

Meeting Minutes

Department of Health and Human Services

National Institutes of Health

National Diabetes and Digestive and Kidney Diseases Advisory Council

I. CALL TO ORDER

Dr. Griffin P. Rodgers, Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), called to order the 176th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m., Wednesday, January 30, 2008, in Conference Room E1/E2, Natcher Building (45), NIH, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Nancy Andrews	Dr. Juanita Merchant
Dr. Janice Arnold	Dr. Brian Monahan
Ms. Janet Brown	Dr. William Mitch
Dr. Charles Elson	Dr. Jerry Palmer
Dr. James Freston	Dr. David Perlmutter
Dr. William Freston	Ms. Margery Perry
Dr. Mitchell Lazar	Dr. Anthony Schaeffer
Dr. David Klurfeld	Mr. James Schlicht
Dr. Mark Magnuson	Dr. Patrick Tso

Also present:

Dr. Griffin P. Rodgers, Director, NIDDK, and Chairperson,
NIDDK Advisory Council

Dr. Brent Stanfield, Executive Secretary, NIDDK Advisory Council

B. NIDDK STAFF AND GUESTS

In addition to Council members, others in attendance included NIDDK staff members, Center for Scientific Review (CSR) Scientific Review Officers, and other NIH staff members. Guests were present during the open sessions of the meeting. Attendees included the following:

Abraham, Kristen – NIDDK	Davila-Bloom, Maria – NIDDK
Agodoa, Lawrence – NIDDK	Davis, Chris – NIDDK
Akolkar, Beena – NIDDK	Desanti, Andrea – Fisher BioService
Appel, Michael – NIDDK	Doherty, Dee – NIDDK
Amir, Syed – CSR	Donohue, Patrick – NIDDK
Bethum, Najma – CSR	Doo, Edward – NIDDK
Beverly, Kevin - Social Scientific Systems	Edwards, Michael – NIDDK
Blondel, Oliver – NIDDK	Eggerman, Thomas – NIDDK
Brown, Clarice - Social Scientific Systems	Farishian, Richard – NIDDK
Calvo, Francisco – NIDDK	Faupel-Badger, Jessica – NIDDK
Carrington, Jill – NIDDK	Feld, Carol – Hill Group
Castle, Arthur – NIDDK	Ferguson, Frances – NIDDK
Chang, Debuene – NIDDK	Fonville, Olaf – NIDDK
Chianchiano, Dolph - National Kidney Foundation	Fradkin, Judith – NIDDK
Christiansen, Dane - Digestive Diseases National Coalition	Gallivan, Joanne – NIDDK
Connaughton, John – NIDDK	Gansheroff, Lisa – NIDDK
Copeland, Randi – NIDDK	Garfield, Sanford – NIDDK
Danishes, Florence – NIDDK	Gershengorn, Marvin – NIDDK
	Giambarresi, Leo - American Urological Foundation
	Goter-Robinson, Carol – NIDDK

Gottesman, Michael - NIH OD
Graves, Reed – CSR
Greene, Elizabeth – NIDDK
Harris, Kimberly – NIDDK
Hays, Dustin – NIDDK
Hoff, Eleanor – NIDDK
Hoofnagle, Jay – NIDDK
Horlick, Mary – NIDDK
Hoshiazi, Deborah – NIDDK
Hubbard, Van – NIDDK
James, Stephen – NIDDK
Jerkins, Ann – CSR
Johnson, Michelle – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Ketchum, Christian – NIDDK
Kim, Sooja - CSR
Krensky, Alan – OPASI
Kuczarski, Robert – NIDDK
Kusek, John – NIDDK
Laughlin, Maren – NIDDK
Leak-Elder, Gala – NIDDK
Linder, Barbara – NIDDK
Malik, Karl – NIDDK
Malozowski, Saul – NIDDK
Manouelian, Denise – NIDDK
McGowan, Melissa – NIDDK
McKeon, Catherine – NIDDK
Miles, Carolyn – NIDDK
Miller, David – NIDDK
Miller, Megan – NIDDK
Moxey-Mims, Marva – NIDDK
Mullins, Christopher – NIDDK
Nyberg, Leroy – NIDDK
Perry-Jones, Aretina – NIDDK
Peterson, Jane – NHGRI
Pike, Robert – NIDDK
Podskalny, Judith – NIDDK
Rasooly, Rebekah – NIDDK
Robuck, Patricia – NIDDK
Rosenberg, Mary Kay – NIDDK
Ross, Catherine – Team Placement Services
Salomon, Karen – NIDDK
Sato, Sheryl – NIDDK
Seef, Leonard – NIDDK
Sekis, Branca - Social Scientific Systems
Sheard, Nancy – CSR
Singer, Elizabeth – NIDDK
Smith, Philip – NIDDK
Spain, Lisa – NIDDK

Star, Robert – NIDDK

Woldegiorgis, Gebretateos - CSR

Torrance, Rebecca – NIDDK

Wright, Daniel – NIDDK

Wallace, Julie – NIDDK

Xie, Yining – NIDDK

Williams, Garman – NIDDK

C. ANNOUNCEMENTS

Dr. Griffin P. Rodgers, Director, NIDDK

Council Membership

Dr. Rodgers welcomed the following members and extended his appreciation to them for their willingness to serve on the Council.

- *Dr. David Altshuler--Appointed to the Subcouncil for the Division of Diabetes, Endocrinology and Metabolic Diseases:* An Associate Professor of Genetics and Medicine at Harvard Medical School, Dr. Altshuler is also the Director of the Program in Medical and Population Genetics at the Broad Institute of Harvard and the Massachusetts Institute of Technology. Since receiving his M.D. and Ph.D. from Harvard in 1992, Dr. Altschuler has pursued two intertwined research goals. The first is to characterize and catalogue patterns of human genetic variation. The second is to apply this knowledge to dissect the genetic contributions to common human diseases--in particular type 2 diabetes and cardiovascular risk factors. He is involved in an exciting new research project on premature coronary artery disease. Dr. Altshuler is also working on prostate cancer, systemic lupus erythematosus, rheumatoid arthritis, and age-related macular degeneration. His work has contributed to the understanding of patterns of genetic variation in the human genome and to the creation of publicly available genome-wide maps for genetic analysis. Dr. Altshuler has contributed to the discovery of genes for type 2 diabetes, system lupus erythematosus, and prostate cancer. Dr. Altshuler has been an NIH-supported researcher since 2002. He is presently a Principal Investigator on three NIH-supported research projects and a co-investigator in the Center for High Throughput Single Nucleotide Polymorphism Genotyping and Analysis, which is led by the National Center for Research Resources, NIH.
- *Mr. James Schlicht--Appointed to the Subcouncil for the Division of Diabetes, Endocrinology and Metabolic Diseases:* Mr. Schlicht is the Executive Vice President for Government Affairs and Advocacy of the American Diabetes Association (ADA) and will serve as a public member of the Council. Prior to joining the ADA, he worked in government affairs for a number of pharmaceutical companies, including Bristol-Myers Squibb, Johnson & Johnson, and AstraZeneca. After receiving a Master's degree in Public Administration from Syracuse University, Mr. Schlicht performed management and budget analyses for the Federal Government. Later, he served as a staff member to Congressman Cecil Heftel of Hawaii. In his position with the ADA, Mr. Schlicht

has had a key role in the development of new cost estimates for diabetes. These were discussed at a recent congressional session that Dr. Rodgers attended along with representatives from the Centers for Disease Control and Prevention.

- *Dr. Nancy Andrews--Appointed to the Subcouncil for the Division of Kidney, Urologic, and Hematologic Diseases.* Dr. Andrews is the Dean of the Duke School of Medicine, the first woman to have that appointment and the only woman to lead one of the Nation's top 10 medical schools. Prior to her appointment at Duke, she was a Dean for Basic Science and Graduate Studies at Harvard Medical School. She has been a long-time NIH grantee and has had research support from the NIDDK since 1998. She is a member of the Institute of Medicine of the National Academies of Science, and was elected to the American Academy of Arts and Sciences in 2007. She was also a Howard Hughes Investigator from 1993 to 2006. She previously presented to the NIDDK Council on the work she and her colleagues were doing on the maintenance of iron homeostasis and the elucidation of the pathophysiology of hemochromatosis in the anemia of chronic disease.
- *Dr. James Freston--Reappointed to the Subcouncil for Digestive Diseases and Nutrition.* Dr. Freston is the Boehringer Ingelheim Chair of Clinical Pharmacology and a Professor Emeritus of the University of Connecticut Health Center in Farmington. His research interests include the clinical pharmacology of digestive diseases, including acid-related disorders and drug-induced liver injury. He is a research member of the NIDDK-funded National Drug-Induced Liver Injury Network.

NIH Grantees

Dr. Rodgers made the following announcements regarding NIH grantees:

- *Dr. Seymour Benzer:* A long-time NIDDK grantee, Dr. Benzer died on November 28, 2007, at the age of 86. Originally trained as a physicist, Dr. Benzer was one of the founding figures in the science of molecular biology in the 1950s. His research interests subsequently moved from bacteriophage genetics to *Drosophila* genetics. During his distinguished career, Dr. Benzer contributed to an increased understanding of circadian rhythm, sexual behavior, memory, development of the visual system, and the aging process. In addition to winning numerous awards and mentoring many younger scientists, Dr. Benzer was the subject of the scientific biography, Time, Love, Memory, by Pulitzer Prize-winning author, Jonathan Weiner. At the time of his death, Dr. Benzer had turned his attention to the genetics of obesity in *Drosophila*, studies for which the NIDDK had awarded him an R01 grant in 2004. The NIDDK was saddened to learn of Dr. Benzer's death.
- *Dr. Mario R. Capecchi and Dr. Oliver Smithies:* Sharing in the 2007 Nobel Prize for Physiology or Medicine are two long-time grantees of the NIH, Dr. Mario R. Capecchi of the University of Utah School of Medicine, and Dr. Oliver Smithies

of the University of North Carolina at Chapel Hill. They have been honored, along with Sir Martin J. Evans of Cardiff University, for their discovery of principles for introducing specific gene modifications in mice by the use of embryonic stem cells. They pioneered the powerful technology known as gene targeting. Experimental mice developed with this technology have furthered basic studies of biological processes, as well as investigations of cancer, heart disease, cystic fibrosis and other serious health problems. Using their technique, researchers can breed mice with specific diseases in order to test treatment modalities. The NIDDK has supported projects conducted by Dr. Smithies since 1977, when he was awarded a grant to study DNA control of the synthesis of human hemoglobin. The NIDDK is currently supporting a research project for which Dr. Smithies is the Principal Investigator. The focus is the roles of bradykinin, nitric oxide, and mitochondrial DNA damage in the complications of diabetes.

Current and Former NIDDK Staff Members

Dr. Rodgers made the following announcements:

- *Dr. Christine Maric:* Dr. Maric has accepted a faculty position at the University of Mississippi in Jackson. For the past year, Dr. Maric served as a part-time Scientific Program Officer in the NIDDK Division of Kidney, Urologic, and Hematologic Diseases. In that position, she made significant contributions with respect to the programs on renal pathophysiology and acute kidney injury. In addition to her work for the NIDDK, she has served in two positions at Georgetown University--as Assistant Professor in the Division of Endocrinology and Metabolism, and as Director of Diabetes Research at the Center for the Study of Sex Differences in Health, Aging, and Disease. Dr. Maric has been a recipient of numerous awards, including the New Investigator Award of the American Physiological Society, Renal Section; the American Society of Hypertension Young Scholar Award; and the Carl W. Gottschalk Scholar Award from the American Society of Nephrology. The NIDDK wishes Dr. Maric well in her new appointment.
- *Dr. Deborah Hoshizaki:* Joining the Division of Kidney, Urologic and Hematologic Diseases, Dr. Hoshizaki will serve as a Scientific Program Officer for programs on the kidney and on urogenital development and repair. Her areas of expertise include genetics and developmental biology. Previously, Dr. Hoshizaki served as an Associate Professor at the School of Life Sciences at the University of Nevada. She received her Ph.D. from the University of California at Berkeley. Her post-doctoral experience includes fellowships with the Albert Einstein College of Medicine and the American Cancer Society. The NIDDK welcomes Dr. Hoshizaki.
- *Dr. Josephine Briggs:* On January 24, 2008, the NIH Director, Dr. Elias Zerhouni, announced the appointment of Dr. Josephine Briggs as the Director of the National Center of Complementary and Alternative Medicine, NIH. Dr.

Briggs served from 1997 to 2006 as the Director of the NIDDK's Division of Kidney, Urologic, and Hematologic Diseases. She subsequently served as a Senior Scientific Officer with the Howard Hughes Medical Institute in Bethesda. Dr. Briggs received her M.D. from Harvard Medical School and completed her residency training in internal medicine and nephrology at Mount Sinai School of Medicine, followed by a research fellowship in nephrology at Yale School of Medicine. She was a Professor of Internal Medicine and Physiology at the University of Michigan from 1993 to 1997. She brings a focus on translational research to the study of complementary and alternative medicine. The NIDDK is proud of Dr. Briggs and wishes her the best in her new NIH leadership position.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 175TH COUNCIL MEETING

A motion was made, and unanimously passed by voice vote, to approve the summary minutes of the 175th NIDDK Advisory Council (September 2007) as submitted.

III. FUTURE COUNCIL DATES

Dr. Rodgers emphasized that the Institute is working to have one-day Council meetings. However, the NIDDK is continuing to reserve two days on the calendars of Council members for some meetings so that it can retain the flexibility to schedule longer sessions should circumstances warrant. The current schedule is:

May 23, 2008

September 24-25, 2008

February 18-19, 2009

May 13-14, 2009

September 9-10, 2009

IV. ANNOUNCEMENTS

Dr. Brent Stanfield, Director, Division of Extramural Activities, NIDDK

Confidentiality/Conflict of Interest

Dr. Stanfield 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 only for the purpose of review and discussion during the closed portions of the meeting. The outcome of the closed-session discussion may be disclosed only by NIDDK 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 in order to avoid an actual or perceived conflict-of-interest. This is unnecessary with *en bloc* votes, for which all members may be present and may participate. A Council member from a multi-campus institution of higher education may participate in discussions of any matter affecting one campus of that multi-campus institution if his or her disqualifying financial interest is employment at a separate campus of the same multi-campus institution and is in a position with no multi-campus responsibilities.

Council Operating and Early Concurrence Procedures

Dr. Stanfield asked the Council to vote on whether to continue with the proposed Council Operating and Early Concurrence Procedures, which he had sent to the Members previously for their review. He noted that a vote on procedures is required each year. The proposed procedures are unchanged from last year. A motion was made and seconded to approve the procedures. The motion was then approved by voice vote.

V. ADVISORY COUNCIL FORUM:

Part I - OPASI Update and Director's Vision

Alan M. Krensky, M.D.

Director, Office of Portfolio Analysis and Strategic Initiatives (OPASI)

Dr. Rodgers introduced Dr. Krensky, who began his new position at the NIH in July of 2007. Dr. Krensky received his M.D. from the University of Pennsylvania in 1977. Before joining the NIH, he served at Stanford University as a Professor of Pediatrics and was Chief of the Division of Immunology and Transplantation Biology. Dr. Krensky now directs the NIH Office of Portfolio Analysis and Strategic Initiatives--OPASI (<http://opasi.nih.gov/>).

Dr. Krensky began his presentation by reviewing key provisions of the NIH Reform Act of 2006--the first omnibus reauthorization of the NIH in 14 years. This Act underscored congressional interest in trans-NIH strategic planning and research collaboration. It authorized establishment of a new Division of Program Coordination, Planning and Strategic Initiatives--DPCPSI. This Division includes OPASI, which the NIH Director had previously established administratively. The new Division also includes other programmatic offices in the Office of the NIH Director for activities such as AIDS, behavioral research, women's health research, and prevention.

The Act also authorized establishment of a Common Fund to support trans-NIH research. Previously, the NIH Roadmap for Medical Research (<http://nihroadmap.nih.gov/>) was established administratively by the NIH Director, in consultation with the Institute and Center Directors, for this type of cross-cutting research activity, which was supported by funds contributed by the Institutes and Centers. Now, this function is established in statute with line-item funding approved by the Congress.

Several mechanisms and processes are also established by the Act to help guide the future directions of the NIH. One is a Council of Councils to guide trans-NIH priority-setting. It is chaired by the OPASI Director, with a representative from the National Advisory Councils of each Institute and Center. Dr. Juanita Merchant, NIDDK Advisory Council member, sits on the Council of Councils. There is also a new Scientific Management Review Board to evaluate the organizational structure and authorities of the NIH and report to the Congress every seven years. The Act also provides for a public process to review potential organizational changes.

Within the context of the new authorities provided by the NIH Reform Act, Dr. Krensky reviewed the OPASI mission. The OPASI will provide NIH components with the methods, tools, and information necessary to improve portfolio management. In concert with multiple other sources of input, the OPASI will help to identify important areas of emerging scientific opportunities or public health challenges. The OPASI will help to accelerate investment in these areas--focusing on those that involve multiple NIH components. Another OPASI function will be to coordinate and make more effective use of NIH-wide evaluation processes.

Dr. Krensky explained that the structure and interactions of the OPASI support these functions. The OPASI Director also serves as a Deputy Director of the NIH—reporting directly to the NIH Director. The OPASI plays a crucial role with respect to the NIH Steering Committee, which is a governance mechanism for the NIH and a source of policy and operational advice for the NIH Director. There is also an OPASI Working Group, through which three Institute Directors advise the OPASI Director about the directions of the Office. Dr. Stanfield of NIDDK serves on this working group. There are three branches in OPASI. One deals with portfolio analysis, one with strategic initiatives, and one with evaluation.

One of the new “thought-leadership” questions the OPASI is exploring is how to look fully at a scientific portfolio in order to evaluate the science over the long-term for both processes and outcomes. Furthering these efforts is a new computer-based, data-collection system for all NIH that will enable individuals to review an entire research portfolio for a specific disease. This system is called the “Research, Condition and Disease Categorization” or RCDC. The OPASI will also be making efforts to increase understanding of the burden of illness and how that can inform the portfolio. In addition, new tools will be sought to identify gaps in the understanding of health and disease, new challenges, and emerging opportunities. These analytic functions, combined with evaluation efforts, will undergird the development of trans-NIH strategic initiatives such as the NIH Roadmap for Medical Research.

The Roadmap has, in a sense, been a learning laboratory. All 27 Institutes and Centers have come together to determine which initiatives to pursue, and how they will be funded and implemented. The Roadmap is a dynamic and revolving process designed to provide “incubator space” to pilot new programs, try new funding mechanisms, and test new ways of approaching problems. Ongoing initiatives will “graduate” within 5 or 10 years, while new ones revolve into the Roadmap incubator. By 2014, the first cohort of

initiatives will have transitioned out of the Roadmap--either to completion, or to continued funding by one or more of the NIH Institutes and Centers.

Dr. Krensky said that new programs for the Roadmap will continue to be developed based on community input, cross-cutting relevance, and prioritization by NIH leadership.

Criteria for Roadmap funding include that an initiative must be truly transformative; must synergistically promote and advance the individual missions of the Institutes and Centers; be applicable to issues beyond the scope of any one or small number of NIH components; have a high likelihood that no other entity would undertake the work; and have a high probability of producing research results that will benefit the public health and be in the public domain. The Roadmap budget represents 1.7 percent of the NIH budget or \$495 million. This budget supports the work of hundreds of investigators at research institutions across the country.

The Roadmap continues to be centered around three main themes: re-engineering the clinical enterprise, new pathways to discovery, and research teams of the future. Within these themes, the topics of the initial Roadmap initiatives are: molecular libraries; building blocks, pathways and networks; structural biology; bioinformatics and computational biology; nanomedicine; interdisciplinary research; high risk/high reward research; clinical research; and public-private partnerships.

The largest Roadmap initiative is on the development of molecular libraries--a new program for screening small molecules for a variety of pathways and new drug discovery and for making them available to the research community. The NIH Director's Pioneer Awards and New Innovator Awards came out of the Roadmap, as did the new Clinical and Translational Science award program that is now housed in the National Center for Research Resources. New interdisciplinary programs are breaking down barriers and forging new research alliances between and among disparate fields.

Dr. Krensky noted that the NIH is still experimenting with the process for identifying new Roadmap initiatives. The process thus far has been a long one, which involved garnering input from the community in multiple ways and providing opportunities for Web-based public input. The process for identifying the second round of Roadmap initiatives--dubbed Roadmap 1.5--began in early 2006 and was completed in May 2007. A group of 300 final concepts were considered at a retreat of Institute and Center Directors, who distilled the list to five final topics. Two of those are going forward with initiatives--the human microbiome and epigenetics. The three topics that were not selected were protein capture agents and proteomics; standardization of human disease phenotypes; and inflammation as a common disease mechanism.

The epigenetics initiative is similar in intent to the genomics initiative--to develop new technologies, develop new maps, and try to make connections with human disease. Likewise, the microbiome initiative will attempt to develop and apply new tools for studying the human microbiome and for analyzing its role in human health and disease. Both initiatives are broadly relevant to the missions of the Institutes and Centers.

Beyond the Roadmap and the Common Fund, the OPASI and the new statutory Division in which it is housed have a role in trans-NIH coordination. Some current topics include obesity, the neurosciences, regenerative medicine, informatics, pharmacogenomics, health disparities, and children's health.

In closing his presentation, Dr. Krensky described the ways that the OPASI may affect transdisciplinary research and the factors for its success. The Office is likely to play a major role in transdisciplinary research because of its statutory responsibilities and the resources that it can bring to bear. The OPASI will house Roadmap initiatives, which by definition, are more likely to cross disciplinary and organizational boundaries. To the extent that Roadmap initiatives are large, infrastructure-type projects, they will be open to access by multiple disciplines and research areas and the OPASI will foster their broad use. The OPASI's portfolio analysis tools will promote a broader understanding of NIH investments and promote connections across disciplines, NIH components, and disease-focused research. This last function will be important for NIH communications with advocacy groups, the Congress, and other stakeholders, and will foster new connections in support of the national research endeavor. The OPASI will thus promote a new paradigm of trans-NIH coordination that will help the 27 Institutes and Centers to work together beyond their individual missions.

The success of the OPASI will be measured in several ways. Of paramount importance will be the extent to which it serves science, which means that planning should be evidence-based. The OPASI will also need to maintain transparency, to communicate its plans and activities through its website (<http://www.opasi.nih.gov>) and other means, and to manage change. In the end, the success of the OPASI will be measured in its ability to fill gaps, alleviate redundancies, and add value to strategic planning and to the portfolio of the largest biomedical research institution in the world.

Council Questions and Discussion

What will be the metrics for measuring the OPASI's success in filling gaps and alleviating redundancies? Dr. Krensky replied that there is a growing field of science that is addressing the types of metrics that can be used. Analyzing the numbers of publications and the impact of the journals in which they appear is one approach that has been used. Yet, some Nobel Prize winners have said that their Prize-winning work was not published initially in the most influential journals because it was too new. Other approaches are to consider citation analysis, obtaining patents, starting companies, developing drugs, improving the treatment of disease, and other indicators of research outputs. The OPASI is wrestling right now with the question of metrics. Institute and Center Directors will be involved in this process. That may include the development of new evaluation tools, which will be used in conjunction with the professional judgments of experts in scientific fields. The OPASI will also look to ideas emerging from scientific meetings and the research being done in other countries. Continuous input will be sought from the scientific community about cutting-edge issues.

How will decisions be made regarding when Roadmap funding for an initiative should end? Dr. Krensky pointed out that the first issue is whether the initiative should leave the

Roadmap incubator at five or ten years. There is a process through which the NIH Institute and Center Directors are now beginning to make those determinations. A transition planning group is considering whether specific initiatives should remain in the Roadmap for the full ten-year period. The group is also gauging whether there is a scientific interest among one or more NIH components in funding and managing initiatives post-Roadmap. For some initiatives, it is considered too early to know; however, there is agreement at this time that the molecular libraries initiative should move forward in a long-term mode.

How do you balance extramural and intramural research in the Roadmap? The overriding objective is to fund excellent science. The extramural community is strongly encouraged to compete for funding under the Roadmap. Currently, slightly less than five percent of the overall Roadmap budget is funding intramural projects; whereas about 10 percent of the entire NIH budget is expended on intramural research.

Is there a budget for the OPASI? If so, is it used as seed money to start certain initiatives? Are the Institute Directors assessed on their ability to further trans-NIH initiatives, such as the obesity initiative, and can OPASI funds be provided to move initiatives forward? Dr. Krensky responded that the obesity initiative is outside of the Roadmap. It is an example of trans-NIH collaboration in which multiple Institutes and Centers are using their own individual funds to support new efforts. If the obesity initiative had a transforming, new, cross-cutting idea appropriate to the Common Fund, that idea could be presented to the Institute and Center Directors as a proposed initiative. There will be meetings in February 2008 to prioritize new areas. As for the OPASI budget, it is currently \$7 million and that is for staff and operations, not scientific research. The \$495 million is for the Common Fund, which, in addition to Roadmap initiatives, can also support workshops and other projects. The Institute and Center Directors make the decisions about how these scientific funds will be expended. Each of them has one vote, irrespective of the size of his or her organization. It will be important to see if this process encourages the pursuit of truly new ideas, such as might be funded in a venture capital paradigm.

Is it anticipated that funds will be saved through the collaborative processes of the Roadmap and Common Fund? If so, how will those saved funds be distributed? Will those who fostered the collaborations benefit from efficiencies that are realized? Dr. Krensky said that he was not in a position to answer the question. However, he surmised that the Congress would probably look to the Scientific Management Review Board to provide an overarching view of NIH operations. Clearly, each of the 27 Institutes and Centers will remain committed to its own mission and research priorities. At the same time, however, there are many cross-cutting areas—such as proteomics—where savings may be realized through the use of common platforms. The OPASI is working to foster an NIH research environment in which both Institute-specific and cross-cutting programs can flourish and realize mutual benefits.

Is the OPASI developing approaches now to evaluate its own performance? Is an evaluation team in place? Dr. Krensky said that there is an evaluation team in place that does evaluations, largely on the well-known social science constructs. However, it has

become clear to him that the evaluation of science programs is different and that additional approaches are needed. The NIH has already performed an assessment of the Pioneer Awards from which it learned a great deal about process evaluation. To evaluate the success of the program in terms of the career outcomes of the award recipients may well take 20 years. Currently, the OPASI is searching for very senior level “thought leaders,” who can contribute to the evaluation function as it applies to science programs. Thus, while some of the OPASI evaluation team is in place, it is not yet fully formed. Also, data acquisition and analysis will play a crucial role in evaluation.

When will there be opportunities for the research community and the public to submit suggestions to the OPASI? Dr. Krensky said that this process is ongoing and that input is always welcome. In addition, there will be periodic information requests announced by the OPASI. Dr. Krensky particularly encouraged the Council members to share ideas with NIDDK scientific program staff members, who work closely with their counterparts in other Institutes and Centers and gain NIH-wide consensus for proposals.

VI. REPORT FROM THE NIDDK DIRECTOR

Dr. Griffin Rodgers, Director, NIDDK

Budget Update

Dr. Rodgers updated the Council on the Fiscal Year 2008 budget process, which had included a few continuing resolutions before a final year-long budget emerged. Initially, the House proposed an increase of 1.5 percent for the NIH, while the Senate proposed an increase of 2.5 percent. A conference committee agreed on 2.8 percent—a level higher than either chamber. However, there were difficult negotiations by congressional leaders before final agreement was reached on a so-called omnibus appropriation that covered several agencies. Under the omnibus measure, the NIH proper received a 1.1 percent increase over Fiscal Year 2007; however, most of that increase includes funds transferred directly to the Global HIV/AIDS Fund. For the NIDDK, the final appropriation for Fiscal Year 2008 is at the same level as Fiscal Year 2007. With a few minor exceptions, the other Institutes and Centers will also be operating at last year’s funding level.

Despite this lower-than-expected appropriation, the NIDDK will be able to raise its general R01 payline to the 17th percentile for Fiscal Year 2008 primarily due to a decline in the number of applications to the NIDDK. Dr. Rodgers provided data, by Council round, showing that, overall, the numbers of R01 applications received for potential NIDDK funding has decreased from 893 two years ago to 822 for the May 2008 Council. These data illustrate that investigators are placing less demand on the system. Thus, the Institute has adopted a general payline at the 17th percentile. It will fund new investigators to the 19th percentile—consistent with its practice of giving priority to the researchers who are new to the peer review process.

While on the subject of new investigators, Dr. Rodgers also reported that the NIH-wide Fiscal Year 2007 goal of funding 1,500 new investigators has also been adopted for

Fiscal Year 2008. The NIDDK expects to contribute 116 awards toward meeting this goal.

Special Statutory Funding Program for Type 1 Diabetes Research

Dr. Rodgers reported that the Special Statutory Funding Program for Type 1 Diabetes Research has been extended through Fiscal Year 2009. These funds will enable pursuit of a new initiative--the Type 1 Diabetes Pathfinders Award. Awards will be made this year to support up to eight creative new investigators in their pursuit of innovative research on type 1 diabetes.

The budget of the Special Statutory Funding Program for Type 1 Diabetes is separate from and in addition to the regular NIDDK appropriation. Because the NIDDK is uncertain as to the continuation of these funds beyond Fiscal Year 2009, the Institute is arranging a series of special assessments by external experts of the large clinical programs under way in this Program. The NIDDK will consider the input from these experts regarding the priorities that will need to be set if the funds for this program come to an end in Fiscal Year 2009.

Compendium of Recent Research Advances and Emerging Opportunities

Dr. Rodgers called the Council's attention to the newly issued document, "NIDDK Research Advances and Emerging Opportunities." This is an annual compendium of major advances made in the previous year with NIDDK support. The document also provides the perspectives of patients who are grappling with serious diseases and the hope that they find through research. Also included are snapshots of the NIDDK's education and outreach efforts. Dr. Rodgers recommended that the Council members share the compendium with their colleagues at their home institutions as illustrative of the progress being made through NIDDK-funded research.
(http://www2.nidDK.nih.gov/AboutNIDDK/ResearchAndPlanning/Advances/Advance_2008.htm)

Council Questions and Discussion

Has any analysis been performed regarding the amount of time that is saved by Study Section reviewers because of the triaging/streamlining process--a process that may be psychologically detrimental to applicants? Council members were reminded that NIH is engaged in a self-study of the peer review process, as reported at the last Council meeting by Dr. Lawrence Tabak, the NIDCR Director, who has a leadership role in this effort. Two groups have been formed--an external working group of the Advisory Committee to the Director, NIH, and an internal working group of the NIH Steering Committee. The NIH has issued Requests for Information to the community for suggestions about enhancing the peer review process and has held regional meetings. With respect to triaging/streamlining, comments were received that the advent of electronic systems should permit all applicants to receive a score. Dr. Rodgers noted that there have been a number of attempts to try to lighten the load of Study Section reviewers and to use Internet-assisted reviews in the way that some editorial boards review journal articles. Dr.

Stanfield said that options for changing various aspects of the NIH peer review system have now been presented to the Advisory Committee to the Director, NIH. A final report is due to the NIH Director at the end of February 2008. It is not known what the recommendations will be.

A Council member urged the group to consider the advantages of triaging/streamlining. As noted, to the extent that triaging saves Study Section time, more people may be likely to serve on a Study Section if they know the meetings will be shorter. Also, there will be more time to discuss grants that are at the margin. Importantly, investigators with unscored applications do in fact receive written feedback on them. Moreover, there are no major differences between the commentary they receive and the commentary that is provided to investigators whose applications are scored. In a way, it may be a good thing if new investigators or those who are competing for first-time renewal are told that their proposals have no chance of funding in their present form. That message may be better than doing them a disservice by misleading them with a score that implies possible funding. Triaging may keep them from continuing to invest their time on a proposal that will not go anywhere. Although the triaging process could be better, it does have those advantages. Dr. Stanfield reminded members that Study Section reviewers do provide written critiques on unscored applications. Moreover, about 40 percent of streamlined applications do receive scores when they are resubmitted to NIH--presumably with revisions based on the written critiques.

Of the 40% of streamlined applications that are resubmitted and receive scores, how many are funded? Dr. Stanfield indicated that he did not have data regarding funding success of amended applications readily available, but he would obtain it. He then suggested that, given the Council's interest in the streamlining process and other aspects of peer review, it might be useful to invite Dr. Scarpa or Dr. Tabak to a Council meeting to discuss the various peer review pilot studies.

Will triaging/streamlining increase the numbers of investigators who are dropping out of the system? Dr. Rodgers noted that the NIDDK is trying to prepare new investigators for participating in the peer review system by holding meetings for recipients of career awards. The NIDDK training directors try to guide these individuals through the process of applying for their first R01 grants by holding mock Study Section meetings and giving them practical advice about grantsmanship. Another point at which investigators may drop out of the pipeline is at the review of their first competitive renewal application. The NIDDK is exploring ways to help them deal with this hurdle. Dr. Rodgers urged the Council members to provide comments about the peer review system to NIH. He also asked them to share their views with NIDDK staff members so that they are better equipped to assist investigators who are applying for their first R01 grant and those who are seeking their first renewal.

VII. ADVISORY COUNCIL FORUM:

Part 2 -- Roadmap 1.5 Updates

Microbiome Initiative Update

Dr. Jane L. Peterson, Associate Director, Division of Extramural Activities,

National Human Genome Research Institute

Dr. Peterson set the stage by describing the human microbiome as an extended view of the human life form and an integral part of the genetic landscape. The microbial census in the human body exceeds the total number of human cells by about tenfold--with most microbes residing in the intestine. The skin, the oral cavity, the nose, and the vagina are also heavily populated with microbes. Studies have demonstrated the diversity in the proportions of bacteria present in the gut and oral cavity of humans. Researchers have also found a shift in gastrointestinal flora associated with obesity in both mice and humans. These and other findings provided a strong rationale for intensifying research on the human microbiome. Drs. David Relman, Jeff Gordon and others have helped to lay the research foundation for this initiative.

Momentum for the concepts behind this Project grew at an international meeting attended by NIH scientific staff, who subsequently invited several leaders in the field to discuss the concepts with the NIH. From this it became clear that the NIH should establish a Human Microbiome Project and seek funding from the Institutes and Centers. At the same time, there were parallel discussions underway of an NIH Roadmap 1.5 program. For about a year and a half, an NIH Human Microbiome Working Group--composed of representatives from 22 Institutes and Centers--held workshops, meetings, and discussions for the development of ideas to submit for funding consideration under this NIH Roadmap process. A decision was made in the summer of 2007 that the Human Microbiome Project (HMP) would become an NIH Roadmap 1.5 initiative (<http://nihroadmap.nih.gov/hmp/>). In December 2007, the NIH issued a press release that described the initiative (<http://www.nih.gov/news/pr/dec2007/od-19.htm>).

The Project has four Institute Directors as co-chairs: Dr. Francis Collins, National Human Genome Research Institute (NHGRI); Dr. Anthony Fauci, National Institute of Allergy and Infectious Diseases (NIAID); Dr. Lawrence Tabak, National Institute of Dental and Craniofacial Research (NIDCR); and Dr. Griffin Rodgers, NIDDK.

The goal of the Human Microbiome Project is to characterize the microbes that inhabit the human body and examine whether changes in the microbiome can be related to health and disease. It is a five-year project with a total budget of \$115 million that will be allocated in stages. Data and research resources are to be released immediately to the research community. With funds available under the Roadmap, it was possible to “jumpstart” the Project in September 2007, by making supplemental awards to enhance ongoing work. Currently, research announcements are soliciting applications for a data analysis coordination center, technology development, software tool development, and studies on the ethical, legal and social implications of this research. Dr. Peterson provided a brief description of the major components of the initiative.

- *Jumpstart Component:* The initial step is the sequencing of up to 600 genomes from both cultured and uncultured bacteria, plus several non-bacterial microbes. Funds for the Jumpstart component were provided to four NIH-supported, large-

scale sequencing centers at Baylor College of Medicine, the Broad Institute, Washington University, and the J. Craig Venter Institute so that they could start exploring how to study the normal human microbiome. This jumpstart component is building on work already under way through funding from the National Institute of Human Genome Research. There is a two-part mission: (1) to obtain strains from a variety of sources for sequencing and for placement in reference databanks, and (2) to recruit healthy individuals who will provide samples from five body sites. These sites are the digestive system, the mouth, the skin, the nose, and the female urogenital tract. From these samples, the researchers will isolate and cultivate bacteria for sequencing in order to characterize human microbial communities. If cultivation is not possible, they will use other technologies for amplifying genomes in order to do the sequencing. One known avenue is metagenomics--a process through which DNA sequencing is performed on an entire microbial community in a so-called "shotgun" approach. Other approaches may include 16S RNA sampling, expression profiling, and possibly proteomics. Bioinformatics tools will be essential to this process.

Working groups are addressing a variety of issues such as standards, annotation metrics, and strain lists. Dr. Bob Karp of the NIDDK is leading the working group focused on gastrointestinal samples. Other working groups are developing the clinical protocol to recruit the healthy volunteers and to determine the methods and metrics for the metagenomic technology.

The timing of the Human Microbiome Project is fortunate relative to the advent of new sequencing technology. While not yet fully implemented, the new technology shows promise of reducing sequencing costs by tenfold and significantly increasing data throughput. The hope is that this new technology can be harnessed to look very deeply into metagenomic sequencing.

- *Reference Data Set Generation:* This component is a follow-on to the Jumpstart stage. The goal is to sequence 400 prokaryotic microbes isolated from the human body. These will be combined with the 600 microbes isolated in the Jumpstart stage. The total reference collection in a public database will thus reach an estimated 1,000 genomes. Metagenomic sequence analysis begun in the Jumpstart stage will be continued in order to characterize the complexity of the microbial communities in the five body sites from which samples have been obtained. One of the critical questions to be answered is whether it is possible to detect a core microbiome at each site.
- *Demonstration Projects:* These will be investigator-initiated projects to use the resources that have been generated to determine the feasibility of correlating changes in the human microbiome with health and disease. This component will use a new mechanism called UH2 and UH3 awards. This cooperative agreement mechanism will provide for a one-year pilot phase followed by a ramp-up. It is expected that there will be a large number of pilot projects that will be reviewed at the end of the first year. The most promising projects will then be ramped-up to demonstrate the correlation of the microbiome with health and disease.

- *Technology Development:* In support of the Reference Data Set and Demonstration Projects, the NIH is soliciting projects for the development of new tools for computational analysis (e.g., for complex metagenomic datasets), and new technologies to culture or isolate organisms that currently cannot be cultured.
- *Computational Tool Development:* The data sets produced by metagenomic sequencing and related components will be very large and complex, requiring novel analytical tools for distilling useful information from vast amounts of sequence data, functional genomic data, and subject metadata. Large quantities of sequence data may also need new analysis methods.
- *Data Analysis and Coordination Center:* This Center will provide for data consolidation and serve as a place that investigators can go to find out the latest information and coordinate their activities.
- *Studies of Ethical, Legal and Social Issues:* These studies will look at issues of privacy, forensic uses, and the clinical and health implications of research on the human microbiome.

Dr. Peterson provided a general timeline for the components of the Human Microbiome Project. The Jumpstart component is under way, and most of the other projects are planned for funding in September 2008. The Reference Data Set and Demonstration Projects will be funded approximately one year later.

Dr. Peterson closed by mentioning the recent development of an International Human Microbiome Consortium. In December 2007, the NIH held a meeting attended by representatives from Europe, Canada, Australia, Japan and China. All of those countries are interested in either developing microbiome research programs or they already have programs under way. There was agreement to establish the Consortium to generate a shared resource of human microbiome data, to coordinate international efforts, to reduce redundancy, and to provide a venue for international communication of strategies and results. One of the tenets of the Consortium is that members will be expected to release data rapidly, in much the same way as the investigators in the NIH Human Microbiome Project.

Dr. Peterson underscored that the development and implementation of this initiative has involved and will continue to involve many individuals, both within and external to the NIH. Input will continue to be sought as the initiative moves forward.

Council Questions and Discussion

What disease-focused research can be funded under this initiative? Dr. Peterson replied that the solicitation for demonstration projects was written in an open manner so that investigators can submit proposals to study whatever diseases are of interest to them. The NIH will take program balance into consideration in making funding decisions.

What will be the priority order of organisms studied? Dr. Peterson replied that bacteria, viruses and eukaryotic microbes will be included. The beginning of the Jumpstart period will focus on the prokaryotic genomes and the metagenomic sequencing. Later on, work will be done on viruses and the eukaryotic microbes that are more difficult to study.

Will data be released before it has undergone peer review? Dr. Peterson affirmed that would be the case, consistent with the tradition in genomics research. When this policy was first adopted in the field, there were concerns about “junk” data; however, the community has wholeheartedly embraced the data availability and has been able to evaluate it. Of course, the Centers will use some filters and will not put out failed runs. With the current technology, there are standards about how long runs have to be before the data are released to the public. With the new technology, it will not be possible to release data in the same way because there are no single reads. This is an issue that will need to be addressed and the NIH National Center for Biotechnology Information will likely play a role.

It is the intention to sequence all the organisms or a subset of them? Dr. Peterson replied that she does not think that it will be possible to sequence them all unless technology becomes available to sequence those that cannot be cultivated. Of course, metagenomics sequencing will permit whole genome sequencing of the entire microbial mix, so, in that sense the sequencing can be comprehensive. Although it will not be possible to reconstruct the entire genome, there can be expression studies that will provide an understanding of which genes are particularly active. The Demonstration Project component will be well suited for this type of research. Also, the Demonstration Projects will permit the study of model organisms. Although the focus of the initiative is on humans, there are follow-up studies that will not be possible in humans. In those instances, investigators may wish to propose the study of a particular syndrome in an animal model such as the mouse.

Epigenomics/Epigenetics Initiative Update

***Dr. Philip Smith, Deputy Director, Division of Diabetes, Endocrinology
and Metabolic Diseases, NIDDK***

Dr. Smith reported that the Roadmap Epigenomics/Epigenetics Program was started in Fiscal Year 2008 (<http://nihroadmap.nih.gov/epigenomics/>). As noted in the January 2008 news release announcing the initiative (<http://www.nih.gov/news/health/jan2008/od-22.htm>), the NIH plans to invest more than \$190 million over the next five years to accelerate the epigenomics field.

This initiative derives from one of the concepts approved through the planning process for the Roadmap 1.5--with input from the community and the various NIH components. Guidance for the initiative is provided by a core working group comprised of scientific staff from participating NIH Institutes and Centers; however, there are many more individuals involved in planning and developing the research solicitations. The initiative is co-chaired by two Institute Directors: Dr. Sam Wilson, the current Acting Director of

the National Institute of Environmental Health Sciences (NIEHS), and Dr. Nora Volkow, Director of the National Institute on Drug Abuse (NIDA). *Ex officio* leadership is being provided by Dr. T-K Li, Director of the National Institute of Alcohol and Alcohol Abuse (NIAAA), and Dr. James Battey, Director of the National Institute on Deafness and Other Communication Disorders (NIDCD).

Dr. Smith addressed some of the definitional issues in framing this initiative. Epigenetics focuses on processes that regulate how and when certain genes are turned on and off, whereas epigenomics pertains to analysis of epigenetic changes across many genes in a cell or an entire organism.

For the purpose of the new initiative, the working group has defined epigenetics as the study of the regulation of gene activity that is not dependent on gene sequence. This definition can encompass heritable changes in gene activity and expression--in the progeny of cells or of individuals. It can also include stable, long-term alterations in the transcriptional potential of a cell--changes that are not necessarily heritable.

Epigenomics--which is the formal title of the Roadmap initiative--takes that same construct and applies it across the genome. Thus, while epigenetics refers to single genes or sets of genes, epigenomics refers to global analysis of epigenetic changes. These differences are analogous, respectively, to specific candidate gene studies *versus* genome association studies that were done in the past. The advent of new technologies now permits the study of epigenomics, which is a higher order of investigation than the studies being pursued through the hundreds of individual epigenetic grants that the NIH currently funds.

The new initiative began with the hypothesis that epigenetic mechanisms underlie the origins of health and susceptibility to disease. Several goals have been laid out, including: (1) to develop epigenomic mapping data and infrastructure to facilitate research in human health and disease; (2) to evaluate epigenetic mechanisms in aging, development, environmental exposure, and disease processes; (3) to develop new technology for single-cell analysis and remote imaging of epigenetic activity in living cells, tissues, and whole animals; and (4) to establish international partnerships, new antibody reagents, standard research practices and platforms, and public databases.

The challenges are enormous because of the size and complexity of human genetic machinery. The human genome has about 3.8 billion base pairs that are packed into little spheres about five microns in diameter through the tight bundling of DNA strands around proteins, primarily histones. This genetic material is then supercoiled into large aggregates that eventually form chromosomes. Epigenetic processes can interact with the chromosome structure to affect the genetic transcription (copying process) that determines the essential character of a cell--whether it will be a liver, muscle, brain or other type of cell. Numerous residues can modify the way that histone proteins package the DNA and influence control over whether or not a particular gene or genetic locus can be accessed by the cell's machinery to transcribe genes. It is already known that an epigenetic factor found in some dietary sources--the methyl group--can tag DNA and activate or repress genes.

Dr. Smith noted that there is a significant body of evidence to suggest that epigenetic mechanisms are involved in several diseases through methylation processes or histone modifications that affect gene expression. Epigenetics can also come into play in the well-studied process of genetic imprinting in which an allele inherited from one parent is active, while an allele inherited from other parent is silenced. If the single active gene is subsequently knocked out through some sort of damage, disease can result. An example of this is Prader-Willi syndrome, which is within the NIDDK's research mission. In Prader-Willi syndrome, about 70 percent of the gene knockouts are from mutations or deletions of DNA, while about 30 percent are due to epigenetic changes that silence the gene.

Changes in DNA usually require a very strong environmental perturbation. However, epigenetic mechanisms are very sensitive to environmental changes and therefore provide a reasonable model for studying the ways that the environment can affect the health of an organism through interaction with the genome. One example is work by Drs. Rob Waterland and Randy Jirtle (*Mol Cell Biol.* August, 2003. Vol. 23) in the agouti mouse. By *in utero* manipulation of levels of folate (a methyl donor) in pregnant agouti mice, the researchers affected methylation, which in turn, affected gene expression as evidenced in the pigmentation of the offspring mice and their body weight. This research shows the power of epigenetic changes to modify the phenotype of an organism and the relative sensitivity of epigenetic mechanisms to environmental influences such as diet.

Dr. Smith emphasized that incredible advances in high-throughput methodologies have revolutionized genetic studies such that it is now possible to assess epigenetic mechanisms across the entire genome. To illustrate, he brought the Council's attention to an array of 371 human embryonic stem cell genes thought to be involved in development and growth. The array showed that human embryonic stem cells have a unique epigenetic signature, despite differences in their derivation and culturing. This methodology could enable the mapping of the whole genome for these kinds of genetic fingerprints and their correlation with human development and disease.

Dr. Smith elaborated on the major elements of the Epigenomics Program:

- *Epigenomics Mapping Centers:* To establish references for the field and create the infrastructure to apply epigenetic strategies to any number of tissues. The project will start off with an objective of developing 24 reference epigenomes in human embryonic stem cells.
- *Epigenomics Data Management Center:* To collect and validate the data and transmit the results to the National Center for Biotechnology Information for archiving. Data will be released as soon as it is validated and that process is not within the control of the individuals who generate the data.
- *Discovery of Novel Epigenetic Marks:* To discover, validate and map new marks that might include novel post-translational modifications, non-coding "marks," or a modification in chromatin structure.

- *Technology Development:* To improve throughput resolution and increase the sensitivity of existing technology for single-cell analysis. Also, to improve imaging capabilities in cells, tissues and whole animals. New technology will contribute to more sophisticated experiments; enable more investigators to use epigenetics; and identify epigenetic biomarkers of health and disease. The working group sees opportunities to create new tools for epigenetic analysis of a single cell. For example, in many tissues, such as the brain, the difference between cells that are adjacent to each other is critical to understanding the function of that tissue. In addition, it would be very valuable to be able to image epigenetic changes or states *in vivo*.
- *Epigenomics and Disease:* To correlate the data with potential disease pathways through demonstration projects led by the Institutes and Centers based on the reference epigenomes. Through these efforts, researchers will determine how the epigenome undergoes changes with conditions of aging, development, gender, and environmental exposures. They will also find out how the epigenome changes with diseases or conditions that cut across the NIH, such as inflammation, pain, and obesity. This part of the initiative will be funded on a 50-50 basis through Roadmap funds and Institute/Center funds.
- *Antibody Production:* To provide a resource for the field based on existing programs within the Neuroscience Blueprint and other efforts. Investigators are encouraged to respond to a Request for Information and suggest the reagents they think would be most valuable.

Dr. Smith indicated that four Requests for Applications had already been issued with receipts dates in February, March or the Fall of 2008. For some components, it is expected that research solicitations will be re-released; for example, the solicitation for Epigenetics and Disease is expected to be issued annually for the next five years. Dr. Smith also provided a general timeline for various parts of the initiative. Most components are expected to run for approximately five years. However, those focused on the Data Management Center, Technology Development, and Epigenomics and Disease are expected to remain active for ten years. A variety of funding mechanisms will be used to support this multipronged initiative.

Dr. Smith acknowledged the many individuals who have contributed to the development and implementation of this initiative.

Council Questions and Discussion

With respect to the different methylation sites, are there patterns for different cell types? Is it possible that the tissue culture medium is similar for different classes of cells, such as the embryonic stem cells approved for NIH funding, and whether that might play a role in the results observed? Dr. Smith replied that the researchers analyzed tissue culture conditions and concluded that the differences they saw were due to the cell's origin, not the culture conditions.

Is it known how conserved some of these epigenetic marks are between lower and higher organisms? Dr. Smith responded that most of the epigenetics work that has been supported over the years has been in lineage determination and development. There are epigenetic mechanisms in plants that are not seen. Researchers have searched for modifications in mammals, zebrafish, *Drosophila*, and yeast. The key question is whether there are key epigenetic regulators. Just because a “mark” is seen doesn’t mean that it’s a regulatory mechanism. This issue is one that will be addressed through the validation efforts of the Mapping Center.

Controversy exists in this field as to whether heritability of the mark needs to be part of the definition. This is particularly important because only one of the marks, the DNA methylation, is known to be heritable. Peer reviewers may have a bias toward studies involving heritability and may not consider parts of this initiative to fall within the traditional definition of epigenetics unless the NIH emphasizes the definition it is using. Dr. Smith responded that the component of the initiative that addresses Epigenetics and Disease will consider biological processes, as well as disease processes. From communications he has had thus far with the community, the leaders and investigators in the field do not want to be restrained by old definitions. It will, however, be important to ensure that peer reviewers are educated as to the goals of the initiative, including the discovery of totally new marks irrespective of heritability.

Is there an effort to look at how the mother influences the health of the fetus? Dr. Smith noted that there has been a long-standing interest in the intrauterine environment and its relationship to disease susceptibility. A research solicitation was issued on this topic in the past; a workshop was held last Fall; and the NIDDK is planning some efforts in Fiscal Year 2009. The NIDDK is particularly interested in this area as it relates to obesity and to gestational diabetes. An important question is whether there are ways to modify the intrauterine environment to reduce the burden of disease in the offspring.

VIII. SCIENTIFIC PRESENTATION

Liver Disease in Alpha-1-Antitrypsin Deficiency: Protein Misfolding, Aggregation, and the Role of Autophagy

Dr. David H. Perlmutter

Dr. Rodgers introduced Dr. David H. Perlmutter, who is Physician-in-Chief and Scientific Director of Children’s Hospital of Pittsburgh at the University of Pittsburgh Medical Center. He is also the Vira I. Heinz Professor and Chair of the Department of Pediatrics at the University, as well as Professor of Cell Biology and Physiology.

Dr. Perlmutter’s presentation focused on the interesting biological questions raised by alpha-1-antitrypsin deficiency disease, which is caused by a single-gene defect. He described several projects that highlighted the importance of the process of autophagy, and the enormous power of basic science in furthering clinical applications.

IX. REPORT OF THE AD HOC SCIENTIFIC DIRECTOR REVIEW COMMITTEE

NIH requires the review of the Scientific Director, who leads the Institute's intramural research program every four to six years. In accordance with the process prescribed in the NIH Manual Chapter 3005, Council considered the final report of the *ad hoc* committee charged with reviewing the NIDDK Scientific Director and made recommendations based on the report in a special closed session of the meeting.

X. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

A total of 1,369 grant applications, requesting support of \$322,953,348 were reviewed for consideration at the January 30, 2008 meeting. Funding for these 1,369 applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 1,022 applications requesting \$233,638,136 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 January 30, 2008 meeting.