Brent Stanfield, Executive Secretary, NIDDK Advisory Council

*Attended the afternoon portions of the meeting.

B. NIDDK STAFF AND GUESTS

Abankwah, Dora – NIDDK
Abraham, Kristin – NIDDK
Anderson, James – NIH OD
Appel, Michael – NIDDK
Arreaza, Guillerno – NIDDK
Barnard, Michele – NIDDK
Begum, Najma – NIDDK
Bishop, Terry – NIDDK
Bleasdale, John – CSR
Blondel, Olivier – NIDDK
Bloom, Maria – NIDDK
Carrington, Jill – NIDDK
Castle, Arthur – NIDDK
Chianchiano, Dolph – Nat. Kidney Found.
Connaughton, John – NIDDK
Copeland, Randy – NIDDK
Cowie, Catherine – NIDDK
Curtis, Leslie – NIDDK
Dayal, Sandeep – NIDDK
Densmore, Christine – NIDDK
Doherty, Dee – NIDDK
Donohue, Patrick – NIDDK
Doo, Edward – NIDDK
Edwards, Michael – NIDDK
Eggerman, Thomas – NIDDK
Eggers, Paul – NIDDK
Evans, Mary – NIDDK
Everhart, James – NIDDK
Flessner, Mike – NIDDK
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gallivan, Joanne – NIDDK
Gansheroff, Lisa – NIDDK
Garfield, Sandy – NIDDK
Garte, Seymore – CSR
Graves, Reed – CSR
Greenwel, Patricia – CSR
Grey, Michael – NIDDK
Guo, Xiaodu – NIDDK
Gutkin, Claire – CSR
Haft, Carol – NIDDK
Hardy, Dianne – CSR
Harris, Mary – NIDDK
Hentges, Justin – NIH OD
Hilliard, Trude – NIDDK
Hoff, Eleanor – NIDDK
Hoofnagle, Jay – NIDDK
Horlick, Mary – NIDDK
Hoshizaki, Deborah – NIDDK
Howards, Stuart – NIDDK
Hubbard, Van – NIDDK
Hunter, Christine – NIDDK
Hyde, James – NIDDK
James, Stephen – NIDDK
Jerkins, Ann – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Karimbakas, Joanne – NIDDK
Ketchum, Christian – NIDDK
Khan, Mushtaq – CSR
Kim, Sooja – CSR
Kimmel, Paul – NIDDK
Kirkali, Ziya – NIDDK
Kochis, Daniel – Amer. Soc. of Neph.
Kranzfelder, Kathy – NIDDK
Krishnan, Krish – CSR
Kuczmarski, Robert – NIDDK
Kusek, John – NIDDK
Laughlin, Maren – NIDDK
Lescheck, Ellen – NIDDK
Linder, Barbara – NIDDK
Malik, Karl – NIDDK
Malozowski, Saul – NIDDK
Manouelian, Denise – NIDDK
Mascone, Lisa – NIDDK
Martey, Louis – NIDDK
Maruvada, Padma – NIDDK
Martinez, Winnie – NIDDK
McKeon, Catherine – NIDDK
Micklin, Michael – CSR
Miller, David – NIDDK
Miller, Megan – NIDDK
Moxey-Mims, Marva – NIDDK
Morris, Ryan – CSR
Mullins, Chris – NIDDK
Narva, Andrew – NIDDK
Naus, Wendy – Lewis-Burke Assoc.
Newman, Eileen – NIDDK
Nguyen, Van – NIDDK
Nicholson, Katherine – NIDDK
Nurik, Jody – NIDDK
Papier, Wendy – NIDDK
Patel, D. G. – NIDDK
Pawlyk, Aaron – NIDDK
Perry-Jones, Aretina – NIDDK
Pike, Robert – NIDDK
Podskalny, Judith – NIDDK
Pope, Sharon – NIDDK
Ranganathan, Rajesh – NIH OD
Rankin, Tracy – NIDDK
Rasooly, Rebekah – NIDDK
Redmond, Randy –NIDDK
Rench, Jerry – RTI Inter.
Roberts, Tibor – NIDDK
Rodriguez, Michell – SRI Inter.
Rosenberg, Mary Kay – NIDDK

Rushing, Paul – NIDDK
Rys-Sikora, Krystyna – NIDDK
Salaita, Christine – NIDDK
Salomon, Karen – NIDDK
Sahai, Atul – CSR
Sankaran, Lakshmanan – NIDDK
Sato, Sheryl – NIDDK
Savage, Peter – NIDDK
Sheard, Nancy – CSR
Sheperd, Aliecia – NIDDK
Shoneck, Ted – Tunnell Consulting
Silva, Corrine – NIDDK
Smedberg, Paul – Amer. Soc. of Neph.
Smith, Philip – NIDDK
Spain, Lisa – NIDDK
Star, Robert – NIDDK
Staten, Myrlene – NIDDK
Tatham, Thomas – NIDDK
Torrance, Rebecca – NIDDK
Tuncer, Diane – NIDDK
Van Raaphorst, Rebekah – NIDDK
Wallace, Julie – NIDDK
Wellner, Robert – NIDDK
Woynarowska, Barbara – NIDDK
Wright, Daniel – NIDDK
Xie, Yining – NIDDK
Yates, Robert – Soc. Sci. Sys.
Zeidner, Rita – NIDDK

C. ANNOUNCEMENTS

New Council Members

Dr. Germino officially welcomed the following new Council members: Drs. Domenico Accili, Judy Cho, Robin Nwankwo, Thomas Robinson, William Steers, and Mark Zeidel. These individuals attended the last Council meeting on an *ad hoc* basis and were introduced to the Council at that time. (See February 2011 Council minutes at: http://www2.niddk.nih.gov/NR/rdonlyres/C92538FB-C0AC-4456-97D9-9234B945851F/0/NIDDKCouncilMinutesFeb20104510_final.pdf)

New NIDDK Staff Members

Dr. Padma Maruvada has joined the Division of Digestive Diseases and Nutrition (DDN) as Program Director for the Nutrition Program. She was previously a Program Director at the National Center for Research Resources (NCRR).

Retirements

Dr. Lucy Greene, the NIDDK Executive Officer and Associate Director for Management, retired at the end of April, 2011. Dr. Greene joined the NIDDK in 2006, following an appointment with the National Cancer Institute. Before coming to the NIH, she spent almost 15 years at the Smithsonian's National Museum of American History. An excellent manager, she assisted the NIDDK with many difficult administrative management decisions.

Awards

Scott Hultgren, Ph.D., a long-standing NIDDK grantee, is among the new members elected to the National Academy of Sciences this year. Dr. Hultgren is the Helen L. Stoever Professor of Molecular Microbiology, and Director, Center for Women's Infectious Disease Research, Washington University School of Medicine, St. Louis, Missouri. His research focuses on understanding the molecular details of host-pathogen interactions in urinary tract infections (UTIs). This research is yielding new insights into

infectious diseases and their relationship to cancer, as well as better strategies for treatment and prevention of UTIs. Dr. Hultgren's work has been funded by the NIDDK since 1997, including an American Recovery and Reinvestment Act (ARRA) Challenge Grant. He presently has R01 funding from the NIDDK and the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Hultgren is also the Principal Investigator of an NIH Specialized Center of Research focused on Sex/Gender Factors Affecting Women's Health.

"In Memoriam"

Dr. Vanessa Ameen, who joined the NIDDK's Division of Digestive Diseases and Nutrition as a Senior Scientific Advisor in January 2010, died on February 21, 2011. Specializing in pediatrics and gastroenterology, Dr. Ameen was recruited to the NIH from private industry, where she had been medical director for several large pharmaceutical manufacturers. Dr. Ameen had also held positions at Temple University, Indiana University, and the Medical College of Wisconsin.

Dr. Shanthi V. Sitaraman, an NIDDK grantee who was Professor of Medicine in the Division of Digestive Diseases at Emory University School of Medicine, died on April 9, 2011. Dr. Sitaraman's research focused on inflammatory bowel diseases. In addition to being a highly productive researcher, she was an exceptionally talented and devoted physician, as underscored by her receipt of the Crohn's and Colitis Foundation of America's 2011 Premier Physician Award.

New NIDDK-Sponsored Bowel Control Awareness Campaign

The National Digestive Diseases Information Clearinghouse will launch the "*Bowel Control Awareness Campaign"* on June 1, 2011. The campaign stems from panel recommendations at an NIH state-of-the-science conference. The goal is to raise awareness about the symptoms, diagnosis, treatment and management of bowel problems among health care professionals and the public, and to improve patient and provider communications. The campaign was developed by the NIDDK, in coordination with professional and advocacy organizations.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 185th COUNCIL MEETING

Dr. Germino

Following a motion that was made and seconded, the Council accepted, by voice vote, the Summary Minutes of the 185th Council Meeting.

III. FUTURE COUNCIL DATES

Dr. Germino

Dr. Germino reviewed the upcoming Council dates. Most meetings are expected to be held on a single day--Wednesday. However, the NIDDK Council members are asked to reserve both days (Wednesday and Thursday) in case a longer meeting is needed.

2011
September 7-8 (Wednesday and Thursday)

2012
February 15-16 (Wednesday and Thursday)
May 16-17 (Wednesday and Thursday)
September 12-13 (Wednesday and Thursday)

IV. ANNOUNCEMENTS
Dr. Stanfield

Confidentiality

Council members were reminded 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

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 the member does not participate in, and is not present during 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, 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. Council members were asked to look at the statement in their folders regarding conflict of interest in their review of applications. Council members were asked to read it carefully, sign it and return it to the NIDDK before leaving.

Council members were reminded that, at Council meetings when applications are reviewed in groups without discussion, that is, "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. With respect to multi-campus institutions of higher education: An employee may participate in any particular matter affecting one campus of a multi-campus institution of higher education,

if the employee's financial interest is solely employment in a position at a separate campus of the same multi-campus institution, and the employee has no multi-campus responsibilities.

V. REPORT FROM THE NIDDK DIRECTOR

Dr. Germino on Behalf of Dr. Rodgers

Budget Update

Dr. Germino updated the Council on the status of the budget. With respect to FY 2011, following a series of short-term Continuing Resolutions and narrow avoidance of a government shut-down, a Continuing Resolution for the remainder of the Fiscal Year became law on April 15, 2011. For FY 2011, overall funding levels for the NIH and NIDDK are, respectively, $30.925 billion and $1.792 billion. These levels are a reduction below the FY 2010 appropriation (not including stimulus funds provided by the American Recovery and Reinvestment Act). The reduction for NIH is about 1 percent. For the NIDDK, the reduction is about 0.9 percent or approximately $16 million. The NIH and the Institutes and Centers (ICs) are now working out the grant funding policies for the remainder of FY 2011.

For FY 2012, the President's Budget request for NIH is $31.987 billion--an increase of about 3.4 percent above the FY 2011funding level. For NIDDK, the request is $1.838 billion--an increase of about 2.6 percent above FY 2011funding level. The Senate appropriations hearing on the FY 2012 President's Budget request for the NIH was being held the same day as the NIDDK Council Meeting--May 11, 2011. The House hearing has not been scheduled.

The NIH web site contains the FY 2012 budget statement of the NIH Director. (http://www.nih.gov/about/director/budgetrequest/fy2012budgetrequest.pdf)
The NIDDK web site has posted the FY 2012 budget statement of the NIDDK Director. (http://www2.niddk.nih.gov/AboutNIDDK/BudgetAndLegislativeInformation/Budget_Request_for_FY2012_May_11_2011.htm)

VI. UPDATE: NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

Dr. Ranganathan, Senior Advisor to the NIH Director for Translational Medicine

Dr. Germino introduced Dr. Rajesh Ranganathan to update the Council regarding plans for a new NIH National Center for Advancing Translational Sciences (NCATS). The Center is envisioned to establish and provide focused, integrated, and systematic approaches for building new bridges that link basic discovery research with therapeutics development and clinical care. It is also expected to include the recently authorized Cures Acceleration Network (CAN). Before joining the NIH, Dr. Ranganathan was a Director in the Scientific Strategy and Portfolio Management Group of the Novartis Institutes for BioMedical Research Inc., where he also founded and led the Global Office

of Scientific Education. Dr. Ranganathan earned a doctorate in neurobiology at the Massachusetts Institute of Technology, and completed his postdoctoral training at Harvard Medical School and the Fred Hutchinson Cancer Research Center in the area of mammalian sensory regulation.

Dr. Ranganathan described plans for establishing a new NIH Center for Advancing Translational Sciences (NCATS), a priority for NIH Director, Dr. Francis Collins. The Center's concept derives from the long-standing NIH involvement and success in therapeutics development and translational science. An inventory of NIH translational activities from a budgetary perspective found hundreds of relevant projects. Thus, translational science is already central to the NIH mission, and the NCATS would strengthen, enhance, and capitalize on this existing research base.

Dr. Ranganathan discussed some of the scientific and business imperatives and challenges in the translational research landscape. He suggested that recent advances in scientific areas--such as genomics, proteomics, chemical biology, and computational biology--make the timing right for the new Center. At the same time, existing pharmaceuticals are not fully meeting patient needs across the spectrum of human health conditions, especially in rare and neglected diseases. Strategies in the pharmaceutical sector are changing dramatically by moving away from what might be considered standard strategies for producing "blockbuster" drugs toward approaches for developing drugs for "niche" markets. This development has, in turn, resulted in a contraction of research in many disciplines that are seen by industry as too risky for investment--such as neurologic and infectious diseases. On the financial side, industry's funding models for early-risk science, especially through venture capital, are changing quite significantly, with a decreasing appetite for risk-taking. The high return on investment now sought by venture capital investors means a lack of private-sector funding for the type of early science that falls on the research continuum between NIH basic studies and the eventual marketing of clinically tested and approved drugs by larger pharmaceutical or biotechnology companies. The resulting translational gap means that many meritorious basic discoveries are not being pursued for potential therapeutic application.

In May 2010, the NIH Director, Dr. Francis Collins, asked a congressionally mandated Scientific Management Review Board, composed of external and internal experts, to deliberate on the best ways that the NIH could advance translational research. The Board, which is charged with considering NIH organizational issues, spent several months reviewing data and conducting discussions with a variety of stakeholders before providing the NIH Director with a report that recommended the creation of a new Center focused on translational medicine and therapeutics--NCATS (See the Board's report at: http://smrb.od.nih.gov/documents/reports/TMAT_122010.pdf).
The Board also suggested a more extensive analysis of such a Center's potential impact on the NIH organization to ensure a seamless transition during the proposed organizational change. To this end, the NIH Director used three panels to guide the planning process. The first panel, composed of Institute and Center Directors, provided recommendations on February 17, 2011, with respect to the mission, functions, and organization of NCATS. The second panel was a Working Group, established under the

Advisory Committee to the NIH Director, to obtain input from many investigators, representatives from academia, and professionals from industry regarding the kinds of relationships that the NIH could appropriately build with the private sector through NCATS. This group was asked to identify models of private/public partnerships, and bottlenecks in drug discovery. The third panel focused on the existing Clinical and Translational Science Awards (CTSA) Program, which is intended to be part of NCATS (http://www.ncrr.nih.gov/clinical_research_resources/clinical_and_translational_science_awards/index.asp). The objective of this panel is to further the integration of the CTSA Program into NCATS by October 1, 2011--the start of FY 2012. The CTSA Program is currently located in the NIH National Center for Research Resources (NCRR).

Dr. Ranganathan shared with the Council the mission statement developed for NCATS: "To advance the discipline of translational science and to catalyze the development, testing, and implementation of novel diagnostics and therapeutics across a wide range of human diseases and conditions." He elaborated on the meaning of the phrase: "advancing the discipline of translational sciences." The intent is to improve the processes in the drug development pipeline by experimenting with innovative approaches in an open-access model that brings academia together with industry and patient advocacy groups to address problems that plague the translational research process. These problems include the long time it takes to move a discovery from the bench to the bedside, and the high costs associated with drug development. The planned Center would choose compelling projects that can serve as experimental test-beds for novel methods to move discoveries through the pipeline, including facilitating interactions with regulatory agencies. This work could be characterized as process engineering experiments, which would be best done in real-world settings to meet urgent, unmet needs for treating diseases. The NCATS would also be expected to play a role in the development of devices and diagnostics, with a view toward fostering personalized medicine.

To illustrate the first part of the NCATS mission, Dr. Ranganathan provided an example of process engineering as it relates to predictive pre-clinical toxicity testing. He noted that the traditional approach of the U.S. Food and Drug Administration (FDA) in moving new drugs forward in the pipeline is to use animal toxicity results as predictive of possible toxic effects that could occur in human studies. In some diseases, such as cardiovascular and blood diseases, there is a high concordance between animal and human toxicity results. However, the concordance is much lower in other diseases, such as liver disease. An NIH component such as NCATS could work with the FDA and the pharmaceutical industry to consider other models, such as cell-based models, for pre-clinical toxicology studies, which could potentially result in changes in regulatory guidelines. For instance, there is an existing collaborative program, called Tox-21, in which the Environmental Protection Agency, the NIH, and the FDA are working together to apply new technology for advancing the state of toxicity testing, including the development of better predictive models of human responses to environmental toxicants (http://www.epa.gov/ncct/Tox21/).

There are also current investments within the NIH Chemical Genomics Center in which many compounds are arrayed in high-throughput format for activity testing across a

variety of cell-culture and other systems. In the future, it may even be possible that induced pluripotent stem cell (iPS cell) technologies may enable the development of *in vitro* models of organ systems for the purpose of drug testing. Retrospective analysis of clinical trial data in partnership with the FDA might be yet another means of developing prospective risk assessors. Dr. Ranganathan emphasized that, in testing new approaches, the NCATS would need to focus on compelling therapeutic projects highly relevant to patients in order to gain widespread confidence in its data, and momentum for its efforts.

Dr. Ranganathan also elaborated on the meaning of the second phrase in the NCATS mission statement: "catalyze the development, testing, and implementation of novel diagnostics and therapeutics across a wide range of human diseases and conditions." He emphasized that the Institutes and Centers (ICs) will continue to maintain their current translational activities. The role of the NCATS would be to facilitate the movement of compounds through the pipeline more quickly by furthering partnerships and collaborations and tackling impediments. For example, working with the Institutes, the NCATS may be able to identify and remove different types of bottlenecks, such as issues with drug formulation, pharmacology/pharmacodynamic assessments, and clinical trial design. The NCATS would thus facilitate--not subsume or duplicate--the translational research activities conducted and supported by the ICs. It would also complement--not compete with--the private sector. Although the NCATS is expected to have a relatively modest budget, it would be able to help identify and address some of the therapeutic needs that are not being met by the private sector for various reasons. The NCATS would also help to reinforce the NIH commitment to basic research because translational science is not linear; rather, it can produce advances that feed back to the laboratory bench for study, as well as forward to clinical applications.

With approval from the Secretary of the Department of Health and Human Services, the Office of Management and Budget, and the Congress, the NCATS has been included in the FY 2012 President's Budget request and it is planned for establishment on October 1, 2011. The NCATS is expected to have seven proposed components: (1) Clinical and Translational Science Awards (CTSA) Program, (2) Therapeutics for Rare and Neglected Diseases--TRND, (3) Office of Rare Diseases Research, (4) Rapid Access to Interventional Development--RAID, (5) components of the Molecular Libraries Program, (6) the NIH-FDA Regulatory Science Initiative, and (7) the new Cures Acceleration Network. It is expected that relocated programs would maintain their respective budgetary resources for FY 2012, whereas establishment of the new Cures Administration Network would require that funds be appropriated for that purpose in FY 2012. Dr. Ranganathan highlighted several of the planned NCATS components:

- *CTSA Program: Strives to improve human health by transforming the research and training environment to enhance clinical and translational research.* The current 55 Centers in this Program have a strong focus on training, capacity-building, and collaboration. They have also promoted centralization of Institutional Review Boards to help improve the clinical trial process.

- *TRND: Seeks to speed new drug development for rare and neglected diseases.* A congressionally-mandated program, TRND features a collaborative approach between intramural and extramural laboratories. Projects can enter the Program at a variety of stages across the therapeutic pipeline, often at the pre-clinical stage. The disease topics in the TRND pilot projects are: schistosomiasis, hookwork; Niemann-Pick Disease Type C; hereditary inclusion body myopathy; sickle cell disease; and chronic lymphocytic leukemia. The projects will be taken to the point that an external organization can step-in to support clinical development. This concept of a transitional "hand-off" point will also inform NCATS as a whole, because the goal of the NCATS is not to do Phase III clinical trials or provide drugs in the market place. Rather, the NCATS would seek sponsors that are sufficiently interested in a drug to see it as a financially viable investment option. The "hand-off" point would vary for different projects and diseases.

- *NIH-FDA Regulatory Science Initiative: Intended to advance translational and regulatory science through cooperative research grants and through NIH-FDA interactions.* To date, grants have been awarded in four high-priority areas: (1) innovative approaches to adaptive clinical trial design, (2) nanoparticle characterization, (3) a novel strategy to predict ocular irritancy, and (4) a heart-lung micromachine model to test the safety and efficacy of drugs. An NIH-FDA Leadership Council, established in 2010, is working to ensure that regulatory considerations are integral to biomedical research planning, and that the latest science informs the regulatory review process. Working groups have been established to explore the following potential areas of collaboration: (1) pre-clinical research, (2) clinical research and trials, (3) drug rescue and repurposing, (4) bioinformatics, statistical design and analysis, (5) tobacco issues and emerging priorities in public health, and (6) a shared culture. With respect to drug rescue and repurposing, Dr. Ranganathan said that he was encouraged by a recent NIH-Industry Roundtable meeting on this topic. Many drugs that were not previously pursued for various reasons may have unexplored therapeutic value. Given current economic conditions, industry may be more inclined than in the past to repurpose such drugs, because earlier investments in their research and development may provide cost advantages.

- *Cures Acceleration Network (CAN): Would award grants for conducting and supporting research leading to revolutionary advances for highly needed cures.* The Network was authorized by the Patient Protection and Affordable Care Act (P.L. 111-148) for first-year funding at $500 million; however, funds have not yet been appropriated. The FY 2012 President's Budget requests $100 million to establish the Program. Twenty percent of the Network's funds could be awarded through a flexible spending authority that is similar to the Defense Department's DARPA Program.

In closing, Dr. Ranganathan emphasized that the NCATS will be joining a broad NIH family that is already committed to translational research. The new Center's undertakings will be furthered by the productive interactions it is able to forge with the ICs, the FDA, industry, and patient advocacy groups. He noted that the NIH has benefited greatly from the input it has received thus far in planning the NCATS, and he encouraged the Council

members and others to provide additional feedback on the NIH website (http://feedback.nih.gov/).

Council Questions and Discussion

Drug Repurposing--The concepts behind the NCATS are worthwhile, particularly the idea of repurposing pharmaceuticals. Will the urgency of a problem influence this strategy in NCATS? Dr. Ranganathan replied that, at least in the pilot phase, the hope is that mutually agreeable terms can be worked out with respect to proprietary and other issues for the repurposing of drugs. He mentioned a recent example in which a major pharmaceutical company made a large amount of its compounds available to a university for research purposes, provided that the company would have first right of refusal to commercialize emerging discoveries.

NCATS Activities on Continuum of Translational Efforts--Will NCATS efforts encompass only the creation of T1 space or will they also include implementation science? Dr. Ranganathan noted that the NCATS mission statement includes development, testing, and implementation of therapeutics. Therefore, it is expected that the NCATS will work across the T1 space from the perspective of trying to improve the translational process. The CTSAs already have community-engagement efforts and they participate in comparative effectiveness trials and outcome studies. The issue is to find better ways to do these activities.

*[**Explanatory note regarding T1 space**: Although definitions of translation research may vary in their wording, T1 translation has generally been considered as the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans. T2 translation has been considered the translation of results from clinical studies into everyday clinical practice and health decision making. [For example, see Woolf, S.H. "The Meaning of Translational Research and Why It Matters." JAMA 299(2), 211-213, 2008.]*

Prevention--Will the focus of the NCATS be exclusively or primarily on treatments and cures, or will there also be creative thinking about ways to promote wellness and prevention? Dr. Ranganathan said that the importance of prevention efforts is clearly recognized--noting that the NCATS will have to prioritize its activities within a limited budget. He encouraged the Council members to share with him any ideas they have about potential undertakings, specifically from an experimental perspective.

Requests for Applications (RFAs)--Recognizing that NCATS will have limited funding, will it promote the development of Requests for Applications (RFAs) by the Institutes and Centers? Dr. Ranganathan replied that the operational details regarding the issuance of RFAs have not yet been determined. However, it is possible that one role the NCATS could play is to serve as a hub for catalyzing opportunities across the Institutes and Centers. In that way, the NCATS would be able to leverage resources. He noted, for example, that the NIH CTSA Centers also receive support from the medical schools and academic departments in which they are located. One scenario is that a grantee could turn to the NCATS for help in overcoming an early translational hurdle, and then the investigator could apply to have the relevant Institute pick up the costs of subsequent

clinical studies. The NCATS would not have a mechanism to fund clinical trials in every therapeutic arena.

Collaboration with the Food and Drug Administration (FDA)--How will this collaboration be effected? Also, once a product is approved and marketed, will there be post-approval efforts by the NCATS to assess its effectiveness? What will happen with respect to training in regulatory science? Dr. Ranganathan underscored that it is important for researchers to understand the regulatory landscape so they know whether they are pointed in a useful direction in developing a particular research project. The NCATS regulatory science initiative is in its early stages of development; therefore, elements of it are yet to be determined. The Leadership Council has met once and their working groups are being formed. Already, promising initial conversations have occurred with the FDA leadership. The external community appears very interested, as reflected in discussions with industry groups. The NIH has been told by industry representatives that two of the most important contributions it can make are to improve the regulatory science process, and to identify biomarkers that would be acceptable to the FDA in moving clinical trials forward.

Funding--What will be the source of funds to support the ambitious mission and agenda of the NCATS? If the NCATS is not going to subsume or duplicate existing activities in the Institutes and Centers, that means that new funding will be necessary for the planned Center to achieve its mission at a time when the NIH budget appears to be in a somewhat steady state. Dr. Ranganathan replied that there is a definite hope that the authorization of the Cures Acceleration Network will result in the appropriation of new funds. Additionally, the NCATS hopes to leverage funding through catalytic efforts. Obviously, the number and scope of NCATS projects will be largely dependent upon the resources made available to it.

Evaluation--In the future, how will we know whether the NCATS was a good investment in terms of improving the cost-effectiveness of bringing new compounds and diagnostics to the market place? Dr. Ranganathan expressed his hope that the success of the NCATS would not be evaluated by the number of projects it spearheads to the market place. Rather, he believes the metrics should be along the lines of reducing the number of failures in Phase I and Phase II clinical trials; decreasing the amount of time expended on the drug discovery and commercialization process; and/or increasing confidence in data that will aid the Institutes, industry and the entire community.

VII. UPDATE: DIVISION OF PROGRAM COORDINATION, PLANNING, AND STRATEGIC INITIATIVES (DPCPSI)

Dr. James Anderson, Director

In introducing Dr. Anderson, Dr. Germino noted that the Division he directs is identifying emerging scientific opportunities, public health challenges, and gaps in scientific knowledge that merit further research. The Division plans and implements trans-NIH initiatives supported by the Common Fund and coordinates research related to AIDS, behavioral and social sciences, women's health, and disease prevention. Before

joining the NIH, Dr. Anderson was a Principal Investigator on NIH grants--the majority from the NIDDK--for almost twenty years. He has served as Professor and Chair of the Department of Cell and Molecular Physiology in the School of Medicine, University of North Carolina at Chapel Hill, and as Professor of Medicine and Cell Biology and Chief, Section on Digestive Diseases, Yale School of Medicine. He has extensive clinical experience in both internal medicine and hepatology.

Dr. Anderson described the activities of the NIH Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI), which he directs. The NIH Reform Act of 2006 (P.L. 109-482) called for the establishment of the Division within the Office of the NIH Director. The Division's Office of Strategic Initiatives coordinates the NIH Common Fund, which was authorized in the same legislation to provide resources to support the facilitation of trans-NIH research. Dr. Anderson noted that the Common Fund includes the transformative research activities that were begun under the NIH Roadmap Initiative framed by the former NIH Director, Dr. Elias Zerhouni. He said that the Division also includes several standing offices that provide sustained efforts to stimulate and coordinate trans-NIH research activities. These include the Office of AIDs Research, the Office of Research on Women's Health, the Office of Disease Prevention (including components that address dietary supplements, rare diseases, and medical applications of research), and the Office of Behavioral and Social Science Research.

Operational Framework of the NIH Common Fund

Dr. Anderson said that his presentation would focus on activities undertaken through the Common Fund, which provides short-term investments to address specific challenges and to catalyze work funded by the ICs. The Common Fund supports cross-cutting programs that require participation by at least two ICs, or those that would otherwise benefit from strategic planning and coordination. The vision for the Common Fund is that it should: (1) serve as a test-bed for high-risk, enabling, or emerging scientific opportunities, (2) establish and test new ways of supporting research to foster innovation, (3) accelerate the pace of discovery and improve the translation of research findings into medical and health interventions for public benefit, and (4) provide temporary funding investments of 5-10 years to catalyze research. There is an expectation that tools, technologies, and data generated in Common Fund programs will be useful to the broad research community. After a short-term period of support, the research resources or infrastructure generated and tested in Common Fund programs will need to transition to other sources of support. The Common Fund's budget for FY 2011 is $543 million. Dr. Anderson said that a substantial portion of the funds is used to support investigator-initiated research. (http://commonfund.nih.gov)

Importantly, Common Fund programs must meet certain eligibility criteria. They must be transformative, with a high potential to dramatically affect biomedical and/or behavioral research over the next decade. Outcomes must synergistically promote and advance individual missions of the NIH ICs to benefit health. Program areas must cut across the missions of multiple NIH ICs and be relevant to multiple diseases or conditions.

Common Fund programs must also focus on something that no other entity is likely or able to do, and the research results must benefit public health.

Dr. Anderson noted that Common Fund programs are catalytic in spurring discovery. Several programs focus on the development of new tools, infrastructure, and data to support or establish new fields of study (for example, the Molecular Libraries Program, Human Microbiome Project, Genotype-Tissue Expression Resources Project, and Protein Capture Reagents Project). Other programs foster the development of new technologies and approaches to overcome barriers to progress in a field (for example, the Structural Biology Program, and the Technology Centers for Networks and Pathways). Still other programs are pioneering new approaches to foster innovation and creativity (for example, the Interdisciplinary Research Program, High-Risk High-Reward (HRHR) Program, Pioneer Awards, New Innovator Awards, Transformative R01 (TR01) Awards, and Early Independence Awards). There were over 20 different programs/projects initiated through the Common Fund during the 2004-2010 time period. The four with the largest expenditures, in descending order, were the programs on High-Risk, High-Reward Research, Molecular Libraries, Interdisciplinary Research, and Clinical Research.

In developing Common Fund programs, the Division uses the flexible research authority provided in statute, and a process that includes the development of well-defined goals and milestones. If goals are not met, funding can be terminated. Dr. Anderson described the two-phase Common Fund Strategic Planning process. In Phase 1, broad scientific needs and opportunities are identified through external input via targeted meetings, Requests for Information, and input from professional organizations, along with internal input from NIH scientific leaders. One question is: Is there a major obstacle that several ICs face in moving a research area forward? In Phase 2, broad program areas are refined into specific initiatives through a broad vetting process. Final decision-making about whether to undertake a specific program is based on discussions and priority setting by the IC Directors and the NIH Director. In general, goals for new programs are communicated to the research community through purpose-driven Requests for Proposals.

Examples of Translational Research Supported by the Common Fund

Dr. Anderson provided some examples and highlights of several Common Fund Programs, with particular emphasis on those that foster translational research.

- *Human Microbiome Project: Focuses on understanding how microbes work in our bodies.* The ultimate goal of the Human Microbiome Project is to develop a database that correlates genotypes of many individuals with patterns of gene expression in many tissues. This will be accomplished in a phased effort involving the collection and analysis of tissue samples from human donors. To this end, a reference set of microbial genome sequences is being developed from five sites in the body. This resource should enable scientists to conduct demonstration projects on microbial contributions to disease; develop new technologies for isolating and sequencing individual microbes and complex populations; develop new computational tools; perform coordinated data analyses; establish a repository of research resources; and

assess the ethical, legal and social issues surrounding this research area. Thus far, the project has produced sequenced genomes of over 500 microbial strains and discovered over 29,000 novel proteins encoded by the human microbiome. This work has relevance to Crohn's disease, dermatitis, obesity, abdominal inflammation, acne, undiagnosed fever, and other health problems. The Project also includes a Genotype-Tissue Expression Resource (GTEx) Program to understand how genetic sequences regulate protein levels.

- *Protein Capture Reagents Project: Intended to address the needs of scientists for a reliable, renewable community resource for detecting proteins encoded by the genome.* The Project will produce new antigens for the research community to make protein capture reagents; scale-up existing monoclonal antibody technology; and develop new renewable capture technologies.

- *Structural Biology of Membrane Proteins Project: Seeks to overcome hurdles to membrane protein isolation and the determination of 3-D structure for the purpose of enhancing research and drug development.* For example, the Project has solved the 3D structure of a chemokine G-protein coupled receptor that is important for HIV infection and the growth and the metastasis of many cancers. It has also solved the 3-D structure of a dopamine receptor subtype that has a role in movement, cognition, and emotion, and that may help researchers design new medical approaches for schizophrenia, Parkinson Disease, and drug addiction.

- *Molecular Libraries Program: Offers biomedical researchers in the public sector access to large-scale screening capacity to identify small molecules that can be optimized into chemical probes to advance biological discovery and drug development.* Resulting information is deposited in the open-access database PubChem. Since 2005, 235 probes have been identified. Probe reports include information on the probe structure and characteristics, recommendations for scientific use, assay results, bibliographical material, and medicinal chemistry data.

- *High-Risk/High-Reward Program: Supports exceptionally creative scientists who propose highly innovative approaches to major contemporary challenges in biomedical research* (https://commonfund.nih.gov/highrisk/). Using novel approaches to peer review and funding mechanisms, the Program provides a "space" for the NIH community to seek support for potentially transformative projects that are high-risk, with the potential for significant impacts, but for which preliminary data are not easily obtained. Dr. Anderson focused on three awards funded by the Program--the NIH Director's Pioneer Award (https://commonfund.nih.gov/pioneer/), the NIH Director's New Innovator Award (https://commonfund.nih.gov/newinnovator/), and the Transformative R01 Award (https://commonfund.nih.gov/T-R01/)--all of which are intended to encourage creative, outside-the-box thinking. A fourth award was created in FY 2011 to support exceptional early-career scientists who possess the intellect, scientific creativity, drive, and maturity to flourish independently immediately following their graduate training, eliminating the need for traditional post-doctoral training. Started in a pilot mode, this new award, the NIH Director's Early

Independence Award (EIA), has roots in several successful programs in academia (https://commonfund.nih.gov/earlyindependence/). It is intended as a means of addressing the delay in research activity reflected in trend data from 1980-2009 showing steady increases in the age at which M.D., Ph.D., and M.D.-Ph.D. investigators receive their first R01-equivalent award from the NIH.

Dr. Anderson cited two examples of publications that describe some of the research findings emerging from the High-Risk, High-Reward Program: "Novel High-Throughput Technology To Test Compounds for Nerve Regeneration" by C. Samara et al., *PNAS,* Oct. 26, 2010, and "Antibiotic Use Alters Composition of Gut Microbes" by L. Dethlefsen and D.A. Relman, *PNAS Early Edition,* 2010.

Dr. Anderson closed his presentation by noting that plans are under way to transfer some components of the Division to the planned Center for Advancing Translational Research (NCATS), as described in Dr. Ranganathan's presentation. These transfers are expected to include components of the Molecular Libraries Program, the Clinical Research Program, and the Regulatory Science Program, as well as the Rare Diseases Program.

Council Questions and Discussion

What is the Division doing to address one of the real hurdles in advancing science--acquiring more knowledge about functional biology? There are many tools, such as high-throughput screening and optimized chemicals, but the effects of modulating drug targets are not yet known. Dr. Anderson replied that the Division is working on linking data, such as information from medical records, imaging studies, and genome-wide association studies. He expects that the next round of Common Fund programs will have these types of components.

With respect to the molecular libraries, are there mechanisms to disseminate compounds to investigators and remove a major research roadblock? Dr. Anderson responded that these chemicals are available in an accessible repository.

Is there a way that the Division can make or gain access to compounds that are within the purview of pharmaceutical companies that are reluctant to make them available for additional studies in animal models? It would be useful to be able to study such compounds in genetically altered animals to gain insights into pathways and phenotyping. Dr. Anderson said that these types of discussions are under way with pharmaceutical companies, and that, when feasible, this activity would be pursued through the planned National Center for Advancing Translational Science.

With respect to developing knock-out mice as a useful resource to the community, are there secondary efforts to provide conditional knock-outs in cases where a total knock-out may not be helpful because of embryonic lethality or a research impediment that develops with an early-stage phenotype? Are there also efforts to develop good deleter strains to knock-out genes in particular cell types of interest? Dr. Anderson replied that there is a project under way to address these types of issues, but it is not attempting to

create conditional knock-outs for every gene. Dr. Anderson noted that much of the focus is now on more in-depth phenotyping with high-profile genes that appear to be involved in many disease processes. It may also be possible to induce an embryonic cell to develop into a cell type of interest, thereby avoiding the need to develop a knock-out mouse.

Scientists who are conducting research exclusively with mammals should take advantage of the excellent systems presented by drosophilia, zebrafish, and C. elegans. A modest amount of additional support could make repositories for these non-mammalian systems more robust and widely used. Dr. Anderson noted that this is a very good thought.

How confident is the Division that the data repository and analysis infrastructure is sufficiently robust to assess all the collected data? Dr. Anderson replied that there are many other functions in the Division that he had not mentioned including a nascent effort using information-technology tools to evaluate the portfolio. The Division is trying to understand the portfolio of each NIH component in terms of gaps and commonalities in order to improve coordination at the program level across the NIH.

In determining which of the many lines of research should be pursued, weight needs to be given to the relevance of a potential project to human health. Dr. Anderson noted that such priority-setting is an integral part of the Division's decision-making process.

VIII. ADVISORY COUNCIL FORUM: "NIDDK Centers Program"
Dr. Germino, Deputy Director, NIDDK

Dr. Stanfield prefaced Dr. Germino's presentation on the NIDDK Research Centers Program with some background information. He noted that the Program encompasses the fields of diabetes, digestive diseases, kidney diseases, obesity, cystic fibrosis, molecular therapy, urology and hematology. It grew from 59 Centers in 1995 to nearly 80 Centers in 2003--the close of the NIH five-year budget-doubling period. The Council discussed the Centers Program at its February 2010 meeting, including the size of the Program, approaches to evaluating it, ways to encourage greater accessibility to and sharing of core facilities and resources, and the balance of support for institutional versus regional or national resources. Based on that discussion and other input from Council members, the NIDDK decided to conduct a series of visits to several academic institutions that have multiple NIDDK Center grants. Dr. Germino's presentation was intended to provide an interim update and preliminary findings regarding those visits and to garner further advice from the Council.

Dr. Germino said that the Research Centers Program is an important part of the NIDDK portfolio, and that the Institute wants to maximize its efficiency, effectiveness and impact. Therefore, the NIDDK is re-examining the outcomes of a 2003 Centers evaluation, and also addressing suggestions about Centers made by the Council at its meeting in February 2010. (See minutes of that meeting at: http://www2.niddk.nih.gov/NR/rdonlyres/C92538FB-C0AC-4456-97D9-9234B945851F/0/NIDDKCouncilMinutesFeb20104510_final.pdf)

As part of this effort, the Institute conducted a number of visits to institutions with multiple NIDDK Research Center grants in order to gain additional information about their operations--especially synergistic interactions. Dr. Germino emphasized that these visits were for information-gathering purposes, not auditing. The NIDDK is still processing the information it obtained, but wanted to give the Council a preliminary, interim update.

Dr. Germino gave a brief description of the NIH Research Centers mechanism for the broad audience attending the Council meeting. Centers typically serve dozens of Principal Investigator "members" and associates who have related research interests. NIH-funded Centers usually have administrative and scientific Cores that provide centralized services, and often will have a competitive Pilot and Feasibility program supporting the early phases of promising research, as well as Enrichment Activities. Ideally, Centers will foster a collaborative research environment and play an important role in training the next generation of scientists. Dr. Germino stressed the importance of recognizing that the Centers are heterogeneous, even those within a particular category; therefore, generalizations cannot be made about Center types or the Program as a whole based on examples.

Overview of NIDDK Research Centers Program

Dr. Germino pointed out that the following mechanisms are the primary ones used by the NIDDK to support Research Centers, and they have thus been the focus of evaluative efforts: P30 Core Center Grants, P50 Specialized Centers, P50 Specialized Centers of Research, P60 Comprehensive Centers, U24 Cooperative Agreement (for the Mouse Metabolic Phenotyping Centers only), and R24 Resource Related Research Projects (for the Digestive Diseases Research Development Centers only). The latter two designations are not typical mechanisms/codes for Centers, but the NIDDK is using them to fund activities that are "Center-like" and they are therefore included in budget data on the Centers Program. Other mechanisms that have not been a focus of evaluation, but that are included in the NIDDK's Centers Program budget, are: P20 Planning Centers for Interdisciplinary Research in Benign Urology; U54 Rare Diseases Clinical Research Consortia; NIDDK partial support for the Centers of other NIH components; and PL1 grants that are largely funded by the Office of the NIH Director but administered by the NIDDK.

In terms of budget, funding for the NIDDK's Research Centers Program has grown over the last 15 years, as has the overall Institute budget. In 1995, the budget for the Centers Program approached $60 million. In FY 2010, the budget was over $100 million.

Dr. Germino provided a historical perspective on the development of the NIDDK Research Centers Program. In FY 2010, the NIDDK provided support for 87 Research Centers, most of which had their origin in congressional language. For each type of Center, Dr. Germino provided the numbers funded in FY 2010 and the date of inception: 16 Diabetes Research Centers (1973); 12 Nutrition-Obesity Research Centers (1979)--with origins in earlier Centers; 17 Digestive Diseases Research Centers (1984); 8 George

O'Brien Kidney Research Centers (1987); 4 George O'Brien Urology Research Centers (1987); 2 Pediatric Nephrology Research Centers (1991); 3 Molecular Therapy Core Centers (1993); 5 Molecular Hematology Research Centers (1994); 4 Polycystic Kidney Disease Research Centers (1999); 4 Mouse Metabolic Phenotyping Centers (2001); 3 Specialized Centers on Women's Health Research (2002)--in conjunction with the NIH Office of Research on Women's Health; 4 Digestive Diseases Research Development Centers (2003); and 5 Cystic Fibrosis Research and Translation Core Centers (2005). Dr. Germino pointed out that over 50 of the 87 Centers currently funded are in cities that have four or more NIDDK-funded Centers. These geographic proximities suggest the possibility of fostering synergies and/or or efficiencies among them.

Consistent with the Council's recommendations with respect to the outcomes of the 2003 Centers evaluation, the NIDDK has attempted to broaden the use of Pilot and Feasibility projects in the Centers, and has also changed the emphasis given to certain mechanisms. Specifically, the Institute has reduced the numbers of P50 Specialized Centers, while expanding the numbers of P30 Centers, which currently account for nearly 70 percent of the Centers' budget, excluding funds provided through the American Recovery and Reinvestment Act (ARRA). The P60 Centers account for about thirteen percent of the Centers' budget; the P50s account for about seven percent; and the combined R24/U24 mechanisms also account for about seven percent.

The NIDDK is also giving careful consideration to suggestions made by the Council at its February 2010 meeting. The Council suggested that the NIDDK: (1) identify synergies between/among Centers, (2) encourage interaction between Centers, and foster regional and national cores, (3) enhance access to Center resources, (4) assess the value and use of the Pilot and Feasibility Program, and (5) use the Centers to promote clinical and translational research. In an effort to gain information relative to these suggestions, the NIDDK conducted several site visits to its Centers.

Site Visit Process and Preliminary Information Gathered

Between December 2010 and March 2011, the NIDDK visited five academic institutions, each of which houses five NIDDK Research Centers, and thus has opportunities for synergies. The purpose of these visits was to gather information for enhancing the Program--especially with regard to achieving maximum efficiency through synergistic interactions and cross-fertilization among Centers. The institutions visited were: the University of Pennsylvania, Yale University, Washington University in St. Louis, University of Washington, and Vanderbilt University. The 25 Centers visited provided a broad sampling of Center mechanisms, with the exception of the Digestive Diseases Research Development Centers (R24 grants), none of which were housed at the institutions visited. The NIDDK visitors were the NIDDK Director or Deputy Director, the relevant Program Directors, the Director of the Division of Extramural Activities or his Deputy, and a Health Science Policy Analyst from the NIDDK Office of Scientific Program and Policy Analysis.

In planning these site visits, the NIDDK decided, for several reasons, to take a qualitative rather than a quantitative approach. First, investigators tend to find retrospective, quantitative data analyses (e.g., structured questionnaires and surveys) very burdensome. Second, quantitative analyses are typically undertaken when there is a need to resolve perceived problems in a Program--and that was not the case with the Centers Program. Third, the NIDDK wanted to take a cost-effective, time-sensitive, exploratory approach--on a compressed schedule. In advance of the visits, the NIDDK sent all the Centers in the Program the questions that would be posed during the visits. In that way, even the Centers that were not visited were fully aware of the process. These questions focused on membership, types of Core users, Core operations, prioritization of services, and degree of institutional support. The NIDDK also made clear that the information it collected would be reported in the aggregate, without reference to specific Centers.

The NIDDK conducted two-day visits to the five institutions. The visits included remarks by the NIDDK team and institutional representatives; presentations by Core Directors; tours of Core facilities; discussion about operational aspects of each Center; presentations by recipients of Pilot and Feasibility awards; and open discussion/feedback. Dr. Germino gave some examples of the types of information the NIDDK gathered:

- *Center Membership:* The discussion regarding membership provided the NIDDK with information regarding whether investigators are members of more than one Center; differences among members, users and research-base investigators; members' interactions within and among NIDDK Centers and with other NIH-funded Centers; and extent of involvement with the NIH Clinical and Translational Science Awards (CTSA) Program. Center membership at the sites that were visited ranged from 30 to over 100 scientists, including full and associate members both within and outside of the home institution. The majority of Centers required that their members have Federal funding, typically NIDDK funding. In some cases, membership was required in order to use the Core facilities.

- *Synergistic Interactions:* The NIDDK sought information about synergies that improve cost-effectiveness; foster interactions at local, regional and national levels; and reduce barriers. The NIDDK team found examples of synergistic collaborations and coordination among investigators with complementary interests, such as co-retreats among diabetes and obesity Centers and courses organized by the Mouse Metabolic Phenotyping Centers with some of the diabetes and kidney Centers. Some Centers share Core personnel and engage in the sharing and co-funding of Cores. Some investigators were members of more than one Center, often due to cross-cutting research interests. Some Center Directors have administrative duties that cut across the Centers at their institutions.

- *Research Cores:* The NIDDK visited 43 per cent of the Cores at the five institutions visited that were funded through the NIDDK Research Centers Program (42/97). Discussions covered several topics including uniqueness; kinds of services offered and their prioritization and promotion; physical location of the Centers and types of users; fee structure and degree of institutional support; training components; and adaptation

of services based on investigators' needs and usage patterns. Cores were typically located in adjacent buildings at a site, with dedicated space for Core services. The Directors of the Cores were individuals in different career paths and career stages. Some Cores seemed to benefit when they had the resources to acquire professional Core staff who could dedicate their efforts to managing the Core, including equipment and training. Most Cores operated on an open-access basis--on a first-come, first-served basis--with little prioritization of requested services. The contributions of Cores were valued in multiple ways, including the benefits of economies-of-scale and the recognition by investigators that they were gaining access to research resources not available in their own laboratories. There were some instances of overlapping services for various reasons. Cores offered a mix of standard and specialized services and had evolved in response to the needs of members. There were few defined business plans. Cores engaged in cost-setting guided by OMB Circular A-21 ("Cost Principles for Educational Institutions"), and they followed defined institutional policy. The general practice was to provide Core services without charge, or to charge all users the same amount (with no "discount" for Center members). Some institutions had or were developing a comprehensive list of research Cores to share with investigators.

- *Pilot and Feasibility Programs:* The visited sites had a strong commitment to Pilot and Feasibility Programs. Awards were typically made to new investigators, or to established investigators wishing to explore a new field of interest or a new research direction. These programs tended to be distributed internally within each Center due to the excellence of the internal candidates, and the logistical issue of transferring indirect costs to another institution if awards were made externally. The NIDDK discussed with the Centers possible ways for overcoming institutional barriers so that these programs could be broadened to include investigators beyond the Center.

- *Training and Enrichment Programs:* Although the Centers mechanisms do not provide direct support for training, the Centers visited by the NIDDK considered the training and the development of young scientists to be an important part of their missions through Pilot and Feasibility efforts and other components of the Center. Aspects of training-related activities included mentoring and consultation provided by Core staff, and enrichment activities such as research seminars, annual symposia/retreats, technology seminars/courses, and videocast seminars to researchers at other locations. Some Centers offer summer research programs and the opportunity for a "year out" for individuals who want to have a research experience during their medical education.

- *Institutional Support:* Institutional support ranged in amount and type. Some sites had very little or no institutional oversight, whereas others had significant institutional coordination.

Dr. Germino concluded his presentation by again emphasizing that the Centers are very diverse in their operations. While institutions vary in their administration and oversight of these programs, in each of the intuitions that were visited there were a number of examples of synergies occurring. Interestingly, the NIDDK site visits were typically the first interaction among all NIDDK-funded Centers at a given institution. These visits

also provided an opportunity for all NIDDK staff who oversee Research Centers to come together to discuss common issues.
Dr. Germino outlined the next steps that the NIDDK plans to take with respects to its Research Centers Program. The Institute will look for a stimulating, non-burdensome way to gain additional information, with a continuing emphasis on synergy. The information gathered will be used to develop a written report to the Council. That report and the Council's further input will inform the Institute's decisions about ways to enhance the Research Centers Program. To assist with this process, Dr. Germino asked the Council members to consider the following questions and give the NIDDK their thoughts.

- Are there additional strategies that the NIDDK should pursue regarding collecting data on the Research Centers?
- Are there other specific topics from the preliminary observations that the NIDDK should explore further?
- What information would be helpful in determining the size, number, composition, and focus of Centers the NIDDK should support? How should size be determined?
- How should applicants report their research base when related NIDDK Centers have members in common?
- How should NIDDK balance flexibility to meet local needs with the need to achieve its program goals?
- Should NIDDK implement mechanisms to broaden/strengthen interactions between Centers (e.g., Web-based meetings, regional meetings)?
- Should NIDDK make the Pilot and Feasibility Program more uniform across Centers?

Dr. Germino thanked all the individuals who contributed to the site visits--extending special appreciation to the following points-of-contact at the universities: Dr. Robert Alpern (Yale), Dr. Nicholas Davidson (Washington University, St. Louis), Dr. Raymond Harris (Vanderbilt), Dr. Mitchell Lazar (University of Pennsylvania), and Dr. Jerry Palmer (University of Washington).

Council Questions and Discussion

The Council members considered the site visits and presentation useful and they offered the following comments.

Overarching Goals--What is the goal of the NIDDK Research Centers Program? What sorts of activities does the Institute want to foster with its investments? What are the strategic objectives of the Research Centers Program and how do they relate to NIH strategic objectives? Before additional data gathering and analysis, it would be advisable for the NIDDK to articulate the overall goal of its Research Centers Program, even though it is heterogeneous. For example, is the primary goal of the Program to provide some form of disease-focused or institutional support? If so, there may be philosophical parallels to the investigator-initiated, non-directed nature of regular

research grants (R01 grants), which essentially provide the flexibility to "let a thousand flowers bloom." If this is the goal, then the Institute has already done due diligence in evaluating the Program, and further analyses are not really necessary. On the other hand, if the goal of the Program to accomplish more specific objectives (e.g., synergistic regional or national resources) by using a more organized, uniform, directed approach, then a different type of evaluation would be appropriate. If an overarching goal is not articulated, then the NIDDK could simply continue to gather information annually--perhaps through informal meetings--or ask the Centers questions periodically. Such questions, by their very nature, are likely to stimulate reflective thinking and Program improvements. However, without agreement on goals and objectives, spending additional time on evaluation and measurements may not be useful.

Disease-Specific Goals--Can goals be stated for at least a subset of Research Centers--the disease-focused Centers? Given the diversity among the Centers, it may not be possible to articulate an overarching goal. However, the NIDDK could attempt to state the goal(s) that the disease-focused or discipline-specific Centers have in common (e.g., diabetes, kidney, urology, and digestive diseases Centers). Trends and patterns with respect to issues such as uniformity and synergy may be better analyzed with such an approach, which clusters together similar types of Centers for the purpose of evaluating their progress in reaching established goals. The NIDDK's fiduciary decisions would probably benefit from looking across the disease-focused Centers with respect to their Cores and Pilot and Feasibility projects.

Cores--Cores need to be dynamic and flexible. Cores are central to the mission of the Centers. It is important to distinguish between and support their two main purposes: (1) to provide services, which tend to be institution-based, and (2) to foster implementation of new technology.

Pilot and Feasibility Projects--How can NIDDK enhance and demonstrate the value of Pilot and Feasibility Projects in terms of leveraging investigative talent? Although these projects are a relatively small percentage of the Centers' budgets, they have been leveraged historically to develop and nurture junior investigators. The support they receive is thus translated in many different ways into producing a cadre of scientists who then compete successfully for Research Career Development Awards (K awards) and regular research grants (R01 grants). The return on investment from these Pilot and Feasibility activities is substantial and should be analyzed.

Comparative Analyses--Is it possible to determine the output and quality of one type of investment relative to another? At some level, evaluation is a quality-improvement exercise. The Institute must decide whether spending funds on one type of program is more or less productive than spending funds on an alternative program. To make an informed decision requires quantifying the yield from the respective programs in terms of goals. For example, with regard to nurturing scientific talent, one could ask how the "yield" from the Pilot and Feasibility Projects in the disease-focused Research Centers Program compares with that from the Research Career Development Programs or the

Bridge Programs. If the NIDDK develops quantitative or semi-quantitative metrics, it can look in a direct way at programs with similar goals.

Corporate Model--Perhaps the NIH should consider whether it is missing an opportunity to follow a corporate model--using the Core Centers as a supply chain for histology, transgenic mice, and similar projects. A collaborative model could be developed similar to the approach used in clinical trial groups that have a central data coordinating center. The model could reduce barriers and foster collaborations among institutions in these times of fiscal constraints. Duplicative activities could be eliminated and economies of scale realized. The success of clinical trials groups demonstrates that there are ways to overcome barriers to collaborations within and among institutions.

Dr. Germino thanked the Council members for their comments, which can help enhance the NIDDK Research Centers Program. As to whether it is preferable to adopt a cost-effective corporate model, a smaller local model, or a hybrid model, Dr. Germino noted that this may be a philosophical issue. With respect to metrics, he said that there have been many attempts to conduct retrospective, quantitative assessments of programs such as Centers and Program Project grants by looking at publications and other measurable outputs. However, there does not seem to be a good way to determine prospectively whether the same amount of funds would be more productively invested in these mechanisms *versus* regular research grants. Dr. Germino noted that higher levels of funding are likely to produce greater productivity through any mechanism used, and this fact has stymied comparative analyses among different types of programs. That is part of the reason the NIDDK did not take a quantitative approach to evaluating its Centers Program at this point in time. Moreover, there are some Center effects, such as synergy, which are very difficult to measure quantitatively. A Center may foster important collaborations within and outside of an institution that may not have occurred otherwise. Moreover, when a community develops a new Research Center, investigators come together in new ways--providing cohesiveness to the community that may not have existed previously. Analysis of quantifiable outputs is not likely to capture these types of intellectual, synergistic interactions. Dr. Germino said that the goals of Pilot and Feasibility projects can be defined relatively well in Requests for Applications, and this component of Centers may be amenable to some short-term assessments. Long-term, retrospective analyses would probably be required to determine whether Centers reach their ultimate goal of having a salutary effect on science.

IX. SCIENTIFIC PRESENTATION: "Genetics of Chronic Kidney Disease"

Dr. John Sedor, Professor of Medicine and Physiology, Case Western Reserve

Dr. Sedor has been the recipient of numerous awards and NIDDK grants. He served as director of an NIDDK O'Brien Renal Research Center at Case Western Reserve, and as a participating investigator in the Family Investigation of Nephropathy of Diabetes (FIND) Consortium. Since 1989, he has served as a member of NIDDK review groups and NIH study sections. Dr. Sedor's research interests span basic and clinical nephrology, with a particular focus on understanding genetic mechanisms of progressive kidney disease.

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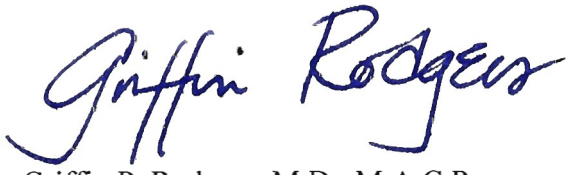
X. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1,797 grant applications, requesting support of $475,215,556 were reviewed for consideration at the May 11, 2011 meeting. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 1,059 applications requesting $284,197,180 received second-level review through expedited concurrence. All of the expedited concurrence applications were recommended for funding at the Scientific Review Group recommended level. The expedited concurrence actions were reported to the full Advisory Council at the May 11, 2011 meeting.

XI. ADJOURNMENT

The NIDDK leadership thanked the Council members for their attendance and valuable discussion. There being no other business, the 186th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m., May 11, 2011.

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



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