DRAFT

Meeting Minutes
Department of Health and Human Services
Public Health Services
National Diabetes and Digestive and Kidney Diseases Advisory Council

February 4–5, 2004

I. CALL TO ORDER

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Director, Dr. Allen M. Spiegel, called to order the 164th National Diabetes and Digestive and Kidney Diseases Advisory Council meeting on February 4, 2004, at 8:30 a.m. in Conference Room 10, C Wing, 6th Floor, Building 31, National Institutes of Health (NIH), Bethesda, MD. Dr. Spiegel opened the meeting with the following general announcements:

< Four new members are joining the Advisory Council: Dr. Janis Abkowitz, Section Head in the Division of Hematology, University of Washington Medical Center, and Director of the Hematology Clinic at the Seattle Cancer Care Alliance and University of Washington Medical Center, is joining the Kidney, Urologic, and Hematologic Diseases Subcommittee; Dr. Roberto Coquis, a physician in private practice, and President of Nephrology Consultants of South Florida in Ft. Lauderdale, is joining the Kidney, Urologic, and Hematologic Diseases Subcommittee; Dr. Rudolph Leibel, Professor and Head of the Division of Molecular Genetics and Co-Director of the Naomi Barrie Diabetes Center, Columbia University College of Physicians and Surgeons, is joining the Diabetes, Endocrinology, and Metabolic Diseases Subcommittee; and Dr. Ronald Ruecker, a physician in private practice with the Internal Medicine Subspecialty Associates Group in Decatur, Illinois, is joining the Digestive Diseases and Nutrition Subcommittee.

< Within NIDDK, Dr. Stephen James has been appointed Director of the Division of Digestive Diseases and Nutrition (DDN), after serving as Deputy Director of the Division for approximately 2 years. The former Director, Dr. Jay Hoofnagle, has been appointed Chief of the newly created Liver Disease Research Branch within the DDN Division. Dr. Crystal McDade-Ngutter has joined the Division of Nutrition Research Coordination as a member of the Department of Health and Human Services Emerging Leaders Program, and will be working with Dr. Van Hubbard to develop and implement various initiatives on nutritional sciences and obesity research.

< At the NIH level, two new appointments have been made within the Office of the Director: Dr. Norka Ruiz Bravo, formerly Director of Extramural Activities at the National Institute of General Medical Sciences, will serve as Deputy Director for Extramural Research; and Mr. Richard Turman, formerly with the American Association of Universities, and the Office of Management and Budget, will serve as Associate Director for Budget.

< Dr. Gerald Keusch has resigned from his position as Director of the Fogarty International Center, and will be returning to Tufts University Medical Center.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Janis Abkowitz
Dr. Robert Alpern
Mr. David Baldridge
Dr. Jose Caro
Ms. Mary Clark
Dr. Roberto P. Coquis
Dr. Raymond DuBois
Dr. Robert Eckel
Dr. Richard Goodman
Dr. Earl Harrison (*Ex officio*)
Dr. Carolyn Kelly
Dr. James W. Kikendall (*Ex officio*)
Dr. Sum Lee
Dr. Rudolph Leibel
Ms. Nancy Norton
Dr. Daniel Porte (*Ex officio*)
Dr. Vicki Ratner
Dr. Ronald Ruecker
Dr. Linda Sherman
Dr. E. Darracott Vaughan
Dr. W. Allan Walker

Also present:
Dr. Allen Spiegel, Director, NIDDK, and Chairperson, NDDK Advisory Council
Dr. Griffin Rodgers, Deputy Director, NIDDK
Dr. Robert Hammond, Executive Secretary, NDDK Advisory Council

B. NIDDK STAFF AND GUESTS

In addition to Council members, others in attendance included NIDDK staff members, representatives of the NIH Office of the Director (OD), Center for Scientific Review (CSR) Scientific Review Administrators, and other NIH staff members. Some NIDDK staff listed below attended via videocast from 2 Democracy Plaza, Room 701. Guests and members of the public were present during the open sessions of the meeting. Attendees included the following:

Kristen Abraham, NIDDK
Karen Adams, NIDDK
Linda Addison-Hardy, NIDDK
Beena Akolkar, NIDDK
Beth Anderson, Ped/Adol Ger Assn
Sara Arnold, Health & Med Counsel
David Badman, NIDDK
Michele Barnard, NIDDK
Terry Bishop, NIDDK
Sharon Bourque, NIDDK
Josephine Briggs, NIDDK
Lauren Burke, ASH
Francisco Calvo, NIDDK
Joan Chamberlain, NIDDK
Dolph Chianchiano, Nat. Kid. Fd.
Michelle Cissell, JDRF
John Connaughton, NIDDK
Catherine Cowie, NIDDK
Leslie Curtis, NIDDK
Florence Danshes, NIDDK
Maria Davila-Bloom, NIDDK
Patrice Davis, NIDDK
Jane DeMouy, NIDDK
Tony Demsey, OD/OER
Christine Densmore, NIDDK
Devon Drew, NIDDK
Linda Edgeman, NIDDK
Michael Edwards, NIDDK
Thomas Eggerman, NIDDK
Paul Eggers, NIDDK
Gayla Elder-Leak, NIDDK
Donald Ellis, NIDDK
Nancy Emenaker, CSR
Jody Evans, NIDDK
James Everhart, NIDDK
Richard Farishian, NIDDK
Ned Feder, NIDDK
Olaf L. Fonville, NIDDK
Judith Fradkin, NIDDK
Randi Freundlich, NIDDK
Joanne Gallivan, NIDDK
Lisa Gansheroff, NIDDK
Sanford Garfield, NIDDK
Derek Gault, NIDDK
Janet Gregory, NIDDK
Carol Haft, NIDDK
Frank Hamilton, NIDDK
Mary Hanlon, NIDDK
Dana Harris, NIDDK
Mary Harris, NIDDK
Barbara Harrison, NIDDK
Kim Hetkowski, NIDDK
Trude Hilliard, NIDDK
Gladys Hirschman, NIDDK
Eleanor Hoff, NIDDK
Jay Hoofnagle, NIDDK
Thomas Hostetter, NIDDK
Ann Karen Howard, NIDDK
Van Hubbard, NIDDK
Donna Huggins, NIDDK
Joyce Hunter, NIDDK
Donna James, NIDDK
Stephen James, NIDDK
Ann Jerkins, CSR
Teresa Jones, NIDDK
Robert Karp, NIDDK

Christian Ketchum, NIDDK
Sooja Kim, CSR
Carolyn Kofa, NIDDK
Robert Kuczmarski, NIDDK
Maren Laughlin, NIDDK
Kim Law, NIDDK
Todd Le, NIDDK
Ellen Leschek, NIDDK
Maxine Lesniak, NIDDK
Monica Liebert, Am. Urol. Assoc.
Barbara Linder, NIDDK
Helen Ling, NIDDK
Saul Malozowski, NIDDK
Denise Manouelian, NIDDK
Ronald Margolis, NIDDK
Dan Matsumoto, NIDDK
Michael K. May, NIDDK
Crystal McDade-Ngutter, NIDDK
Julie McDermott, NIDDK
Catherine McKeon, NIDDK
Barbara Merchant, NIDDK
Catherine Meyers, NIDDK
David Miller, NIDDK
Megan Miller, NIDDK
David Mineo, NIDDK
Marva Moxey-Mims, NIDDK
Christopher Mullins, NIDDK
Leroy Nyberg, NIDDK
Diana O'Donovan, NIDDK
Denise Payne, NIDDK
Aretina Perry-Jones, NIDDK
Bobbie Peterson, MBS
Judith Podskalny, NIDDK
Rebekah Rasooly, NIDDK
Janet Reise, NIDDK
Patricia Robuck, NIDDK
Michelle Rodrigues, SRI
Mary K. Rosenberg, NIDDK
Paul Rushing, NIDDK
Lakshmanan Sankaran, NIDDK
Sheryl Sato, NIDDK
Jane Schriver, NIDDK
Salvatore Sechi, NIDDK
Leonard Seeff, NIDDK
Jose Serrano, NIDDK
Kathleen Shino, NIDDK
Elizabeth Singer, NIDDK
Philip Smith, NIDDK
Larry Soler, JDRF
Jennifer Soloman, Constella Grp
Robert Star, NIDDK
Renetta Washington, NIDDK
Dorothy West, NIDDK
Gina Wrench, NIDDK
Susan Yanovski, NIDDK
Charles Zellers, NIDDK

II. CONSIDRATION OF SUMMARY MINUTES OF THE 163rd COUNCIL MEETING

A motion was made, and unanimously passed by voice vote, to approve the summary minutes of the 163rd NDDK Advisory Council (September 2003) as submitted.

III. FUTURE COUNCIL DATES

Dr. Spiegel asked Council members to take note of future Council meeting dates as follows:

May 26–27, 2004
September 22–23, 2004
February 23–24, 2005
May 19–20, 2005
September 14–15, 2005
February 15–16, 2006
May 31–June 1, 2006
September 20–21, 2006

IV. ANNOUNCEMENTS: CONFIDENTIALITY AND CONFLICT OF INTEREST

Dr. Robert Hammond

Dr. Hammond outlined the procedures to guarantee confidentiality and avoid conflicts of interest, discussed the scope and applicability of these procedures, and requested Council compliance. Members were asked to sign and return a conflict-of-interest statement and were

reminded that materials furnished are considered privileged information and are to be used for the purpose of review and discussion during the closed portions of the meeting only. The outcome of the closed-session discussions may be disclosed only by staff and only under appropriate circumstances; all communications from investigators to Council members regarding actions on applications must be referred to NIDDK staff.

Furthermore, Council members should recuse themselves when individual applications from their institutions are discussed to avoid an actual or perceived conflict of interest. This is unnecessary with en bloc votes, for which all members may be present and participate. Council members from multi-campus institutions of higher education may participate in discussion of applications from sites that are within the same institution, but are separate from the campus to which they are appointed, if the employee's disqualifying financial interest is employment in a position with no multi-campus institution. Thus, individuals may act upon other campus actions regarding second-level review.

V. REPORT FROM THE NIDDK DIRECTOR

Dr. Allen Spiegel

Dr. Spiegel began by reporting on the status of two topics covered at the September 2003 Advisory Council meeting: The NIH Roadmap Initiatives, and the National Research Council/Institute of Medicine Report.

< The NIH Roadmap Initiatives: On September 30, 2003, Dr. Elias Zerhouni, Director of the NIH, formally announced the NIH Roadmap Initiatives, now in their implementation phase. Funding for the Roadmap, which will double in amount from fiscal year (FY) 2004 to FY 2005, is a collective, rather than institute-specific, resource. Information on the Roadmap is available at www.nihroadmap.nih.gov.

The NIDDK has taken the lead role on three Roadmap initiatives: (1) A metabolomics initiative that will encourage the development of more powerful technology for analyzing all small molecules found in the body, or of interest for biomedical research and health; (2) two interdisciplinary research training initiatives; and (3) translational research core resources.

The Roadmap Implementation Committee will determine the role of institute and center advisory councils in the second-level review of applications for the Roadmap initiatives. Dr. Dushanka Kleinman, Deputy Director of the National Institute for Dental and Craniofacial Research, has been appointed Assistant Director for Roadmap Implementation.

< National Research Council and Institute of Medicine Report: On October 2, 2003, Dr. Zerhouni; Dr. Harold Varmus, former Director of NIH and currently President and Chief Executive Officer of the Memorial Sloan-Kettering Cancer Center; and Dr. Harold Shapiro, President Emeritus and Professor of Economics and Public Affairs, Princeton University, testified at a joint hearing of the two congressional committees with authorizing authority over the NIH—the Senate Health, Education, Labor and Pensions Committee; and the House

Energy and Commerce Committee, Subcommittee on Health. These committees sanction the legislation that defines the scope of the NIH in terms of the institutes and centers and their missions. The subject of the hearing was the 2003 National Research Council and Institute of Medicine of the National Academies report, entitled "Enhancing the Vitality of the National Institutes of Health: Organizational Change to Meet New Challenges." Dr. Shapiro was chairman of the committee that produced the report. The report recommendations continue to be a topic of active discussion by NIH leadership and the outside community.

Dr. Spiegel then discussed NIH efforts to address the problem of obesity, which has reached epidemic proportions in the U.S. and around the world. At the NIH level, the Trans-NIH Obesity Research Task Force, created in April 2003 by Dr. Zerhouni, has drafted a comprehensive strategic plan for research, which is supported by significant resources. After considerable internal and external input, the draft strategic plan Task Force will be released February 2004, and will be available both in printed form and electronically (http://www.obesityresearch.nih.gov/about/strategic-plan.htm). The web site also will link to the joint initiatives of the Task Force and to sites relevant to obesity prevention and treatment for access by the public and practitioners. Dr. Spiegel and Dr. Barbara Alving, Acting Director of the National Heart, Lung, and Blood Institute, are heading this effort. In addition to institute-specific funding for obesity research, $22 million has been allotted in the President's Budget Request for FY 2005 to fund six trans-NIH initiatives developed by the Task Force.

Within the NIDDK specifically, Dr. Spiegel noted the creation of an obesity research working group led by Drs. Philip Smith and Susan Yanovski. The group is addressing a series of upcoming research initiatives directed at the epidemic. While obesity has a major public health impact as a cause of type 2 diabetes, other diseases and health complications that are within the NIDDK mission that are associated with obesity warrant specific trans-Institute research efforts.

Discussion

A Council member inquired as to whether there were novel mechanisms for coordinating intramural and extramural research for obesity and the Roadmap initiatives. Dr. Spiegel first indicated that although the obesity effort is similar to the Roadmap initiatives in that it represents a coordinated trans-NIH effort, it is not considered part of the Roadmap because it highlights specific diseases or organs, whereas the Roadmap is directed at mainly extramural activities, with the exception of the Re-engineering Clinical Research initiative.

Currently, possibilities are being explored as to how the intramural Clinical Research Center (CRC), located on the NIH Bethesda campus, can interface with the more than 80 General Clinical Research Centers around the country with regard to obesity research. One proposal is that an intramural trans-NIH obesity center with a clinical orientation would be housed in the CRC. Innovative mechanisms are necessary for coordinating intramural and extramural obesity research. The NIH can and must be a major contributor to addressing and ultimately solving the problem of obesity; however, it cannot be the sole repository for a solution to the epidemic, and other branches of Government are therefore addressing the crisis as well. In this regard, the DHHS Secretary's Prevention Steering Committee addresses five areas: (1) health literacy

(Surgeon General), (2) tobacco (CDC), (3) communication of health messages (Public Affairs), (4) diabetes (NIH), and (5) obesity (FDA). The groups have implemented a Department-wide series of activities to assess what each agency is currently doing, where gaps exist, and what opportunities are available.

The diabetes and obesity groups, chaired by Dr. Zerhouni and by FDA Commissioner Mark McClellan, respectively, frequently work together. One example of joint efforts under Department leadership is an initiative to prevent and treat pediatric obesity, which received $7 million of the $22 million in the President's FY 2005 Budget Request for trans-NIH obesity research.

The FDA has responded to the obesity epidemic with efforts focused on food labeling, which include clarifying serving sizes and displaying the caloric content of restaurant foods. The USDA is conducting research on economic issues driving the obesity problem (e.g., the creation of calorically dense food at low cost, which is a triumph over food scarcity but a liability in terms of the obesity problem). The NIH can also partner with companies that are concerned about the risks of obesity and are willing to support clinical studies to combat the current epidemic.

Ethical Standards at the NIH

Dr. Zerhouni has created the internal NIH Ethics Advisory Committee to develop ethical standards and oversight guidelines. Ten members representing senior extramural and intramural leadership at the NIH, as well as leaders within the extramural scientific community, comprise the Committee. Dr. Nancy Nossal, an NIDDK intramural scientist, has been appointed to the Committee, which will review outside activity requests submitted by intramural scientists and other members of the NIH community.

A "blue ribbon" panel will be convened to perform a complete review of NIH practices and guidelines with respect to outside activities (e.g., interactions with the pharmaceutical and biotech industries). While it is important that the NIH maintain the public's trust and uphold its reputation for integrity and for appropriate use of public funds, NIH scientists have voiced a desire to benefit the public with the development of diagnostic tests and therapeutics in a manner free of conflict-of-interest issues.

Guidelines for ethical issues regarding research initiatives, including clinical trials, have become more of a focal point as the use of human subjects has increased. While not a regulatory agency, at a minimum, the NIH has an oversight role in terms of raising awareness of relevant issues. The Bayh-Dole Act mandates that scientific research conducted in universities not have a purely commercial consequence but rather that it contribute to public good.

President's FY 2005 Budget Request; NIDDK Research Advances, 2003

A summary of the NIH component of the President's Budget Request for FY 2005, and the NIDDK's FY 2003 "Recent Advances and Emerging Opportunities" document are available on the NIDDK Web site.

REPORT FROM THE NIDDK DEPUTY DIRECTOR

Dr. Griffin Rodgers

In FY 2003, the NIDDK awarded 3,149 research project grants, an 8 percent increase from FY 2002; funded 78 research centers; and supported 1,125 research training slots. Funding for the Intramural Research Program and for Research Management and Support of the extramural program accounted for 9.7 percent and 3.1 percent of the overall budget, respectively.

The FY 2004 increase for NIDDK is 3.7 percent in aggregate, but two major rescissions lowered the overall budget by approximately $180 million to reflect an annual increase of 3.0 percent. This amount decreased further with the transfer of funds to other programs and agencies in the Department, but the addition of the Roadmap funds to the NIDDK appropriation countered the reduction, for an effective increase of 3.4 percent in NIDDK funding for FY 2004 over FY 2003.

In anticipation of lower funding levels following the 5-year doubling period for NIH funding (FY 1999-FY 2003), the NIDDK prepared model budgets representing 2, 4, and 8 percent increases in the NIH FY 2004 appropriation. Having funded to a more conservative payline during the continuing resolution, the NIDDK is using the appropriated budget to fund the remaining approved meritorious grants that fall within the general payline for research project grants.

The number of research project grants has increased from FY 2003 to FY 2004; however, other increases in the budget have been kept relatively low to support these grants. Increases in research training, careers, and other research areas generally reflect additions due to the distributions of Roadmap activities. In FY 2004, the Congress renewed the special type 1 diabetes appropriation for a period of 5 years (through FY 2008), increasing the annual amount from $100 to $150 million.

The President's budget proposal for FY 2005 includes a 2.6 percent increase for the NIH and a 3.3 percent increase for the NIDDK. Funding for the NIH Obesity Research Task Force and its initiatives is $22 million. Dr. Zerhouni has assigned $2.5 million of this amount to fund the trans-NIH Intramural Obesity Research Center, a central obesity funding initiative led by the NIDDK.

The Roadmap initiatives will increase from a base of $128 million in FY 2004 to $236 million in the proposed FY 2005 budget. Funding for the Roadmap will come from the Director's discretionary fund ($60 million) and from individual institutes ($177 million).

Under the assumption of a nearly flat future budget, the general approach taken by the NIDDK will be to maintain a strong emphasis on research project grants and on the investigator-initiated portion of the research portfolio.

The NIDDK may face decreasing pay lines, but the Institute is now operating at a much higher base than before the doubling of the NIH budget. With the normal turnover of grants, the scientific vitality of the NIDDK research portfolio will be ensured for future years.

In FY 2005, it is likely that substantially fewer Requests for Applications (RFAs) may be issued by the NIDDK than in the recent past. However, Roadmap and translational initiatives, together with expanded obesity research efforts—and to some extent the Special Emphasis Program Announcements—will provide the opportunity for NIDDK investigators to participate in new areas of investigative inquiry.

Discussion

A question was raised by a council member regarding how Requests for Applications are reviewed. Dr. Hammond responded that the review process for applications submitted in response to the Roadmap and obesity initiatives will differ from typical applications in many cases. The NIDDK is working with the Center for Scientific Review, which will review some of the applications (i.e., those in the area of metabolomics). The NIDDK Review Branch will manage the review of applications requesting support for interdisciplinary training programs, since the Institute has relevant experience in the review of similar mechanisms.

The NIDDK Review Branch will work with the Roadmap implementation groups in the development of peer review panels for the RFAs. The scientific peer review process for applications under these initiatives is currently being coordinated.

Dr. Spiegel added that under the "Research Teams of the Future" Roadmap initiative, the NIH Director's Pioneer Awards (formerly the NIH Director's Innovator Awards) provide investigators with $500,000 per year for several years. These grants will be reviewed outside the conventional study-section format and will be awarded for high-impact, but necessarily high-risk, research for an investment more in individual scientists than in projects. Conceptually, these grants are of two types: more generic awards that are not targeted to a specific biological problem or disease (e.g., the proteomics initiative), and Institute-supported grants that are developed for specific research areas.

One council member indicated that changes are necessary within the scientific community with regard to the incoming generation of clinician investigators, shifting the focus from independent research enterprises to interdisciplinary working groups. Similar cultural adjustments will be needed to boost multidisciplinary undertakings in academic medical centers, e.g., the creation of systems biology departments or other interdisciplinary types of groups.

With the creation of core facilities under the Roadmap initiatives, one council member indicated that it is important to maintain the concept behind these resources, which is to facilitate the work

of the independent investigator and to support an individualistic approach to scientific inquiry and clinical research.

VI. SCIENTIFIC PRESENTATION

Dr. Rudolph Leibel
Professor and Head, Division of Molecular Genetics
Columbia University College of Physicians and Surgeons

"The Molecular Physiology of the Control of Body Weight"

The prevalence of obesity has increased dramatically in the United States, causing serious health consequences, including a parallel escalation in levels of type 2 diabetes. While there are molecular controls over body weight, the body's innate regulatory defenses against loss of fat are stronger than its defense against weight gain. The defenses against weight loss are designed to maintain a sufficient amount of fat (energy) for reproduction and, from an evolutionary perspective, for protection against the environmental vicissitudes faced by our evolutionary ancestors, in times when food supply was often restricted.

The brain receives signals from the blood and other organs and tissues, and it produces molecules that then affect energy intake and expenditure. For example, leptin, a hormone secreted by fat cells, stimulates brain molecules that lead to reduced food intake. Many rare forms of human obesity result from mutations in genes that encode components of this regulatory system. More common forms of obesity also have a strong genetic influence; it has been estimated from studies of twins that 40-60 percent of susceptibility to obesity is attributable to genes. The genetic bases for these more common forms of obesity, however, are far more complex and risk is likely influenced by many genes that are as yet unidentified.

Genes that promote energy storage in the current environment of plentiful food partly explain the modern obesity epidemic; however, obesity is also difficult to prevent and treat because a loss of weight—fat mass—triggers a compensatory adjustment in the body's energy expenditure that favors weight regain. Therefore, formerly obese individuals—those who have lost weight—require fewer calories to maintain their new weight than do individuals of the same weight who were never obese.

A model to explain this phenomenon is that each individual has a threshold for the action of leptin, which is set by subtle sequence variations in the person's genes. When fat mass is reduced, insufficient leptin is produced to cross this threshold. The resulting consequences include a slowing metabolic rate (energy expenditure), a state of infertility, decreased satiety, and other metabolic effects. In a clinical study, individuals who had lost 10 percent of their body weight, an amount sufficient to bring about substantial health benefits, were injected with just enough leptin to restore pre-weight-loss levels of the hormone. This extra leptin apparently tricked the brain into thinking the fat was still there, and thus reversed many of the problematic compensatory changes that normally accompany weight loss, including decreased energy expenditure.

With respect to therapies for obesity, the dietary and medical approaches available currently are not ideal. Important areas for future research include new molecular targets for drugs; public health approaches to reduce intake of calorically dense foods and increase physical activity; the timing for prevention and treatment in children; genetics; and molecular diagnostics.

VII. ADJOURN FOR LUNCH

Dr. Spiegel thanked all of the presenters and adjourned the open session of the full Council.

VIII. SUBCOMMITTEE MEETINGS

From approximately 1:00 to 5:30 p.m., separate meetings were convened by the Subcommittees for Diabetes, Endocrinology, and Metabolic Diseases; Digestive Diseases and Nutrition; and Kidney, Urologic, and Hematologic Diseases. The Subcommittees met again on Thursday, February 5, 2004, from 8:00 to 9:30 a.m.

IX. REPORTS OF SUBCOMMITTEES: CONSIDERATION OF APPLICATIONS (CLOSED SESSION)

X. EXTRAMURAL POLICIES

Dr. Robert Hammond

Dr. Spiegel reconvened the open session of the full Council at approximately 10:00 a.m. on Thursday, February 5, 2004.

Annual Approval of Council Operating Procedures

Dr. Hammond began the open session with a staff proposal to consolidate the National Diabetes and Digestive and Kidney Diseases Advisory Council (NDDKAC) operating procedures (available on the NIDDK website) from four items into two.

The current four operating procedures are as follows:
1. Advisory Council Operating Procedures (overall)
2. Delegation for Administrative Supplements
3. Implementation of Expedited Concurrence of En Bloc Actions
4. Policy on MERIT Award Extensions

Under this proposal to streamline and clarify the procedures, the “Delegation for Administrative Supplements” procedures and the “Policy on MERIT Award Extensions” procedures will be integrated into the overall “Advisory Council Operating Procedures” document.

The procedures for “Implementation of Expedited Concurrence of En Bloc Actions” will be retained as a separate document, due to technical complexity and the regular distribution to the

NDDKAC En Bloc Concurrence Committee (Drs. Caro, Kelly, Lee, Sherman, Vaughan, and Walker).

A motion for approval of this proposal was approved unanimously.

NIDDK Research Centers

The goal of the enhancement effort for NIDDK Research Center grant programs is to maximize the potential of Centers as research resources that are uniquely well poised to support innovative activities. The four areas of focus are: (1) shared resources (cores), (2) pilot and feasibility studies, (3) clinical and translational research, and (4) interactions with research training and career development programs.

The effort aims to ensure that the key components of Center grants (e.g., cores, pilot and feasibility studies) function as innovative, dynamic components of the Centers programs, responsive to the challenges and opportunities of the 21st century.

XI. ADVISORY COUNCIL FORUM: TRANSLATIONAL RESEARCH

Dr. Spiegel

Introduction

Dr. Spiegel emphasized the mission of the NIH is to improve human health through research. Basic scientific research is critical to advancing knowledge, but to be useful in benefiting human health, it ultimately must translate to clinical practice.

The translational process can be divided into two stages: primary translation—defined as progress between basic research and bedside application, and secondary translation—defined as between the individual or small groups of patients and widespread clinical practice. Although secondary translation is a subject of vital interest to the NIH, the forum focused explicitly on primary translation and the bi-directional movement between bench and bedside research.

NIH Roadmap

Dr. Josephine Briggs

The three overall themes of the NIH Roadmap are: (1) New Pathways to Discovery, which is an effort to increase the molecular tools available; (2) Research Teams of the Future, with an emphasis on interdisciplinary work; and (3) Re-engineering the Clinical Enterprise.

The New Pathways to Discovery theme encompasses bench-related implementation initiatives with potential applications to translational research. These include: Building Blocks, Biological Pathways, and Networks; Bioinformatics and Computational Biology; Molecular Libraries; and Nanomedicine. The Molecular Libraries initiative supports chemical diversity (through a publicly available database), screening, and drug development, as needed.

Two efforts are currently underway to ensure that projects going forward are useful to investigators:

1. The development of translational research centers is a work in progress, shaped by recommendations from outside advisors. The centers will provide regulatory advice to help scientists bring a new product from the bench to clinical use, including laboratory studies to understand therapeutic mechanisms of action, preclinical drug synthesis and toxicity testing, sophisticated manufacturing capacity, and expert advice to ensure that drug development regulations are observed.

2. Translational core resources will give applicants access to centralized contract resources and expertise. The investigator-initiated and peer-reviewed program is not a grant mechanism; rather, it is designed to provide successful applicants with resources not readily available to academic investigators and associated small businesses. Under this program, modeled on the National Cancer Institute's (NCI) Rapid Access to Intervention Development (RAID) program, intellectual property and project control will remain with the originating institution and the originating investigator, respectively.

Potential core services include: manufacturing services and standards; development of analytic methods and pharmaceutical assays; stability testing; product formulation; preclinical pharmacokinetics testing; animal toxicology studies; regulatory support for Investigational New Drug filing; and assistance in overall product development plans. Currently, the RAID program supports only therapeutics development, but support for cell-based therapies, diagnostic development, and devices is being considered, with a pilot anticipated in summer 2004.

RAID/Translational Research Pipeline

Dr. Myrlene Staten

The Type 1 Diabetes--Rapid Access to Intervention Development (T1D-RAID) program is the first NIDDK effort to specifically support translational research. The goal of the program is to facilitate access to preclinical development resources for potential new therapies for type 1 diabetes and its complications. The program is not a grant process; no funds are available for investigators. Instead, successful investigators gain access to preclinical research and expertise so that the basic scientific research can be more easily transitioned into the therapeutic development pipeline.

The NIDDK is partnering with the NCI for the T1D-RAID effort. Eligible organizations include academic institutions, nonprofit research institutions, biotechnology and pharmaceutical companies, and domestic and foreign entities. The complete range of resources necessary to move an Investigational New Drug package through the translational process will be made available.

A panel of external experts from academia and industry meets two times per year to review requests based on scientific merit, the strength of the hypothesis, the novelty of the product, and the feasibility of the research and design plan.

After receiving external input on the applications, the NIDDK and NCI conduct separate internal reviews focused on managing available resources. Review criteria include NIH programmatic issues, priorities, portfolio diversification, and the projected cost of each aspect of the highly scored projects. Biologic agents (e.g., recombinant proteins) go to the T1D-Biological Resources Branch Oversight Committee for technical and feasibility-of-production review.

Three requests were received in the first cycle, covering both the pathogenesis of type 1 diabetes and its complications. The receipt date for the next cycle is April 1, 2004.

Translational Research Pipeline

Dr. Philip Smith

The goal in analyzing the pathway from discovery research ("bench") for new therapeutics ("bedside") is to determine whether there are particular places where the NIH can play a role in translation, what that role should be, and what partners or human resources will be needed at each step in the pathway.

The role of industry can range from very significant to very minimal, depending on market size and patentability. Large market size and high patentability are desirable and, in these cases, industry usually is involved at an early stage. It is important to view the various steps of the

pipeline not as individual issues to address, but rather as a comprehensive process involving people and mechanisms working together as a team. A similar process can be outlined for the development of diagnostics and of biomarkers in general, which may be used in the development of diagnostics and in the development of surrogate markers.

Academic investment is highest under basic discovery research, whereas industry investment is highest under exploratory clinical research. Both academic and industry investment are lowest at the stages of therapeutic discovery research; this is where programs such as the NCI's RAID program will help bridge the translation gap by supporting further development of clinical reagents.

Similar trends are evident along the pathway for biomarker and diagnostic assay development, with abundant industry support for product development, but an overwhelming academic focus on basic discovery research. Small biotech companies often become involved very early on in the process, however, and an investigator who finds a potential reagent for a diagnostic is likely to find an eager industry partner quickly in this sector. Diagnostic assay development is not the only possible outcome of this pathway; there is also a very large market for biomarkers for use in monitoring the efficacy in early phase trials.

The cell therapy bench-to-bedside pathway is a much newer process for most disease-related research. Basic science in the area of development including, most recently, human embryonic and adult stem cells, is a major part of the NIDDK portfolio, and many programs have been developed to encourage this work.

Translational Research: Implementation Through Requests for Applications (RFAs) and Program Announcements (PAs)

Dr. Stephen James

Efforts to foster translational research exist already in the form of RFAs and PAs. One example, ("Bench to Bedside Research on Type 1 Diabetes and Its Complications," RFA-DK-03-001), stemmed from the availability of special funds for type 1 diabetes research, using the R21 and R33 exploratory/developmental award mechanisms. The RFA encourages collaborations between basic science investigators and clinical investigators, and has generated a series of responses that are very specifically focused on biologic therapies.

In addition, the NIDDK is developing special emphasis PAs that will combine the advantages of the RFA and PA mechanisms. RFAs have high visibility, specific goals, and set-aside funds, but they are one-time events. PAs generally do not have set-aside funds but have multiple receipt dates. Special Emphasis PAs have both multiple receipt dates and set-aside funds. Special Emphasis PAs with translational potential that are in various stages of development and are slated for publication this year include:

- Application of proteomics to NIDDK mission-specific goals: Specific translational goals include the identification of surrogate markers for disease, development of better potential diagnostic tests, and identification of new targets and pathways.

- - < Non-invasive imaging: Specific translational goals include the development of novel methods to assess the activity, stage, rate of progression, and complications of diseases.
< Ancillary studies to NIDDK clinical trials: Specific translational goals include assay development for small molecules. This PA will broadly encourage use of resources developed in NIDDK-sponsored clinical trials for additional, novel, investigator-initiated research studies. This PA is intended to leverage the significant investment in clinical trials by making unique resources available to investigators.
< Health disparities: This PA is to encourage research to understand and mitigate issues of health disparities in high priority areas within the NIDDK mission.
< Diet composition and energy balance (already published).

Future needs for the development of translational initiatives include: (1) A systematic analysis of the translational needs of investigators in the NIDDK programs—how will these needs be identified correctly and prioritized? (2) Reassessment of implementation—should the initiatives be highly specific? Should other mechanisms, such as contracts, be used? (3) Evaluation tools and metrics—how will the decisions be evaluated? What measures will be used to verify that the correct targets have been identified? How will success be measured?

Translational Research: Priorities

Dr. Philip Smith

In December 2003, following an NIDDK extramural staff retreat, a trans-NIDDK planning group was formed with a charge to: identify obstacles to translational research; develop a consistent process to prioritize translational initiatives; identify areas where resources would be of general utility (looking for areas where a single infusion of resources may actually benefit many diseases, e.g., RAID, and research training and infrastructure); and adopt or develop mechanisms, where necessary, to address specific obstacles to translation.

Many useful endpoints can be identified as goals of translational research:
< Drug development
< Develoment of biomarkers for disease progression and treatment efficacy
< Development of diagnostics
< Development of cellular therapies
< Development of behavioral therapies

Achieving these translational goals requires identifying: (1) the steps to achieve each endpoint, (2) which steps are not currently addressed in the public or private sectors, and (3) the resources or mechanisms needed at each step.

The following criteria are useful in determining whether the NIH should invest in translation efforts for a specific project:
< Potential for major impact on human health
< Possibility of identifying specific translational steps that, if completed successfully, will lead to measurable translational advances

< Significant unmet need that will likely be overcome only with the commitment of NIH funds
< Potential application of the targeted translational effort to multiple diseases

The selection criteria for potential initiatives include:
< Strong scientific foundation on which to build a translation effort
< Likely progress toward the translation goal
< Partnership opportunities to ensure necessary product development
< Scientific teams, clinical samples or patient populations, and infrastructure to carry out specific translational steps

The process for developing translation initiatives within NIDDK will begin with each programmatic division selecting a number of topic areas spanning a range of diseases, which can be used to validate the necessary steps to move translational methods forward. The divisions will analyze existing portfolios in these topic areas to assess the existing scientific base, test the priority-setting process for selected topic areas, and select a small number of areas across the NIDDK for pilot initiative development.

The NIDDK committee on translation research posed the following questions to Advisory Council members:
< How can we increase the value to the NIDDK investigative communities of the resources for translational medicine being developed through the NIH Roadmap?
< How can we best identify steps in the translational process where NIDDK resources will serve a critical role not served by private sector support?
< Have we chosen the right factors for priority setting consideration? How should we weigh them?
< What steps can we take to encourage more investigator-initiated translational research?
< How can we best encourage broader awareness and knowledge by academic investigators of the intellectual property and regulatory issues important for translational research? Should we consider development of training resources?
< What activities are present in academic medical centers to encourage careers in translational medicine, and are there steps we can take to facilitate these activities?

Discussion

Council members were invited to comment on the Institute's proposed approach to enhancing translational research. In addition to participating in the forum, members were encouraged to submit questions, concerns, and suggestions regarding the effort during the following weeks. Council members offered the following comments:

The Investigator As Translator

< The gaps along the translational pathway are due not only to a problem with the models and the techniques and their application, but also to a lack of individuals to perform the work.

< Many Ph.D. researchers are reluctant to leave basic science or try to refocus their research in a direction up to and including pre-clinical studies.

< Rather than searching for investigators skilled in both the basic and clinical domains, develop a community of translational researchers who would specialize in the application of basic science discoveries to clinical practice.

< Translational research could be conducted under a minority investigator or training award mechanism.

< Create a mechanism or strategy for the reverse direction along the translation pathway so that clinicians may contribute their observations for basic science exploration.

< Establish methods to facilitate communication between basic research scientists and clinicians.

< NIH-supported pilot studies that require basic and clinical investigators to work together would generate interest and stimulate discussion between basic research scientists and clinicians.

Encouraging Careers in Translational Medicine

< It is critically important to provide resources to individuals in training in order to shape the academic environment and encourage careers in translational medicine.

< Offer to the large pool of Ph.D. scientists various training opportunities that encourage the translational aspect of research and correspond with goals of the Roadmap.

< Build an adequate support system for Ph.D. researchers who have become interested in clinical applications. This could include formal coursework in the principles of medicine.

< Offer very basic hypothesis-driven research to encourage Ph.D. scientists to undertake work—such as target validation, animal model development, and screening—and reward their efforts.

< In the area of drug development, establish a specific mechanism to recruit analytical chemists and chemical engineers, for example, to help with the screening process and follow up on lead compounds.

< Clarify what resources are available, and ensure that molecular libraries and screening centers are accessible.

< Create well-curated, accessible molecular libraries, and consider developing extensive siRNA libraries for target identification.

Patient-based Translational Research Centers

< Establish within clinical research centers, such as the NIH-supported General Clinical Research Centers, a means to allow clinical investigators to bring in individual patients with an undiagnosed health problem who may then be studied by other clinicians and basic researchers to potentially diagnose the condition. This would draw Ph.D. scientists literally to the bedside to study these patients through physical, biochemical, and molecular examination. This bedside access would enable researchers to employ the extraordinary tools

currently available to discover the fundamental issues that underlie disease. The interactive setting would foster communication between scientists and physicians, and could ultimately lead to investigators becoming directly interested in the translational studies. Protection of human subjects would need to be handled meticulously.

Institutional Review Board (IRB), Conflict-of-Interest, and Intellectual Property Issues

< Currently, many limitations restrict basic scientists from participating in more clinically oriented research and following up on observations that they have made.

< Improve the efficiency of IRB approval by working to balance the need for absolute human subject protection with the desire to streamline the process and remove the barriers for investigators.

< The NIH should draft templates for conflict-of-interest and IRB approval to be used as standards for research by academic institutions. The institutions could customize the templates. It was observed that this could be a major contribution of the NIH to the conduct of clinical research. (Dr. Spiegel noted that the National Cancer Institute (NCI) is pilot testing a "centralized IRB model" to streamline IRB function. Participating IRBs would not be allowed to customize or deviate from the model. Dr. Spiegel also reminded the group that since the NIH is not a regulatory agency, it really doesn't have the authority to direct or mandate the processes that IRBs use. Dr. Hammond noted that NCI will be issuing a final report on the pilot.)

< Barriers to progress include the different state laws involved, the need for a sufficient number of protocols to make the effort worthwhile, and the reluctance by individual institutes to relegate to the centralized IRB.

< The NIH probably need not spend significant effort on intellectual property issues, which are handled by the universities.

Industry Involvement

< Drug companies and small biotechs frequently are not interested in developing an idea for a product (generated from academic research, for example) for clinical use unless the target is a near-guaranteed success.

< The NIH should encourage translation of basic drug development research to stages where a potential product might attract industry interest, i.e., lower the threshold for industry interest. This also pertains to the area of surrogate marker development for phase I and phase II clinical trials end-points.

< The record of failure in phase III trials (e.g., the low success rate of drug development) relates in part to the lack of significant surrogate markers in phase I and phase II trials.

< Provide more meaningful surrogate markers that, in the smaller and less costly phase one and phase two stages, would be much more predictive and could warn against investing additional time and money if the project is not going to work.

< Implement an educational process to overcome the lack of knowledge about industry.

< Encourage government interactions with private industry.

< Increase the appeal of translational research and clinical trials to industry, which would reduce the amount of very expensive studies to be funded by government sources.

< Establish a mechanism for the development and clinical testing of inventions that the pharmaceutical industry has decided not to pursue. Proposals for inventions of clinical value

would be reviewed through special panels. Successful proposals would be administered through an NIH intramural program which would take on the responsibility of shepherding the invention through all phases of drug development and clinical trials.

Funding

< The use of public funds makes NIH investigators accountable for producing valuable results and effectively leading to the public's health and welfare.
< The proposed translational efforts may take too much money away from other areas of study (e.g., R-type mechanisms), which in turn would suffer a major loss.
< What criteria will determine the studies to be conducted, and how will the limited available funds be allotted?

Overall, Council members indicated that they were pleased with the Institute's current and planned efforts to encourage translation research.

The NIDDK translation research committee will conduct specific analyses and bring the results to the Subcommittees for continued discussion. Participants are encouraged to submit additional questions, comments, and concerns on the subject of translational research.

XII. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1,102 grant applications, requesting support of $243,738,991 were reviewed for consideration at the February 4-5, 2004 meeting. Funding for these 1,102 applications was recommended at a level of $243,738,991. Prior to the Advisory Council meeting, an additional 155 applications requesting $36,472,744 received second-level review through expedited concurrence. All of the expedited concurrence applications were recommended for funding at the requested levels. The expedited concurrence actions were reported to the full Advisory Council at the February 5, 2004 meeting.

XIII. ADJOURNMENT

Dr. Spiegel thanked the Council members for their attendance and efforts. There being no other business, the 164th meeting of the NIDDK Advisory Council was adjourned at 12:04 p.m., February 5, 2004.

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

Allen M. Spiegel, M.D.
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