

Meeting Minutes
Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
September 12, 2012

I. CALL TO ORDER

Dr. Rodgers

Dr. Griffin P. Rodgers, Director, NIDDK, called to order the 190th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m., Wednesday, September 12, 2012, in the Natcher Conference Center (Building 45), Conference Rooms E1/E2, on the NIH campus in Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Domenico Accili	Dr. David M. Klurfeld
Ms. LaVarne Burton	Ms. Robin Nwankwo
Dr. Judy H. Cho	Dr. Jerry P. Palmer
Dr. Robert C. Flanigan	Dr. Thomas N. Robinson
Dr. Christopher K. Glass	Dr. Anil K. Rustgi
Dr. Gregory J. Gores	Dr. John R. Sedor
Ms. Jane Holt	Dr. Alan R. Shuldiner
Ms. Judy M. Hunt	Dr. William D Steers
Dr. Francine R. Kaufman	Mr. John W. Walsh
Dr. Kenneth Kaushansky	Dr. Mark L. Zeidel

Also Present:

Dr. Griffin P. Rodgers, Director, NIDDK, and Chairperson, NIDDK Advisory Council
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. Brent Stanfield, Executive Secretary, NIDDK Advisory Council

B. NIDDK STAFF AND GUESTS

Abankwah, Dora – NIDDK	Blondel, Olivier – NIDDK
Abraham, Kristin – NIDDK	Brown, Sherry – NIDDK
Agodoa, Lawrence – NIDDK	Buchanan, Sarah – Nephrology Care FDN.
Appel, Michael – NIDDK	Burnett, Arthur – Johns Hopkins Univ.
Arreaza-Rubin, Guillermo – NIDDK	Calvo, Francisco – NIDDK
Barnard, Michele – NIDDK	Camp, Dianne – CSR
Begum, Najma – NIDDK	Carrera, Krysten – NIDDK
Bishop, Terry – NIDDK	Carrington, Jill – NIDDK
Bleasdale, John – CSR	

Castle, Arthur – NIDDK
 Cleffi, Katie – Rsrch. Triangle Inst.
 Connaughton, John – NIDDK
 Copeland, Randy – NIDDK
 Cowie, Catherine – NIDDK
 Davila-Bloom, Maria – NIDDK
 Dayal, Sandeep – NIDDK
 Densmore, Christine – NIDDK
 Doherty, Dee – NIDDK
 Donohue, Patrick – NIDDK
 Doo, Edward – NIDDK
 Eggerman, Thomas – NIDDK
 Eggers, Paul – NIDDK
 Ehrhardt, Britt – NIDDK
 Evans, Mary – NIDDK
 Everhart, James – NIDDK
 Farishian, Richard – NIDDK
 Fonville, Olaf – NIDDK
 Fradkin, Judith – NIDDK
 Gansheroff, Lisa – NIDDK
 Garte, Seymour – CSR
 Giambarresi, Leo – Amer. Urological Assoc.
 Gill, Christine – NIDDK
 Goter-Robinson, Carol – NIDDK
 Graves, Reed – CSR
 Grey, Michael – NIDDK
 Guo, Xiaodu – NIDDK
 Haft, Carol – NIDDK
 Hamilton, Frank – NIDDK
 Hanlon, Mary – NIDDK
 Hardy, Dianne – CSR
 Hoff, Eleanor – NIDDK
 Hoofnagle, Jay – NIDDK
 Horlick, Mary – NIDDK
 Hoshizaki, Deborah – NIDDK
 Howards, Stuart – NIDDK
 Hubbard, Van – NIDDK
 Hunter, Christine – NIDDK
 Hunter, Helen – NIDDK
 Hyde, James – NIDDK
 Hypes, Brinkley – OHR, OD
 James, Stephen – NIDDK
 Jenkins, Connie – NIDDK
 Jerkins, Ann – NIDDK
 Jones, Teresa – NIDDK
 Karimbakas, Joanne – NIDDK
 Karp, Robert – NIDDK
 Ketchum, Christian – NIDDK
 Kimmel, Paul – NIDDK
 Kirkali, Ziya – NIDDK
 Kranzfelder, Kathy – NIDDK
 Krause, Michael – NIDDK
 Krishnan, Krish – CSR
 Kuczumarski, Robert – NIDDK
 Kusek, John – NIDDK
 Laughlin, Maren – NIDDK
 Leschek, Ellen – NIDDK
 Malik, Karl – NIDDK
 Malozowski, Saul – NIDDK
 Margolis, Ron – NIDDK
 Maruvada, Padma – NIDDK
 Martey, Louis – NIDDK
 McKeon, Catherine – NIDDK
 McKeython, Miya – NIDDK
 Miller, David – NIDDK
 Miller, Megan – NIDDK
 Moxey-Mims, Marva – NIDDK
 Mowery, Penny – NIDDK
 Mullins, Christopher – NIDDK
 Murphy, Shawn – RPDR Partners HealthCare
 Narva, Andrew – NIDDK
 Newman, Eileen – NIDDK
 Olan, Grant – Amer. Society of Nephrology
 Patel, D.G. – NIDDK
 Pawlyk, Aaron – NIDDK
 Peters, Craig – Children’s National Hospital
 Polglase, William – NIDDK
 Rankin, Tracy – NIDDK
 Rodrigues, Michelle – SRI International
 Rosendorf, Marilyn – NIDDK
 Rushing, Paul – NIDDK
 Salaita, Christine – NIDDK
 Salomon, Karen – NIDDK
 Sankaran, Lakshmanan – NIDDK
 Sanovich, Elena – NIDDK
 Sato, Sheryl – NIDDK
 Savage, Peter – NIDDK
 Scanlon, Elizabeth – NIDDK
 Schmitt, Jill – NIDDK
 Sechi, Salvatore – NIDDK
 Serrano, Jose – NIDDK
 Sherker, Averell – NIDDK
 Shepherd, Aliecia – NIDDK
 Silva, Corrine – NIDDK
 Smith, Jill – NIDDK
 Spain, Lisa – NIDDK
 Star, Robert – NIDDK
 Staten, Myrlene – NIDDK
 Tatham, Thomas – NIDDK
 Torrance, Rebecca – NIDDK
 Van Raaphorst, Rebekah – NIDDK
 Wallace, Julie – NIDDK
 Watson, Joanna – NCI
 Wellner, Robert – NIDDK
 Williams, Shimere – Lewis Burke Assoc.
 Wright, Daniel – NIDDK
 Wright, Elizabeth – NIDDK

C. ANNOUNCEMENTS

Dr. Rodgers made the following announcements:

Retiring Council Members

Dr. Rodgers recognized four Council members who were completing their terms and rotating off the Council with the September 2012 meeting. He thanked them for their service to the NIDDK and the NIH.

Ms. LaVarne Burton is President and Chief Executive Officer of the American Kidney Fund (AKF). Ms. Burton provided the Council with expertise in community outreach and education, and shared the perspectives of patients. She promoted collaboration between the NIDDK and the AKF including involvement in the roll-out of a "Pair Up" initiative designed to empower women to protect themselves, family, and friends from kidney disease. She helped to focus research efforts addressing health disparities.

Dr. Robert Flanigan serves as the Department Chairperson and a Professor of Urology at Loyola University. He is also a practicing physician and is active in multiple community health education and outreach activities. He provided the Council with a broad range of expertise in clinical urology and urology research. Dr. Flanigan helped the NIDDK develop initiatives and solutions to address concerns about workforce pipeline and training issues.

Dr. Christopher Glass is Professor, Department of Cellular and Molecular Medicine, Department of Medicine, University of California, San Diego. He brought to the Council expertise in basic research, including gene expression. His scientific acumen and sound judgment contributed to the discussion of issues of importance to the NIDDK. Dr. Glass provided wise counsel to the Institute as it is striving to maintain quality and cutting-edge science in the face of resource constraints.

Dr. John Sedor is Associate Chair for Research, Department of Medicine, MetroHealth Medical Center Campus, Case Western Reserve University. Dr. Sedor provided the Council with expert advice in both basic and clinical nephrology, especially the pathophysiology and genetics of chronic kidney disease. He has been a tireless advocate for the training of junior investigators. Dr. Sedor also serves as an advisor to a number of large NIDDK studies, and he played a key role in supporting the NIDDK's on-line strategic planning effort, the Kidney Research National Dialogue.

Awards

Ms. Robin Nwankwo, an NIDDK Council member, has received the America Diabetes Association's (ADA) Outstanding Educator in Diabetes Award in recognition of her educational efforts in the field of diabetes and significant contributions to the

understanding of diabetes education. As a diabetes educator and researcher at the University of Michigan Medical School, Ann Arbor, Ms. Nwanko has been a contributor to the development and implementation of empowerment-based educational research studies among urban African Americans. Her current work is a randomized, controlled feasibility trial of church-based diabetes education and peer support.

“In Memoriam”

Dr. John Stokes, who contributed to several NIH clinical research activities, has passed away. His roles at the University of Iowa included Professor, Executive-Vice-Chair for the Department of Internal Medicine, and Director of the Division of Nephrology. He coordinated the University of Iowa site of an NIH clinical trial on nocturnal dialysis. He also led in the planning and execution of many other seminal, multicenter NIH-sponsored clinical trials in nephrology. Dr. Stokes provided *ad-hoc* advice to the NIDDK on numerous occasions, and his expertise will be missed by the research community.

NIDDK Staff Members

Dr. Paul Eggers, Senior Scientific Officer for Kidney and Urology Epidemiology Programs, will be retiring from the NIDDK’s Division of Kidney, Urologic and Hematologic Diseases. During his 12 years with the NIDDK, Dr. Eggers contributed to the United States Renal Data System (USRDS), the Urologic Diseases in America (UDA) project, the Boston Area Community Health Study (BACH), the Data Center for the NIDDK Repository, and other efforts.

Dr. Jill Smith is joining the Division of Digestive Diseases and Nutrition as Program Director for Clinical and Translational Research in Digestive Diseases. Following her graduation from the University of Florida School of Medicine, Dr. Smith completed training in Internal Medicine and a Fellowship in Gastroenterology at the University of Missouri.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 189th COUNCIL MEETING

Dr. Rodgers

Following a motion that was made and seconded, the Council approved, by voice vote, the Summary Minutes of the 189th Council meeting, which had been sent to them earlier for review.

III. FUTURE COUNCIL DATES

Dr. Rodgers

Dr. Rodgers reminded the Council of future meeting dates.

2013

February 13-14 (Wednesday and Thursday)

May 15-16 (Wednesday and Thursday)

September 26-27 (Thursday and Friday)*

Building 31, Conference Rooms 10, 6 and 7

*** The divergence from the familiar Wednesday and Thursday schedule was noted.**

2014

February 5-6 (Wednesday and Thursday)

May 14-15 (Wednesday and Thursday)

September 3-4 (Wednesday and Thursday)

Building 31, Conference Rooms 10, 6 and 7

The NIDDK expects that most meetings will be a single day. However, Council members were asked to hold two days for each meeting to ensure flexibility should a situation arise where a longer meeting is required.

IV. ANNOUNCEMENTS

Dr. Stanfield

Confidentiality

Dr. Stanfield reminded 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. Stanfield reminded the Council that advisors and consultants serving as members of public advisory committees, such as the 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 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. Dr. Stanfield noted that each Council member's folder contains a statement regarding the conflict of interest in his or her review of applications. He asked each Council member 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 regard to multi-campus institutions of higher education, Council members were reminded that 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.

Special Council Review

Dr. Stanfield said that the NIH has established a new policy for Special Council Review, which requires the Council to give additional consideration to applications from Principal Investigators who have more than \$1 million in direct costs annually from active NIH Research Project Grants (RPGs). Prior to each Council meeting, the Electronic Council Book will provide members with a list of competing applications that meet the criteria for this Special Council Review. For each application on the list that may actually be funded, NIDDK staff will provide information about the other funding for the Principal Investigator that brings his/her direct cost total to the \$1 million threshold, and a justification for considering funding. Council members will review these cases and indicate whether or not they have concerns.

Approval of Revised Council Operating Procedures

Dr. Stanfield said that, from time to time, a need arises for the NIDDK to revise the Council Operating Procedures prior to their annual update at the winter Council meeting. He stated that these circumstances have occurred and that revised Council Operating Procedures were therefore included for the Council's review in the pre-meeting materials in the Electronic Council Book, and they were also included in the members' meeting folders at the conference table. The NIDDK needs to modify the Procedures with respect to the following:

- To add procedures for the Special Council Review;

- To accommodate special circumstances for an “earlier” early concurrence of applications on time-sensitive announcements such as the recently published ‘Time-Sensitive Obesity Policy and Program Evaluation’ Program Announcement;
- To remove the section on the NIDDK’s review of applications for the National Center for Advancing Translational Science (NCATS), which now has its own Council;
- To update references to NIH Manual Chapters.

In the absence of any questions or comments, and pursuant to a motion that was made and seconded, the Council approved the revised Operating Procedures by voice vote.

V. REPORT FROM THE NIDDK DIRECTOR

Dr. Rodgers

Update on Fiscal Year 2013 Appropriations Bills

Dr. Rodgers reported that, at the time of the September 2012 Council meeting, the United States Congress had not cleared any of the Fiscal Year 2013 appropriations bills, including the Labor-Health and Human Services bill that funds the NIH and several other agencies. Dr. Rodgers reported on congressional action with respect to that bill.

On the Senate side, the full appropriations committee passed a bill in June that would fund the NIH at the level of \$30.723 billion, an increase of about \$100 million over the previous fiscal year. The funding level for the NIDDK would be about \$2 million above its previous year’s budget of \$1.797 billion.

On the House side, a spending bill has passed the relevant appropriations subcommittee, but has not yet been acted upon by the full committee. It would provide \$30.6 billion for the NIH, which is essentially equivalent to both the Fiscal Year 2012 appropriation and the President’s request for Fiscal Year 2013. Funding for most Institutes would be reduced by about 0.02 percent from the previous year’s levels. Dr. Rodgers noted that the House appropriations subcommittee’s bill contains quite a bit of prescriptive language regarding the allocation of resources, as well as a system for assuring that research activities are of significantly high scientific value and would have a measurable impact on public health.

With the end of the fiscal year fast approaching, it is unlikely that the NIH will receive funding through a regular appropriations bill. Rather, one or more temporary spending measures, so-called Continuing Resolutions, are likely to provide initial Fiscal Year 2013 funds for agencies whose regular appropriations bills have not been enacted. A six-month Continuing Resolution has been introduced in the House, but it awaits Senate action. Such a short-term funding measure would remove some spending issues from the pre-election debate. It may also help to avoid the threat of a government shutdown

during the lame duck session of the Congress, which will occur during the period between the national election in November and the start of the new Congress.

Update on Possible Sequestration

Dr. Rodgers updated the Council on the implications of possible across-the-board reductions in federal spending. As mandated by law, these reductions, which are referred to as a sequestration of funds, would commence in January 2013 unless legislation is enacted to reduce the national deficit by specified amounts. If sequestration occurs, Federal agencies are expected to lose about 7.8 percent from their Fiscal Year 2013 budgets. The NIH would lose an estimated \$2.39 billion, which would bring success rates for grant applications to historically low levels. The Sequestration Transparency Act requires the President to provide the Congress with a report on the percentages and dollar amounts that would be cut from discretionary and mandatory spending accounts at the program, project and activity levels, as well as a list of accounts that are exempt from cuts. The report has not yet been submitted.

VI. “Outstanding Productive Investigator Umbrella Award”

Dr. Robert Star, Director, Division of Kidney, Urologic and Hematologic Diseases, NIDDK

Dr. Star requested the Council’s input regarding a very early-stage idea that the NIDDK has been exploring with other Institutes. He presented the conceptual framework for a possible new program of “Outstanding Productive Investigator Umbrella Awards.” The program is currently being considered as a potential collaborative effort with the National Cancer Institute (NCI). The concept is based in principle on the NCI’s Outstanding Investigator Program, which was created in 1985 after the President’s Cancer Panel recommended finding a way to provide more secure funding for established investigators. The NCI’s Program was terminated in 1995, and it was never evaluated. The new umbrella award concept has generated considerable debate and the NIDDK is eager to have the Council’s views.

The cornerstone of the umbrella award concept is to provide stable, long-term funding to an entire laboratory. Many investigators now devote substantial amounts of time in a continuous process of writing multiple grant applications—a process that can diminish productivity and creativity and may lead to negative attitudes toward research. The umbrella award program would allow highly productive investigators to bundle their current awards (from either NIDDK or NCI) into a single, renewable grant. Umbrella awards would enable investigators to pursue innovative, creative, and high-risk/high-impact research—this type of research tends to require stable, long-term funding that is not usually available in the current fiscal environment.

Dr. Star described some of the key features of the umbrella award concept. Awards are envisioned as being eight-to-ten year R35 grants, with a midpoint retrospective review.

These awards could be renewed as long as the program existed. To be eligible to apply, investigators would need to be continuously funded, highly productive, and substantial contributors to science. Importantly, they would need to agree to devote perhaps as much as 75 percent of their time to the effort, and their institutions would also need to make a major commitment—perhaps at least 25 percent of a Principal Investigator’s salary. In a Letter of Intent, applicants would document that they meet the eligibility requirements; indicate how research would be bundled within their laboratory; and demonstrate that the work is within the NIDDK mission.

The peer review process for umbrella awards would be similar to that for the NIH Intramural Research Program and the Howard Hughes Medical Institute. The review would be conducted by a Special Study Section, with approximately eighty percent of the review focused on the assessment of research already conducted (i.e., retrospective review), including its importance, progress, and impact. About twenty percent of the review would center on the applicant’s proposed general framework for planned research. The review for umbrella awards would therefore be quite different from the current NIH review system for extramural grants, which primarily focuses on a prospective review of detailed research ideas proposed in individual applications. If selected for an umbrella award, an investigator would relinquish all current individual investigator-initiated projects and accept a small reduction in overall funding. This reduction would be a tradeoff for the long-term funding stability provided by an umbrella award.

Dr. Star pointed out some of the potential benefits of umbrella awards. Investigators could spend more time conducting science and less on writing grants. Their research could therefore be more focused and creative. As a result, they would have more positive attitudes about their research careers to convey to trainees. In addition, the NIH would have fewer grants to review.

In closing, Dr. Star introduced some of the questions on which the NIDDK is seeking the Council’s views:

- What would be the overall impact of establishing an umbrella award program?
- What should be included in the program’s design elements, including eligibility criteria (e.g., career stage, funding level, and laboratory size); what kinds of grants would be bundled; would investigators be precluded from submitting additional bundled grants?
- Would Principal Investigators and institutions want this award?
- What would investigators be willing to relinquish for more stable, long-term funding?
- What review issues could be anticipated?
- What level of institutional commitment should be required?
- Should an umbrella award program replace the MERIT award program?

- What percent of the budget for research project grants should be allocated to an umbrella award program?
- What would be the overall perceptions regarding the fairness of an umbrella award program? Is it the wrong time to start such a program?

Dr. Star noted that the issues of perceived fairness and the appropriate timing of an umbrella award program are particularly important because the new program would make larger grants than those possible through the R01 grant mechanism. If a decision is made to move forward with an umbrella award program, the next steps would be to issue a Request for Information to gauge interest in the research community, and to work with the NCI and other Institutes and Centers to refine the concept further.

Council Questions and Discussion

Program Goals and Potential Benefits: *The nurturing of better science should be the primary goal. It is hoped that goal will be furthered by freeing highly creative scientists from the continuous burden of collecting perfunctory preliminary data needed for writing frequent grant applications. Another benefit may be the removal of established investigators from the R01 pool so that younger investigators can have greater opportunities to compete successfully in that pool.*

Possible Limitations on Award and Program Size: *How many NIDDK grantees would be eligible for an umbrella award? Would there be a limit on the total number of awards the program would make? Should there be a few large awards, such as four to six, or a larger number of small awards? Should there be a cap on program growth?* Dr. Star said that decisions would need to be made about the funding threshold for investigators, and about the overall size and growth of the program. Regarding possible funding thresholds, he presented a graph showing examples of thresholds reached by NIDDK investigators at points in time from 2007-2011. For example, for two years during that time period, 46 investigators reached a threshold of \$1 million in funding; 22 reached a threshold of \$1.2 million; and ten reached a threshold of \$1.5 million.

Possible Limitation on Duration of Awards: *Because science changes rapidly, it may be inadvisable to commit funds for long periods of time. There is a danger that long-term funding programs for senior scientists can perpetuate fading ideas and cause a generation of younger scientists to forsake a research career. The data show that many NIDDK investigators who reach the \$1 million funding threshold do not sustain that level of funding over the long term; yet, the umbrella award would lock in “gold-star” funding status for up to ten years. In times of fiscal constraints, the NIH needs the greatest possible flexibility to pursue emerging opportunities, not long-term fiscal commitments. If the umbrella program is initiated, consideration should be given to shorter award periods.* The NIDDK staff said that, according to the NCI’s experience, investigators will

not apply if the award period is too short. Moreover, the NIH staff who developed the idea for the umbrella awards would like to find ways to focus on younger investigators.

Practical Issues for Investigators with Multiple R01s Who Are Likely to Meet a High Funding Threshold: *It would be difficult for investigators who hold multiple R01 awards to sustain creativity with funding levels less than they currently receive, especially if there are no inflationary increases. They would therefore be likely to seek other sources of support. Moreover, investigators with multiple R01s probably received them from several Institutes, and that complexity would raise funding and management issues in an umbrella award program.*

Dr. Star commented that despite the limitations, the NCI Outstanding Investigator program was quite popular. Administering a program across two IC may very well prove challenging. The pilot would start small and would be limited to a single institute.

Review of Umbrella Awards: *How will reviewers assess productivity and innovation? Currently, the most favorable peer review scores don't necessarily correlate with the most innovative science. Could a retrospective assessment of publications be performed? Would it be necessary to have totally different review criteria for this award, and if so, would it be possible to change the culture and behavior of peer reviewers so that they will apply the new criteria?*

Dr. Star indicated that a separate and dedicated review committee would be critical for appropriate review of the applications.

NCI Outstanding Investigator Award Program: *What are the views of this terminated program?* Dr. Star replied that, although the NCI program was never evaluated, it was very popular among investigators and institutions. There were also administrative efficiencies and cost savings. However, the program experienced some problems that the NIDDK would take steps to prevent. For example, the program had a large, non-competing base of funding that grew to be a substantial percentage of the NCI's research project grant budget at the expense of other programs. The NIDDK would address this issue by funding only 85-90 percent of the R01 budgets that are bundled under the umbrella award program. The NCI program also included non-NCI R01 awards; however, the NIDDK would place a limit of one umbrella award on any participating Institute or Center, or have that entity pay its proportional share of costs. Because the NCI program found that investigators had difficulty re-entering the R01 pool when their R35 grants ended, the NIDDK would plan to offer a bridge award. While the NCI program lacked evaluation, the NIDDK's umbrella award program would definitely include an evaluation component.

Re-entry to R01 Investigative Pool: *Given that the NCI Outstanding Investigators had difficulty re-entering the competition for R01 awards, it may be advisable to heavily emphasize the mid-point review planned for the umbrella award. Also, if investigators do*

not receive a favorable review at the midpoint of the award, would resources be provided at that point to help them prepare for R01 competition? NIDDK staff said that there would be some type of bridge support for investigators who did not have favorable reviews at the five-year mark.

Institutional Response: *It would be difficult for institutions to commit 25 percent of the salaries of investigators who receive umbrella awards. It remains to be seen whether institutions could preclude their investigators from applying for such prestigious awards.*

Perceptions: *Perceptions are important, especially among young investigators who are already struggling for NIH funding. Would this award be perceived as a mechanism for favoring well-funded, established investigators, while shutting out newer, younger researchers? Would investigators funded through umbrella awards also be eligible for similar long-term funding through the Howard Hughes Medical Institute, thus adding to perceptions that they are monopolizing funds? Would the umbrella award be targeted to investigators at certain stages of their careers so that it does not turn out to be a terminal award prior to retirement? Assuming that the NIDDK continues to have fairly flat budgets, wouldn't the creation of an R35 funding pool for umbrella awards reduce the funds available to support R01 grants? Investigators look at the way Institutes allocate their budgets among research mechanisms and they may make career choices accordingly. To reduce misunderstandings about the program, it would be important to underscore that the umbrella award program would not require new funds, but rather, the repositioning of funds currently committed to R01 grants.*

Timing: *Given current fiscal constraints and uncertainties, it may not be the most propitious time to undertake a new umbrella award program.*

At the end of the session Dr. Rodgers asked that NIDDK Advisory Council members send to him any additional comments or questions that they might have regarding the Outstanding Productive Investigator Umbrella Award program.

VII. “NIDDK Centers Program Review: Final Report” ***Dr. Gregory Germino, Deputy Director, NIDDK***

Dr. Germino's presentation highlighted the multi-stage, broadly consultative Program Review of NIDDK's Research Centers Program, about which the Council had received previous updates. Dr. Rodgers announced the availability of a final report—emphasizing that it is not a stopping point, but rather, a transition to a next phase of activity.

Dr. Germino provided a summary of the recently completed NIDDK review of its Research Centers Program, which currently funds 87 Centers for a total of about \$100 million annually. He highlighted the process of the Program Review, its findings, some of the actions the NIDDK is currently considering or has already taken in response to the findings, and the input and recommendations received. A final report has been provided

to the Council and is available on the NIDDK web site.

(<http://www2.niddk.nih.gov/Research/Centers/NiddkCtrsPrgReview.html>)

The purposes of the Program Review included: to strengthen a major NIDDK program; to ensure that resources are being used effectively and efficiently; to examine outcomes of a 2003 evaluation; and to address Council's February 2010 suggestions to enhance the program. These suggestions included taking steps to promote synergies and interactions; broadening access to research cores; and examining the value of pilot and feasibility studies.

As a backdrop, Dr. Germino pointed out several characteristics of the NIDDK's Centers Program. The Centers are typically based at institutions where clusters of investigators have related research interests that address a specific theme or scientific discipline of importance to the NIDDK. The broad goals of Centers include: to further collaborative, focused, multi-disciplinary research programs; to promote research training and the development of junior investigators; to leverage and maximize NIDDK resources; to provide flexible, dynamic support for high-risk/high-reward science; and to create synergies that accomplish more through centralized funding than would be achieved if the same funds were awarded to individual investigators. Components of Centers include administrative and scientific "cores," which provide centralized resources; pilot and feasibility (P&F) programs; and enrichment activities--all of which are used by dozens of participating researchers with related scientific interests at a given Center.

Program Review Process

Dr. Germino described the following major points in the Program Review process:

Internal Portfolio Review and Identification of Site-Visit Locations: As a first step, the NIDDK conducted a portfolio review of the Centers with respect to components of the Program, activities being funded, and geographic distribution of the Centers nationally. Based on this review, the NIDDK decided to conduct site visits at 25 Research Centers that were representative of the types of Centers in the Program. These Centers are located at five universities at which NIDDK resources are concentrated; opportunities for synergy are great; and site visits could be conducted efficiently. The identified institutions were: the University of Pennsylvania/Children's Hospital of Philadelphia; Yale University; Washington University, St. Louis; the University of Washington/Fred Hutchinson Cancer Research Center/Seattle Children's Hospital; and Vanderbilt University.

Site Visits: From December 2010 through March 2011, the NIDDK conducted site visits at the Centers. To facilitate the site visits, the Institute provided a list of questions and discussion topics in advance. The visits included a detailed review of the research cores, meetings with Center Directors and institutional leaders, and information-gathering about pilot and feasibility activities. The NIDDK did not request that information be provided

in a standardized format because the Program Review process was not an audit. Rather, the Institute wanted to see how the Centers were interpreting their mission. The semi-quantitative and qualitative information obtained was later aggregated without attribution to any individuals or specific Centers or institutions.

Interim Report and Comment Periods: In May 2011, the NIDDK presented to the Council an interim status report. During November and December 2011, the NIDDK solicited and integrated comments on an interim draft report from all the Centers in the Program, not just those that were site-visited. During May and June 2012, the NIDDK solicited and integrated public comments on the draft report using the Institute's web site. Both comment periods focused on discussion topics under consideration.

Final Report: Based on the input and comments received, the NIDDK prepared a final report to present to the Council in September 2012, and to make publicly available on the Institute's web site. The report contains information from three main sources: the NIDDK portfolio review; the site visits; and input received during the two comment periods.

Highlights of Final Report

The Program Review identified many strong elements of the NIDDK Centers Program and showcased how the Centers are advancing research progress on diseases within the NIDDK mission. The Program Review also identified areas that could be strengthened. Dr. Germino summarized key points from the final report, which is organized by discussion topics. He highlighted the NIDDK's consideration of and responses to the findings, input and recommendations. He emphasized that the NIDDK wants to enhance the Centers Program in ways that will avoid introducing program changes that would place undue administrative burdens on the Centers or unnecessarily limit their flexibility.

Discussion Topic 1: Enhancing Synergy and Center Value:

Findings: Both the site visits and the two comment periods provided many tangible examples of synergy among the Centers, such as co-sponsorship of retreats and courses, co-support of research cores, and the participation of Center Directors in activities with other Centers and institutions. The NIDDK recognized that there are opportunities for synergism that have not yet been fully explored because the site visits themselves were the first interaction among all NIDDK-funded Centers at the participating institutions, as well as a means through which NIDDK staff members shared important experiences and knowledge. There was general support for enhancing coordination and promoting synergy to reduce costs and leverage resources in the pursuit of better science, especially in times of limited budgets.

Recommendations: The NIDDK is considering several steps, including the following: (1) enhancing synergy and Center value through the use of web-based tools, such as using the NIDDK web site as a source of information about Centers and their available

resources; (2) having trans-NIDDK meetings of Center Directors and larger groups of investigators if a specific topic/need is identified; (3) identifying shared areas of research activity and opportunities for synergy with other programs, such as Clinical and Translational Science Award programs and research training programs; and (4) incentivizing Centers to build networks and share resources, possibly by including the consideration of such activity in NIDDK funding decisions.

Discussion Topic 2: Strengthening the Pilot and Feasibility Programs:

Findings: The NIDDK found that Research Centers are strongly committed to Pilot and Feasibility (P&F) components, which they consider very valuable and successful. Most P&F funds are distributed internally within each Center; however, some Centers have found ways to involve a broader base of investigators. According to the Centers, a major barrier to making external P&F awards is transferring indirect costs to another institution. The Centers reported important advantages and strengths resulting from their flexibility to administer aspects of their P&F programs, such as the application criteria, funding amounts, and numbers and durations of awards. Regarding eligibility for P&F awards, there was general support for the current approach, which primarily supports either established investigators who are changing research directions, or early-stage investigators who are entering a scientific discipline. There were some suggestions for broadening eligibility to other groups such as investigators who just missed the payline and need data to resubmit applications, or groups doing larger collaborative projects.

Recommendations: The NIDDK has concluded that the current definition of investigators eligible for P&F funding is appropriate and should be maintained. There are other mechanisms available to investigators with special needs. Rather than mandate administrative changes in response to suggestions, the NIDDK is planning to develop a “best practices” document that would address several issues such as the attention given to mentoring and to monitoring the progress of awardees. This document would also provide some guidance with respect to balancing types of P&F awards, such as awards for high-risk/high-reward science relative to awards for the career development of young investigators. The Institute generally agrees with comments that it is worthwhile, when possible, to open up the P&F component to investigators external to the Centers’ home institutions in order to increase the competitive pool and share resources with the broader investigative community. The NIDDK will include in the “best practices” document examples of the approaches that some Centers have taken to make external P&F awards.

Discussion Topic 3: Core Support and Access:

Findings: The NIDDK found many examples of the value provided by research cores, such as furthering the access of many investigators to research resources at reduced costs; providing training and consultation with respect to equipment and technologies; and promoting or developing new technologies. The Centers support different types of research cores, including highly specialized, unique cores that focus on NIDDK research areas. They also buy into general institutional cores to provide access for Center members. The NIDDK was made aware of some perceptions in the scientific community

that core access may sometimes be limited to a small number of laboratories. There was general support for broadening access to cores.

Recommendations: The NIDDK is looking at several different ways to broaden access to cores, such as using business models (see Discussion Topic 4), and using the web to advertise the availability of core resources. Other actions under consideration include: (1) possibly modifying Funding Opportunity Announcements to emphasize that broad access to cores is important, and (2) possibly providing resources to further that objective. Another possibility is to remain alert to emerging circumstances in which exceptional opportunities may arise to support small centers that would provide highly specialized expertise and services particularly useful to the broad research community (see Discussion Topic 5).

Topic 4: Core Business Models:

Findings: The NIDDK found few defined business models among the Centers. Many of the cores use a charge-back business model, but different types of cores may require other models. The NIDDK observed a lack of standard approaches in the data reported on core usage, which can present challenges for the NIDDK and for peer reviewers in making comparative assessments of Centers. Concerns were raised regarding NIDDK guidelines for some Centers that limit equipment purchase to one time per funding cycle.

Recommendations: The NIDDK will not mandate that cores use any particular business model. Instead, the NIDDK plans to develop information on core business models to disseminate to the Centers. The NIDDK is also considering the development of guidelines for collecting data on core usage. The Institute is having internal discussions about ways to harmonize principles and practices for equipment purchases to provide greater flexibility.

Topic 5. Potential Value of More Small Centers:

Findings: There was a wide range of perspectives on this topic regarding the effectiveness and efficiency that might be associated with smaller centers. Institutions that already have established centers typically found greater value in larger centers and recommended that the NIDDK broaden access to existing cores rather launch smaller, specialized Centers. Smaller institutions tended to favor smaller Centers and recommended that the NIDDK fund such Centers as highly specialized or national resources for the broad research community.

Recommendations: The NIDDK considers the advisability of launching new, smaller Centers an open question. The Institute does not currently plan to expand its Research Centers Program, but will be cognizant of emerging opportunities that might warrant the establishment of a particularly valuable small Center. This topic will remain under active discussion.

Discussion Topic 6: Center Membership:

Findings: The NIDDK found different approaches to and perspectives on Center membership. A Center's members were typically from the local (home) institution, but sometimes also from external institutions. There were different definitions of membership, as well as different categories, such as full and associate members. Sometimes, membership was a requirement for using a research core. Also, because of related research interests, some Principal Investigators were members of more than one Center--such as the Nutrition-Obesity Research Centers and the Diabetes Centers. These differences in approaches to membership can make it difficult for the NIDDK and for peer reviewers to compare the institutional base of Centers. Perspectives on Center membership varied considerably. One perspective was that membership should be inclusive to attract talented investigators to move the science forward. Another perspective was that membership numbers could be inflated if Centers count investigators who are more peripherally involved, such as those who attend seminars but are not otherwise engaged in Center activities.

Recommendations: The NIDDK is developing a best practices document on Center membership to share with the Centers. Additionally, the NIDDK plans to establish requirements for Center membership; to clarify who may be included in the "user base" of a Center; and to outline who may use core resources. Such standard definitions are expected to enable the NIDDK to assess more accurately who is benefiting from Center resources, such as enrichment programs, and also, to enable peer reviewers to compare applications in the review process.

Changes Already Implemented and Next Steps

Dr. Germino reported on some changes the NIDDK has already undertaken. For example, the Institute has modified its guidelines for reporting the research base for some Centers. For Nutrition-Obesity Research Centers and for Diabetes Centers, the NIDDK has asked investigators to list on their applications whether they are members of another Center. In addition, the Institute has modified some Diabetes Centers to promote regional and national resources. Steps have also been taken to enhance access to Center core resources, and to promote expansion of information-sharing through the development of the Centers' web sites. The NIDDK is also going through a process of revamping its own web site and included in this process is enhancing access to information on Center resources.

NIDDK staff members are meeting on a regular basis to develop implementation strategies for the recommendations in the report, with subgroups focused on each discussion topic. Best practices documents are being developed to address Pilot and Feasibility programs, core business models, and Center membership. Work is continuing on redesigning the NIDDK web site to highlight the Research Centers Program. As the NIDDK moves forward to strengthen its Centers Program, it seeks the Council's continuing discussion and input on the following issues:

Enhancing Synergy and Center Value: Should the NIDDK consider some measure of synergy when making funding decisions? How can the NIDDK promote Center interactions with Clinical and Translational Science Awards and other NIDDK programs? How can the NIDDK further enhance opportunities for training?

Strengthening the P&F Programs: How should the NIDDK balance support for high-risk/high-reward projects relative to support for research career development? Should the NIDDK promote the opening up of the P&F programs to extra-institutional investigators?

Core Support and Access: Should the NIDDK aim to broaden core access and continue to support both general and specialized cores? Should the NIDDK increase data collection on core usage so that reviewers can make informed decisions about how cores are or are not being utilized by the community?

Center Membership: How can the NIDDK evaluate meaningful participation of Center members without overburdening the Centers administratively?

Dr. Germino closed by expressing the Institute's appreciation for all the work that Centers performed to prepare for the sites visits, for the very thoughtful input that was submitted by all parties during the two comment periods, and for the many contributions of NIDDK staff members.

Council Questions and Discussion

Several Council members commended the NIDDK for the thoughtful, diligent and constructive Program Review. Specific comments of individual Council members included the following:

Enhancing Synergy and Center Value: This topic prompted many comments:

- *Centers are inherently constructs for synergy and should be assessed in those terms. The synergy expected from Centers is the very reason this award mechanism exists; otherwise, the Center funds could be used for R01 grants.*
- *Synergy probably can't be mandated; however, the experiences gained during the NIDDK Program Review demonstrate that it is possible to create opportunities for potential synergies to be recognized and pursued. The key is to bring people with mutual interests together in the same room.*
- *Synergy can come from fostering interactions among NIDDK-funded Centers within and beyond the home institution, without any regional restrictions.*
- *The recognition and elimination of barriers or burdensome impediments can facilitate synergy. For example, indirect costs procedures can hinder synergistic core use by investigators external to the home institution.*
- *Synergy can be furthered by exploiting opportunities for repositories, both virtual and real, and the development and promotion of relational databases that could link clinical information and outcomes with molecular information. It is possible that*

synergies may emerge from the “big data” that are being generated by some research cores.

- *Center infrastructure can be used to focus synergistically on key areas within the NIDDK research mission and to help develop investigators.*
- *Synergistic efforts can be measured not only in terms of enrichment programs and the nurturing of new investigators, but also in the development of platforms for facilitating new types of interdisciplinary grants through existing collaborative mechanisms.*
- *The value of and need for synergy could be stated very clearly in Requests for Applications, incorporated into the peer review process, and highlighted in various reports. Synergy could be given a quantitative metric in the review process, perhaps under the administrative cores.*
- *If an institution has both a Research Center and a Clinical and Translational Science Award, it should be mandatory that a plan exists or would be developed for interaction between them. Letters from the two Directors would be one mechanism.*
- *The Centers Program could exploit opportunities to demonstrate mentorship activities with respect to advisory committees, workshops, and seminars. Such activities can be concretely linked to existing NIDDK efforts across a continuum of research training and research career awards.*

Pilot and Feasibility Programs:

These programs are widely considered to be excellent. Compelling arguments can be made for using P&F funds for various types of activities; therefore, difficult choices must be made. P&F programs can be particularly helpful for junior investigators, and they can produce a high return on investment. It would be helpful to track the use of P&F funds at individual Centers and across the entire Program with respect to the number of pilot awards that have helped lead to R01 grants, and perhaps even promoted a more rapid attainment of such grants than otherwise would have occurred.

Council members offered somewhat different thoughts on the use of P&F funds for high-risk/high-reward research. One view is that junior investigators are generally considered to be inherently engaged in such research; therefore, enhancing their support would further that type of research. Another view is that too much emphasis should not be placed on Centers for conducting high-risk/high-reward research. Rather, Centers should collaborate with other programs at their home institutions to generate additional funds for such research.

Council members also expressed somewhat different views as to whether the P&F programs should be opened up to investigators beyond a Center’s home institution. One view is that the P&F programs are already highly competitive and therefore the addition of applicants external to the home institution is not necessary to enhance the competitive process. Another view is that the P&F programs should be accessible to external investigators when possible, but the P&F programs must remain focused on the best science and tilt toward new investigators. A third view is that it may be advisable to

include some extra-institutional investigators in P&F programs, provided that they have specific or niche expertise that would bring a new scientific dimension or component to the programs.

Core Support and Access: Broadened core access and support are viewed as desirable, both for the general cores, such as transgenic and sequencing facilities, and for the specialized cores. Certain centralized resources, such as high-throughput sequencing, would not exist at some institutions without a Research Center that has such a core. There has been a lack of development and expansion of niche cores that could serve the national research community.

Business Models and Data Collection: Research Centers that have a charge-back system for services, such as the use of research cores, basically have a built-in accounting system for recording the users of resources and the frequency of use.

Membership: Membership can be a huge issue when an institution is applying or reapplying for Center funding because it is an indicator of scientific strength. The current system for determining membership can be parochial; moreover, it can be an administrative burden if all core usage must be documented. While some components of the current system should be maintained, the determination of membership should have some plasticity in criteria with respect to measuring the contributions of Center membership both intellectually and scientifically. An investigator's record of grants and publications can be an appropriate criterion for Center membership because it points to scientific productivity.

Best Practices: Sharing best practices would be very useful--in printed form, on-line, and through meetings.

VIII. COUNCIL FORUM: “Big Data--What Is It and How Does It Affect NIDDK? Challenges and Opportunities”

Dr. Rodgers introduced the Council Forum by noting that the biomedical research community is using more data-intensive technologies as a means to accomplish activities that range from achieving major discoveries in basic science to identifying important associations between information items contained in clinical data repositories or electronic medical files. The indexing, storage, analysis, and sharing of these data--and the insights derived from the data--are becoming increasingly important.

A. “Overview of Big Data”

Dr. Ron Margolis, Senior Advisor, Molecular Endocrinology, and Associate Director for Grants Administration within the Division of Diabetes, Endocrinology, and Metabolic Diseases

Dr. Margolis said that big data is loosely defined as datasets that are so large and complex that available tools are typically not capable of dealing with functions such as data capture, storage, searching, analysis, condensing, visualization, and communication. Important nuggets of information may be embedded in massive data sets, but if they cannot be extracted, analyzed, presented graphically, and transmitted to others, they have no utility. Some major sources of big data include the physical sciences, consumer data, and social media. In the biomedical sciences, there are enormous amounts of data generated from chemical biology and clinical investigations. For the NIDDK's purposes, big data can be considered the data that result from studies that seek to understand biological processes through data-intensive techniques. Dr. Margolis noted that the meaning of "big" keeps expanding--from kilobytes, to megabytes, to gigabytes, to terabytes, to petabytes, and beyond.

Dr. Margolis gave several examples of governmental efforts to address the challenges of big data.

- In Fiscal Year 2012, the federal government began a \$200 million Big Data Research and Development Initiative that reached across all agencies. The purpose is to develop government-wide frameworks and goals regarding the collection, use, and transparency of big data, and ways to enhance its value. This initiative also supported future needs assessment.
- The National Science Foundation has a \$20 million program, to which the NIH has contributed, on "Core Technologies for Advancing Big Data Science and Engineering."
- The NIH Advisory Committee to the Director (ACD) has a Data and Informatics Working Group, which submitted a June 2012 report. There is also a trans-NIH Big Data Working Group, through which NIH staff will follow-up on and implement the ACD Working Group's recommendations.
- The NIDDK has developed dkCOIN, the NIDDK Consortium Interconnectivity Network.

Dr. Margolis elaborated on the way that dkCOIN serves the needs of basic and clinical investigators by providing seamless access to large pools of data relevant to the Institute's mission. The goal is to develop a community-based network for integration across disciplines to include the larger NIDDK universe of diseases, investigators, and potential users. The Institute has a strong interest in big data because NIDDK-funded investigators are generating massive amounts of data through NIDDK basic science consortia, R01 and Research Center grants, and clinical trials. Refining ways to mine these data may help to identify otherwise unseen trends and relationships that can provide new insights regarding diseases within the NIDDK mission. Another potential benefit of data mining would be reductions in redundancy and duplication of effort. To this end, there is a need for a bioinformatics ecosystem that encompasses tools necessary to derive additional value from the data that are being accumulated.

B. “Secondary Use of Health Care Big Data for Translational Research”
Dr. Shawn Murphy, Medical Director of Research Computing and Informatics, Partners HealthCare; Associate Professor of Neurology at Harvard Medical School; and Associate Director of the Laboratory of Computer Science at the Massachusetts General Hospital

Dr. Rodgers introduced Dr. Shawn Murphy, who developed and currently directs the Research Patient Data Registry (RPDR) for Partners HealthCare. The RPDR is a large data warehouse with data on six million patients; it serves as a central clinical data registry for inpatient and outpatient encounters in order to support clinical research. Dr. Murphy is also Principal Investigator for software development for the NIH-sponsored Informatics for Integrating Biology and the Bedside (i2b2) Center. This Center is an open-source project that integrates data from the hospital medical record and the bioinformatics community into a common software platform, with over 70 operating installations worldwide. Dr. Murphy holds a Ph.D. in Pharmacology from the University of Chicago and an M.D. from the Pritzker School of Medicine at the University of Chicago. His earlier career path includes an internship in internal medicine at Beth Israel in Boston, a neurology residency at the Massachusetts General Hospital (MGH), and fellowships in epilepsy and computer science at MGH.

Dr. Murphy’s presentation centered on the ways that big data are being mined and managed to advance clinical and translational research. His main focus was the work conducted by the Informatics for Integrating Biology and the Bedside (i2b2) Center. (<https://www.i2b2.org/>) This open-source Center is an NIH-funded National Center for Biomedical Computing (NCBC). It is based at Partners HealthCare in Boston, Massachusetts, a not-for-profit, integrated health care system that includes medical and research institutions. (<http://www.partners.org/>) Dr. Murphy acknowledged the enormous number of individuals who have made i2b2 possible.

Dr. Murphy stated that the directors of research enterprises and the community of scientific investigators want to know more about big data because it can be very useful in facilitating clinical trials; helping to identify some of the correlates of common diseases and health problems; furthering hypothesis-driven research; and speeding the translation of findings into medical practice. For example, mining big data can be important for understanding the relationships between genetic and genomic information. The data can shed light on the connections between the presence of certain genes (genotypes) and their expression in disease states (phenotypes). Considerable resources are needed to link the big data that are emerging from studies that use high-throughput genotyping and high-throughput phenotyping techniques.

Mining and managing big data are complicated tasks because the data are not only vast, but also, often intertwined. The challenges include: (1) querying the data to find meaningful nuggets while sifting through piles of information that are not particularly useful; (2) making privacy-related deletions in highly intricate, interwoven big data; and

(3) sharing data--both the big data itself, and the metadata that synthesize important data points and elucidate the data's meaning.

With regard to clinical studies and trials, Dr. Murphy described the role that the i2b2 Center plays in helping investigators query (search) big data in order to identify patients for inclusion in research protocols--in accordance with legal requirements to protect the privacy of patients. Under the Health Insurance Portability and Accountability Act (HIPPA), all patients at Partners HealthCare are notified upon registration that their data may be used for research. Dr. Murphy described three major components of the data query and retrieval process. First, an authorized investigator uses an i2b2 query to determine if there is a sufficient number of patients, in the aggregate, without personal identifiers, who have a disease or condition he or she plans to study. Second, to determine if those patients would be eligible to participate in the research protocol, the investigator must obtain approval for the planned research from an Institutional Review Board in order to conduct additional queries for more specific information. The investigator then explores phenotypes of these patients using i2b2 tools and a translational team of experts, which has been developed specifically to work with medical record data. The detailed information sought may include coded diagnoses, laboratory findings, physical findings, medical procedures performed, and genomic data. In the third step of the process, the i2b2 Center provides refined, detailed data and related reports to the investigator in an organized fashion, noting the different sources of and codes for the data. The Center also provides images, which can be critically important in characterizing the phenotypes of patients. Dr. Murphy noted that there are legal controls on certain types of data, including genomic data. For example, information resulting from non-diagnostic screening tests for the presence of genes cannot be used for research purposes.

By displaying and using an interactive query form, Dr. Murphy demonstrated the way that queries can be constructed and run. Depending on the formulation of a query, it is possible to identify patients who have either a single disease or multiple diseases. In a similar fashion, it is possible to search on combinations of patient characteristics and genes, and also, to identify matched controls. When an investigator submits a query, it is run against approximately 1.5 billion observations about patients. About 3,000 investigators are using these data-mining approaches, which are helping to further many millions of dollars in research activity.

In addition to aiding patient recruitment for clinical trials, a major goal of the i2b2 Center is to perform certain types of clinical and translational studies via computers-- "*in silico.*" For example, using the i2b2 system, researchers were able to see that the occurrence of myocardial infarction was statistically higher in diabetes patients who were treated with a specific medication. This finding has informed medical practice. The ability to identify these types of interrelationships may enable the development of "virtual" clinical trials that will assess existing, well-organized patient data retrospectively, thereby avoiding the high costs of prospective trials.

Dr. Murphy described many highly technical aspects of the architecture and operations of the i2b2 system. He noted that original data are retained at the location where the information is initially generated--surrounded by firewalls and other protections. Through the use of carefully constructed indexes, the i2b2 software can cross institutional boundaries to access that data, and extract, store, and analyze the components that are needed for research purposes. While the i2b2 Center can efficiently search the medical records of millions of patients, Dr. Murphy emphasized that the indexing, culling, refining and interpretation of data is challenging. For example, defining the types of rheumatoid arthritis patients sought for a clinical trial may involve construction of a phenotypic definition involving several codes, as well as the patient's previous medical treatments and test results. The i2b2 Center has leveraged "smart" technologies to drill down into massive amounts of data to find such specific information. For example, to understand and code a physician's short-hand-like notations on a medical record, i2b2 scientists use an approach called "natural language processing." Importantly, the i2b2 Center uses different ways to verify information, including the use of human experts to review the data, often in graphic form, to see if the data make sense.

Dr. Murphy praised the institute's efforts in developing the NIDDK Consortium Interconnectivity Network--dkCOIN. (www.dkCOIN.org/). He pointed out some of the dkCOIN attributes relative to the i2b2 system. Both i2b2 and dkCOIN use ontologies (logically constructed classes, attributes, relationships, etc.) to represent and query the data; they have data connected around a basic unit in a modular fashion; and they have uniform points of access. While i2b2 and dkCOIN share these and other similarities, their fundamental approaches to indexing and querying are quite different. Specifically, the central unit in the i2b2 approach is the patient--with attendant privacy concerns--whereas the central unit in dkCOIN is the gene. In Dr. Murphy's view, the data in the health sciences are largely being indexed in one of these ways; therefore, research investments could help to bridge these two approaches. Another difference is that i2b2 is considered a "closed world" system in which tight data control is needed; attributes such as patients' visit numbers are essential to successful data retrieval; and queries are confined to running against an established database. In contrast, dkCOIN represents an "open-world" system, in which queries, which are similar in approach to web-based searches, can link many attributes together and evolve in different directions beyond a single data source. Dr. Murphy said that researchers will select the most appropriate systems to use depending upon the questions they seek to answer.

In closing, Dr. Murphy noted some of the recommendations of the Data and Informatics Working Group of the Advisory Committee to the Director (ACD), NIH. (<http://acd.od.nih.gov/diwig.htm>) The recommendations address a range of issues such as sharing data across institutional boundaries, developing and maintaining software tools, furthering workforce development, and increasing the speed of data transmission.

Council Questions and Discussion

Leveraging Investments in Big Data Resources:

- *It is important to leverage the outstanding resources of the i2b2 Center, which is moving forward based on important principles. While still evolving, it is a worthwhile undertaking, which can promote synergy across centers and institutions.*
- *The theory of ownership is receding in science as the value of collaboration is increasingly recognized, especially in the field of genetics. The use of concrete, commonly understood terminology would facilitate that process.*
- *It would be helpful to embed computer experts and analysts within research projects along with biomedical scientists, especially geneticists.*
- *Because publishing in scientific journals is a natural way scientists think about data and research results, it should be a central principle for broad dissemination of large data sets, including those from Genome-Wide Association Studies (GWAS).*
- *As mechanisms for handling big data develop further, issues of privacy and intellectual property will continue to be significant and must be addressed.*

Comparing Different Systems: *What is being done to translate data between i2b2 and some of the commercially available systems for maintaining electronic medical records (EMRs)?* Dr. Murphy responded that commercial databases are largely transactional systems in which the rapid turn-around of data may be needed in a hospital setting. In contrast, i2b2 is an analytical system intended to facilitate research, and it is usually updated only once a day.

Answering Mission-Oriented Questions: *The NIDDK should harness informatics and related technologies to answer the questions that are central to the Institute's research mission. The NIDDK could incentivize scientists to use computational technologies to move gene-expression research forward into clinically oriented studies, which could lead to the development of new therapies.*

Stakeholders, Users and Trainees:

- *Practically everyone who is studying biological processes has a stake in big data and should be using or learning to use the very powerful computational tools that now exist. Systems for handling big data should be user-friendly to post-doctoral and graduate students in the laboratory.*
- *The NIDDK could create a whole group of new clinical investigators by making available the tools to use big data. The Institute could enhance the computational training of researchers in sub-specialty fields within its research mission.*
- *Students of modern molecular biology show a remarkable ability to learn the skills necessary to analyze and manipulate large data sets. The NIDDK should encourage and incentivize that type of knowledge acquisition through existing funding mechanisms. For example, NIDDK Research Centers that are generating high-throughput data in core facilities could train experimental scientists to analyze and discuss their own data at a sophisticated level.*

- *It is important to encourage training in computational biology for individuals who have superior mathematical skills. If the NIDDK can create an intellectual home for these individuals by providing training opportunities, the Institute could create an incredibly powerful human resource for mining large data bases and for developing the next generation of analytic tools.*
- *Academia has a role to play in terms of providing promotion and tenure opportunities to highly talented individuals who are working with big data.*
- *The promise for research advances in this area is huge because big data can provide unbiased ways to reveal important associations that can yield biological and medical insights, and that can help to generate new hypotheses about diseases.*

***Quality of Data:** Until more standardized ways are developed to encode and refine data, concerns will exist that the conclusions based on the data are not robust. Also, the fact that human beings still need to interpret some data underscores the need for an effective human/computer interface.*

IX. SCIENTIFIC PRESENTATION: “From Genes to Therapies: Platelets at the Center of the Universe”

Dr. Kenneth Kaushansky, Dean of the School of Medicine and Senior Vice President of the Health Sciences for Stony Brook University

A leading hematologist and Member of the Institute of Medicine, Dr. Kaushansky has conducted seminal research on the molecular biology of blood cell production. His team has cloned several of the genes important in the growth and differentiation of blood cells. An accomplished clinician, he has been a champion of training more physician-scientists to further the translation of research discoveries into improved treatments and technologies for the prevention, diagnosis and management of disease.

X. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1477 grant applications, requesting support of \$406,930,762 were reviewed for consideration at the September 12, 2012 meeting. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, and additional 1109 applications requesting \$365,366,575 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 September 12, 2012 meeting.

XI. ADJOURNMENT

Dr. Rodgers

Dr. Rodgers expressed appreciation to all the presenters and discussants. He thanked the Council members for their attendance and valuable input. There being no other business, the 190th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m., September 12, 2012.

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

A handwritten signature in blue ink that reads "Griffin P. Rodgers". The signature is written in a cursive, flowing style.

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