Meeting Minutes
Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases
February 16, 2011

I. CALL TO ORDER

Dr. Griffin P. Rodgers, Director

Dr. Griffin P. Rodgers, Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) called to order the 185th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m., Wednesday, February 16, 2011, in Building 31, C Wing, 6th Floor, Conference Room 10, National Institutes of Health, Bethesda, Maryland.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

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

** Served as a temporary member for this meeting pending final approval of the Council 2011 slate.*

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

B. NIDDK STAFF AND GUESTS

Abankwah, Dora – NIDDK
Agodoa, Lawrence – NIDDK
Appel, Michael – NIDDK
Arreaza, Guillerno – NIDDK
Barnard, Michele – NIDDK
Bethea, Gina – NIDDK
Beverly, Kevin – Soc. Sci. Sys.
Bishop, Terry – NIDDK
Bleasdale, John – CSR
Blondel, Olivier – NIDDK
Bloom, Maria – NIDDK
Bryd, Davita – Soc. Sci. Sys.
Calvo, Francisco – NIDDK
Carrington, Jill – NIDDK
Castle, Arthur – NIDDK
Connaughton, John – NIDDK
Copeland, Randy – NIDDK
Coulson, Doug – PS Inter.
Cowie, Catherine – NIDDK
Cox, Helen – NIDDK

Curtis, Leslie – NIDDK
Dayal, Sandeep – NIDDK
Doherty, Dee – NIDDK
Donohue, Patrick – NIDDK
Doo, Edward – NIDDK
Eggerman, Thomas – NIDDK
Eggers, Paul – NIDDK
Ezzelle, Jason – Pharm. Prod. Dev. Inc.
Evans, Mary – NIDDK
Farishian, Richard – NIDDK
Flessner, Mike – NIDDK
Fonville, Olaf – NIDDK
Fradkin, Judith – NIDDK
Gallivan, Joanne – NIDDK
Gansheroff, Lisa – NIDDK
Garfield, Sandy – NIDDK
Garofolo, Robert – CSR
Garte, Sy – CSR
Griffey, Sue – Soc. Sci. Sys.
Greene, Lucy – NIDDK
Goter-Robinson, Carol – NIDDK
Grey, Michael – NIDDK
Groves, Reed – CSR
Gutierrez, Elizabeth – NIDDK
Haft, Carol – NIDDK
Hanlon, Mary – NIDDK
Harris, Mary – NIDDK
Hilliard, Trude – NIDDK
Hoofnagle, Jay – NIDDK
Horlick, Mary – NIDDK
Hoshizaki, Deborah – NIDDK
Howards, Stuart – NIDDK
Hubbard, Van – NIDDK
Hunter, Christine – NIDDK
Hyde, James – NIDDK
James, Stephen – NIDDK
Jenkins, Connie – NIDDK
Jerkins, Ann – NIDDK
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Ketchum, Christian – NIDDK
Khan, Mushtaq – CSR
Kim, Sooja – CSR
Kimmel, Paul – NIDDK
Kirkali, Ziya - NIDDK
Kochis, Daniel – Amer. Soc. of Neph.
Kranzfelder, Kathy – NIDDK
Kuczmarski, Robert – NIDDK
Kusek, John – NIDDK
Laughlin, Maren – NIDDK
Lescheck, Ellen – NIDDK
Linder, Barbara – NIDDK
Ly, Diana – NIDDK
Malik, Karl – NIDDK
Manouelian, Denise – NIDDK
Maruvada, Padma – NIDDK
Martey, Louis – NIDDK
Martinez, Winnie – NIDDK
McBryde, Kevin – NIDDK
McKeon, Catherine – NIDDK
Miller, David – NIDDK
Miller, Megan – NIDDK
Moxey-Mims, Marva – NIDDK
Mullins, Chris – NIDDK
Narva, Andrew - NIDDK
Newman, Eileen – NIDDK
Nguyen, Van – NIDDK
Nicholson, Kathrine – NIDDK
Nurik, Jody – NIDDK
Papier, Wendy – NIDDK
Paez, Kathy – Soc. Sci. Sys.
Perry-Jones, Aretina – NIDDK
Pike, Robert – NIDDK
Podskalny, Judith – NIDDK
Pope, Sharon – NIDDK
Rankin, Tracy – NIDDK
Rasooly, Rebekah – NIDDK
Rench, JD – RTI Inter.
Reiter, Amy – NIDDK
Roberts, Tibor – NIDDK
Robuck, Patricia – NIDDK
Rosendorf, Marilyn – NIDDK
Rushing, Paul – NIDDK
Rys-Sikora, Krystyna – NIDDK
Salaita, Christine – NIDDK
Salomon, Karen – NIDDK
Sankaran, Lakshmanan – NIDDK
Sato, Sheryl – NIDDK
Savage, Peter – NIDDK
Scanlon, Elizabeth – NIDDK
Serrano, Jose – NIDDK
Sheard, Nancy – CSR
Silva, Corrine – NIDDK
Smedberg, Paul – Amer. Soc. of Neph.
Smith, Philip – NIDDK
Spain, Lisa – NIDDK
Star, Robert – NIDDK
Staten, Myrlene – NIDDK
Tatham, Thomas – NIDDK
Torrance, Rebecca – NIDDK
Tuncer, Diane – NIDDK
Van Raaphorst, Rebekah – NIDDK
Wallace, Julie – NIDDK
Wellner, Robert – NIDDK
Woynarowska, Barbara – NIDDK
Wright, Daniel – NIDDK
Wright, Elizabeth – NIDDK
Wright, Tatiana – SAIC
Yanovski, Susan – NIDDK
Yates, Robert – Soc. Sci. Sys.
Zeidner, Rita – NIDDK

C. ANNOUNCEMENTS

Dr. Rodgers welcomed the Council members, thanked them for their participation, and made the following announcements.

Ad Hoc Council Members

Dr. Rodgers welcomed six *ad hoc* members to the Advisory Council meeting. He expressed his gratitude that these members agreed to serve on a temporary basis pending approval of the 2011 Council slate.

Joining the Diabetes, Endocrinology and Metabolic Diseases (DEM) Subcouncil are Dr. Domenico Accili and Ms. Robin Nwankwo.

- *Dr. Domenico Accili* is Professor of Medicine at Columbia University and Director of the Columbia University Diabetes and Endocrinology Research Center in New York City. A graduate of the University of Rome, Dr. Accili trained in Internal Medicine at the University Hospital Gemelli, also in Rome. Following a Fogarty Fellowship in the Diabetes Branch within the NIDDK's intramural program, he became Chief of the Section on Genetics and Hormone Action of the National Institute of Child Health and Human Development at NIH. Since 1999, Dr. Accili has served on the faculty at Columbia University College of Physicians and Surgeons and as an Attending Physician at Columbia-Presbyterian Hospital. His research interests include the pathogenesis of diabetes, the integrated physiology of insulin action, and mechanisms of pancreatic beta cell dysfunction. He identified a family of DNA-binding proteins that collectively regulates diverse pathophysiological processes, including liver glucose and lipid production, food intake, insulin production and adipogenesis. His work is supported by NIH, and also by the American Diabetes Association, the Russell Berrie Foundation, and the Brehm Coalition. Dr. Accili's numerous awards include the 2003 Lilly Award for Outstanding Scientific Achievement by the American Diabetes Association. He is an elected member of the Association of American Physicians and the American Society for Clinical Investigation.

- *Ms. Robin Nwankwo*, who is serving as a public member of the Council, is a diabetes educator with special expertise in nutrition and diabetes-self management. Her work has largely centered on communicating diabetes and nutrition self-care needs using methods that respect cultural differences and preferences, and support the adoption of health capacity-building, self-care behaviors. Ms. Nwankwo has more than ten years of professional experience and has served on a number of boards and subcommittees associated with the America Diabetes Association and the American Association of Diabetes Educators. She has also worked within research projects designed to study support programs for community members and patients living with diabetes. Her extensive work with one of the NIDDK's largest patient communities will benefit Council discussions.

Joining the Digestive Diseases and Nutrition (DDN) Subcouncil are Drs. Judy Cho and Thomas Robinson.

- *Dr.Judy Cho, M.D.,* is Associate Professor of Medicine and Genetics and Director of the Inflammatory Bowel Disease Center at Yale University. Dr. Cho's research focuses on Inflammatory Bowel Disease (IBD), with emphasis on identifying genetic variation that affects susceptibility to and expression of the disease. Her laboratory identified amino acid changes in the *Nod2* (*CARD15*) gene that markedly increase susceptibility to Crohn's disease (CD). Because *Nod2* associations do not account for all of the genetic risk in IBD, she is seeking to identify additional genetic variations contributing to these disorders. Dr. Cho's research has been supported by NIDDK since 1998. Dr. Cho earned her M.D. at Ohio State University College of Medicine and then did her internship at Riverside Methodist Hospital in Columbus, Ohio, followed by a residency at Northwestern University. Dr. Cho was then a Clinical and Research Fellow in Gastroenterology at the University of Chicago and continued in several appointments there, rising professionally to become Associate Professor of Medicine with tenure before she moved to Yale in 2006.

- *Thomas Robinson, M.D.,* is the Irving Schulman Endowed Professor in Child Health and Professor of Pediatrics and of Medicine within the Division of General Pediatrics at Stanford University School of Medicine. Dr. Robinson is also Director of the Center for Healthy Weight at Stanford. Dr. Robinson focuses on "solution-oriented" research. The goal of this research is to develop and evaluate health promotion and disease prevention interventions for children, adolescents and their families for directly informing medical and public health practice and policy. His research is largely experimental in design, conducting school-, family- and community-based randomized controlled trials to test the efficacy and/or effectiveness of theory-driven behavioral, social and environmental interventions to prevent and reduce obesity, improve nutrition, increase physical activity, decrease inactivity, reduce smoking, reduce children's television and media use, and demonstrate causal relationships between hypothesized risk factors and health outcomes. Dr. Robinson received his M.D. from Stanford University and his M.P.H. in Maternal and Child Health from the University of California, Berkeley. He completed his internship and residency in Pediatrics at Children's Hospital, Boston, and Harvard Medical School, and then returned to Stanford for post-doctoral training as a Robert Wood Johnson Clinical Scholar. Dr. Robinson joined the faculty at Stanford in 1993, was appointed Assistant Professor in 1996, and was promoted to Associate Professor with tenure in 2003.

Joining the Kidney, Urologic and Hematologic Diseases (KUH) Subcouncil are Drs. William Steers and Mark Zeidel.

- *William Steers, M.D.,* is Chair of the Department of Urology at the University of Virginia. He is the recipient of numerous awards, and has been recognized by the American Urological Association for outstanding achievement. Dr. Steers has been an Editor of the *Journal of Urology* since 2007, and is President of the American Board of Urology. He is also a member of the FDA's Reproductive Medicine Advisory

Panel and he chaired the NIH's clinical trial groups focused on urinary incontinence and interstitial cystitis. Dr. Steers will offer a wealth of clinical expertise to the KUH Subcouncil from his experience of treating patients with urinary incontinence, neurogenic bladder, benign prostate disorders, and erectile dysfunction. His clinical interests span many topics, including sexual dysfunction, prostate disease, and robotic surgery. His research interests include neuropharmacology and genitourinary tract growth factors. An American Urological Association Scholar, Dr. Steers completed his residency in urology at the University of Texas, Houston. He served as a Postdoctoral Fellow at the University of Pittsburgh after earning a Medical Degree from the Medical College of Ohio.

- *Mark Zeidel, M.D.,* is Chief of Medicine at Beth Israel Deaconess Hospital in Boston, Massachusetts. Dr. Zeidel will provide a broad range of expertise in nephrology to the KUH Subcouncil. His research has received continuous funding by the NIH for over 20 years, and he has been recognized by his peers for numerous accomplishments, including elected membership in both the American Society of Clinical Investigation and the Association of American Physicians. Prior to his position at Beth Israel Deaconess Hospital, Dr. Zeidel was named Professor and Chair of the Department of Medicine at the University of Pittsburgh and worked within the University for 12 years. Dr. Zeidel received his Medical Degree from Columbia University College of Physicians and Surgeons. He trained in internal medicine and nephrology at Brigham and Women's Hospital. He was chief of the renal section of the West Roxbury VA and Assistant Professor of Medicine at Harvard before moving to Pittsburgh.

NIDDK Grantees – *In Memoriam*

Dr. Rodgers announced the deaths of several leaders in the NIDDK scientific community.

- *Dr. Christopher Saudek:* The founder and director of the Johns Hopkins Comprehensive Diabetes Center, Dr. Saudek served as the Hugh P. McCormick Family Professor of Endocrinology and Metabolism in the medical school, as well as a member of the faculty of the Johns Hopkins Bloomberg School of Public Health. Dr. Saudek was educated at Harvard and at Weill Cornell Medical College. Before joining Johns Hopkins, he was a fellow at the National Institutes of Health and the Robert Wood Johnson Foundation. Dr. Saudek was president of the American Diabetes Association from 2001-2002. He was a Principal Investigator in the NIDDK's Diabetes Prevention Program clinical trial, and a pioneer in developing implantable insulin pumps.

- *Dr. Dale Benos:* Chairman of the Department of Physiology and Biophysics at the University of Alabama, Birmingham, Dr. Benos was continuously funded by NIH since 1976 and had been supported by NIDDK since 1979. Overall, he served as the principal investigator for 19 individual research grants. Dr. Benos was a dedicated mentor who fostered the career development of many new Principal Investigators, graduate students, and postdoctoral fellows. Internationally recognized for

contributions to the field of physiology and biophysics, he served on several NIH study sections and chaired multiple site visits and special emphasis panels.

- *Dr. Alan Gewirz*: The Willard Robinson Professor of Hematology-Oncology, University of Pennsylvania, School of Medicine, Dr. Gewirz was not only a distinguished physician and scientist in the field of hematopoiesis, but also an author and pilot. In research funded by NASA, he blended his dual passions of science and flying. He was Director of an NIDDK T32 Institutional Training grant for 12 years, and was a tireless advocate for basic science research and for promoting the careers of young scientists.

- *Dr. Mark Pescovitz:* An accomplished transplant surgeon and immunologist at Indiana University, Dr. Pescovitz led the Rituximab Study within the NIDDK's Type 1 Diabetes TrialNet. This pivotal trial was the first to demonstrate that a therapy targeting beta cells may have a beneficial effect on beta-cell function in early type 1 diabetes. Dr. Pescovitz published these exciting results in *The New England Journal of Medicine* in November 2009. In tribute to Dr. Pescovitz, a memorial lecture and dinner will be held during the TrialNet Steering Committee meeting on March 9, 2011.

Current Council Members

Dr. Rodgers made the following announcements regarding current Council members.

- *Brian Monahan, M.D.,* is leaving the Council. A Rear Admiral in the United States Navy, he has served on the Kidney, Urologic and Hematologic Diseases (KUH) Subcouncil since February 2005 as an *ex-officio* member representing the Department of Defense. He is the Attending Physician of the United States Congress and the United States Supreme Court. He can also be called upon to provide emergency care to thousands of congressional staff, security personnel and dignitaries.

- *Ms. LaVarne Burton* has been named Vice Chairperson of the Board of Directors of the National Health Council. This Council brings together diverse stakeholders within the health community to work for health care that meets the personal needs and goals of people with chronic diseases and disabilities. Composed of more than 100 national health-related organizations, the Council's core membership includes 50 of the nation's leading patient advocacy groups. Other members include professional and membership associations, non-profit organizations with an interest in health, and major pharmaceutical, medical device, and biotechnology companies.

NIDDK Staff Members in the Division of Intramural Research

Dr. Rodgers related the following announcements concerning NIDDK intramural scientists.

- *Dr. Marius Clore* is the recipient of the 2010 Hillebrand Award of the Chemical Society of Washington. The award was given in recognition of his pioneering developments in the application of nuclear magnetic resonance spectroscopy for the determination of the three-dimensional atomic structure of proteins in solution and for his work on characterizing weakly interacting complexes, which has provided unique insights into macromolecular recognition.
- *Dr. Adriaan Bax* has been selected by the Spectroscopy Society of Pittsburgh (SSP) as the recipient of the 2011 Pittsburgh Spectroscopy Award. This award will be presented during a symposium session of the Pittcon Conference, held at the Georgia World Congress Center, Atlanta, Georgia, March 13-18, 2011. Dr. Bax will be honored for his work on the development and application of a wide variety of advanced multidimensional NMR techniques to problems of biochemical and biomedical interest. By introducing a constant stream of novel and powerful NMR methods, Dr. Bax has been a major contributor to advancing the structural study of proteins in solution.

- *Dr. Wei Wang* has been selected as a joint recipient of the 2011 Dorothy Crowfoot Hodgkin Award. This prestigious award, supported by Genentech, is granted in recognition of exceptional contributions to protein science, which profoundly influence the understanding of biology. She will be honored at the ninth European Symposium of The Protein Society to be held in May 2011, in Stockholm, Sweden.

- *Dr. Marc Reitman* has returned to the NIDDK as Chief of the newly created Diabetes, Obesity, and Clinical Endocrinology Branch. Dr. Reitman received B.S. degrees from MIT; earned M.D. and Ph.D. degrees from Washington University in St. Louis; and received training in Internal Medicine at Columbia-Presbyterian Hospital in New York. He initially came to the NIDDK's Intramural Program for a clinical fellowship in endocrinology and metabolism and rose to the position of Section Chief. From 2002-2011 Dr. Reitman was at Merck Research Laboratories, where he focused largely on discovering and developing novel drugs for the treatment of obesity and diabetes. In his new position, Dr. Reitman will work to expand understanding of diabetes, energy homeostasis, and endocrinopathy, and to translate basic research findings in these areas into clinical practice. His lab will use mouse models to understand metabolic rate regulation and body temperature regulation, and to investigate medical treatments for obesity.

NIDDK Staff Members in Extramural Divisions and Offices

Finally, Dr. Rodgers related the following announcements regarding NIDDK staff.

- *Dr. Van Hubbard,* Director of the Division of Nutrition Research Coordination, was selected as the recipient of the 2010 Mickey Stunkard Lifetime Achievement Award from the Obesity Society. He presented his award lecture at a plenary session of the 28th Annual Scientific Meeting of the Obesity Society on October 9, 2010, in San Diego, California. The Award is designed to recognize people who, like Albert (Mickey) Stunkard, have a lifetime of outstanding contributions to the field of obesity in terms of scholarship, mentorship, and education.

- *Dr. Aaron Pawlyk* is joining the Division of Diabetes, Endocrinology and Metabolic Diseases (DEM) as a Program Director. He received his Ph.D. degree in Biochemistry from the Texas A&M University and was a post-doctoral fellow in Neuroscience at the University of Pennsylvania's School of Medicine. Dr. Pawlyk has extensive experience in drug discovery in a series of industry positions. Most recently, he was an Associate Professor of Pharmacology at Drexel University's Pennsylvania Drug Discovery Institute, and Director of Pharmacology at ALS Biopharma, LLC. Dr. Pawlyk will lead a program on the pharmacogenomics of diabetes.

- *Dr. Michael Grey* has joined the Division of Digestive Diseases and Nutrition (DDN) as a Program Director. He earned his doctorate from the Department of Biochemistry and Molecular Biophysics at Columbia University. Dr. Grey then did post-doctoral work at the Immune Disease Institute at Harvard Medical School as an American Cancer Society Postdoctoral Research Fellow. Following his post-doctoral work, he was a freelance writer and editor before initially joining NIDDK as a Health Science Policy Analyst in 2009.

- *Dr. Averell Sherker* is joining the Division of Digestive Diseases and Nutrition (DDN) as Senior Scientific Advisor for Viral Hepatitis and Liver Diseases. Dr. Sherker earned his M.D. at Queen's University Medical School in Kingston, Canada. He then completed two years of residency in the Department of Internal Medicine at Mount Sinai Hospital in Toronto and another year of residency at Toronto Western Hospital. Dr. Sherker was also a Foreign Research Fellow in the Department of Internal Medicine at Chiba University School of Medicine in Japan, and a Postdoctoral Research Fellow in the Division of Infectious Diseases at Stanford University School of Medicine. He is Board Certified in Internal Medicine and Gastroenterology. Before joining the NIDDK, Dr. Sherker served as Director of the Center for Liver Diseases at Washington Hospital Center in Washington, D.C. He was also an Associate Professor of Clinical Medicine at Georgetown University School of Medicine.

- *Dr. Michael Flessner* is joining the Division of Kidney, Urologic and Hematologic Diseases (KUH) as a Program Director for Inflammatory Renal Disease. Dr. Flessner received a Ph.D. in Chemical Engineering from the University of Michigan and holds

a Medical Degree from the University of Maryland. He completed his post-graduate training in Internal Medicine at the University of Virginia Medical Center. Dr. Flessner studied renal physiology in the NHLBI Laboratory of Kidney and Electrolyte Metabolism. Following his clinical nephrology fellowship at the University of Rochester Medical Center in Rochester, N.Y., he served there as an Assistant and Associate Professor. Before joining the NIDDK, he served at the University of Mississippi as the John Bower Professor of Nephrology and Hypertension; Professor of Medicine, Physiology, and Biophysics; and Director of the Division of Nephrology. He was a co-investigator with the Genetics of Atherosclerosis (GENOA) trial and the Jackson Heart Study. Dr. Flessner's research interests include basic studies of peritoneal inflammation associated with dialysis, and the application of computational biology to complex biological, genetic and social networks.

- *Dr. Ziya Kirkali* is joining the Division of Kidney, Urologic and Hematologic Diseases (KUH) as a Senior Scientific Officer for Clinical and Translational Research. Dr. Kirkali received his Medical Degree and completed his residency at the Hacettepe University in Turkey. Dr. Kirkali's research interests include clinical and basic research in urologic oncology. He has received numerous awards, including the first American Urological Association (AUA)/European Association of Urology International Academic Exchange Program Award. In addition to his many research activities, Dr. Kirkali was Chair of the AUA International Member Committee. He assisted in founding 10 scientific societies and maintains a board membership for eight professional organizations. He served as a past president of the Urological Research Society and was also former Chairman and Secretary of the European Organization for Research and Treatment of Cancer--Genitourinary Group.

- *Dr. Sandeep Dayal* is joining the NIDDK Office of Scientific Program and Policy Analysis. Dr. Dayal received his Ph.D. in Molecular Biology and Biochemistry from the University of Texas MD Anderson Cancer Center in Houston, Texas. He then entered the NIDDK Intramural Research Program as a post-doctoral fellow in the Laboratory of Molecular Biology, where he worked jointly with Drs. Gary Felsenfeld and Marty Gellert to investigate the role of chromatin remodeling in DNA recombination.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 184th COUNCIL MEETING AND OF REPORT ON INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEACH

Dr. Rodgers

Following motions that were made and seconded, the Council agreed, by voice vote, to accept the minutes of the 184th Council meeting, and to accept the NIDDK's 2011 Biennial Advisory Council Report on Inclusion of Women and Minorities in Clinical Research. The latter report is developed pursuant to provisions in the NIH Revitalization Act of 1993, P.L. 103-43. Both documents had been sent to the Council for consideration prior to the meeting.

III. FUTURE COUNCIL DATES
Dr. Rodgers

Dr. Rodgers asked the Council to reserve the following future meeting dates. The NIDDK expects that most meetings will be a single day--Wednesday. However, Council members are asked to hold both days (Wednesday and Thursday) to ensure flexibility should a situation arise where a longer meeting is required.

2011
May 11-12, 2011 (Wednesday and Thursday)
September 7-8, 2011 (Wednesday and Thursday)

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

IV. ANNOUNCEMENTS
Dr. Malik (for Dr. Stanfield)

Confidentiality

Dr. Malik reminded Council members that material furnished for review purposes and discussion during the closed portion of the meeting is considered confidential. The content of discussions taking place during the closed session may be disclosed only by the staff and only under appropriate circumstances. Any communication from investigators to Council members regarding actions on an application must be referred to the Institute. Any attempts by Council members to handle questions from applicants could create difficult or embarrassing situations for the members, the Institute, and/or the investigators.

Conflict of Interest

Dr. Malik emphasized that advisors and consultants serving as members of public advisory committees, such as the Council, may not participate in situations in which any violation of conflict of interest laws and regulations may occur. Responsible NIDDK staff shall assist Council members to help ensure that the member does not participate in, and is not present during review of applications or projects in which, to the member's knowledge, any of the following has a financial interest: the member, or his or her spouse, minor child, partner (including close professional associates), or an organization with which the member is connected. To ensure that a member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. Dr. Malik noted that a statement was provided for the signature of each Council member, and this statement becomes a part of the meeting file. He drew the attention of the Council members to the statement in their folders regarding conflict

of interest in their review of applications. He asked each member to read the statement carefully, sign it, and return it to the NIDDK before leaving.

Dr. Malik pointed out that, at Council meetings when applications are reviewed in groups without discussion, that is, "en bloc" action, all Council members may be present and may participate. The vote of an individual member in such instances does not apply to applications for which the member might be in conflict. With respect to multi-campus institutions of higher education, Dr. Malik stated that: An employee may participate in any particular matter affecting one campus of a multi-campus institution of higher education, if the employee's financial interest is solely employment in a position at a separate campus of the same multi-campus institution, and the employee has no multi-campus responsibilities. Dr. Malik asked if there were any questions or concerns about confidentiality or conflict of interest. Hearing none, he moved to the next agenda item.

Annual Approval of the Council Operating Procedures

The Council approved, without any concerns, the revised Council Operating Procedures. This year, the NIDDK proposed a revision in the procedures to enable the Institute to use the En Bloc Early Concurrence process at limited additional times, when needed to take optimal advantage of an emerging scientific opportunity. The Council reviews these procedures annually.

V. REPORT FROM THE NIDDK DIRECTOR
Dr. Rodgers

Special Statutory Funding Program for Type 1 Diabetes Research

Dr. Rodgers shared two announcements regarding the Special Statutory Funding Program for Type 1 Diabetes Research, which the NIDDK manages on behalf of the Secretary of Health and Human Services. Funding for this program is separate from the regular NIH appropriation and requires a specific, periodic legislative extension. The Medicare and Medicaid Extension Act of 2010 extended the program at a level of $150 million per year through Fiscal Year 2013. At that point, the Program's funding since its inception in 1998 will total $1.89 billion. The NIDDK invests approximately two-thirds of these funds each year in extramural research, while other NIH components and the CDC invest one-third.

Last year, the NIDDK prepared a brief report highlighting selected accomplishments of the program. This year, as required by law, the Institute prepared a comprehensive evaluation report, which was submitted to the Congress in December 2010. This report describes the scientific accomplishments made possible by the Program and the unique collaborative and innovative research consortia, networks, and resources that have been funded. A public version of this report will be available in the spring of 2011 as a printed publication and on the NIDDK's web site. Dr. Rodgers commended Dr. Judy Fradkin for her leadership of the program, and acknowledged the many contributions of staff members of the NIDDK's Division of Diabetes, Endocrinology and Metabolic Diseases and of the Office of Scientific Program and Policy Analysis.

Strategic Plans for Diabetes Research and Obesity Research

Dr. Rodgers reported that strategic plans for diabetes research and obesity research will soon be available in printed form and on the NIDDK web site. Both plans were developed through a broad consultative process and drafts were posted on the NIDDK web site for public comment.

The diabetes plan is entitled: "Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee." The NIDDK spearheaded its development under the auspices of this statutory coordinating committee, which it chairs. The plan is the result of a highly collaborative process involving multiple federal agencies, external scientists, and patient advocacy groups. A wide range of diabetes research basic, clinical and translational research opportunities are presented. Dr. Rodgers noted that the plan is especially timely given the rising rates of diabetes in the U.S. It will serve as a guidepost for federally-supported diabetes research at NIH and other agencies for the next several decades. Several Council members, past and present, assisted with the development of the plan. Dr. Rodgers expressed his gratitude to them and to the many scientists, patient advocates, members of the public, NIH staff members, and representatives of other government agencies who contributed to the Plan's development.

The new NIH-wide Strategic Plan for Obesity Research is being produced under the auspices of the NIH Obesity Research Task Force, which Dr. Rodgers leads along with the Director of the National Heart, Lung and Blood Institute and the Director of the National Institute of Child Health and Human Development. The plan reflects the rapid progress in obesity research and new scientific opportunities that have emerged since NIH published its first obesity research plan in 2004. The plan is informed by external input from scientists in obesity-related research fields, as well as professional and voluntary health organizations. Research challenges and opportunities identified at meetings and workshops have also helped to shape this plan. Two versions of the plan will be available: a full version for the scientific community and a shorter, non-technical summary. Dr. Rodgers expressed gratitude to all the individuals and groups who aided the planning effort.

Recent Advances and Emerging Opportunities

Dr. Rodgers described the Institute's annual compendium of research advances and emerging opportunities. The latest version highlights NIDDK-supported research advances published in Fiscal Year 2010, and also includes longer-term stories of discovery, as well as scientific presentations made at Council meetings. Profiles are included of patients who are benefiting from NIDDK-supported clinical research. This year's compendium highlights the NIDDK's 60th Anniversary activities and contains a feature on the 2010 Lasker Award Winner in Basic Medical Research, NIDDK grantee Jeffrey Coleman. Dr. Rodgers acknowledged the efforts of the NIDDK Divisions and the Office of Scientific Program and Policy Analysis in preparing the compendium.

NIH Scientific Management Review Board

Dr. Rodgers updated the Council on activities of the NIH Scientific Management Review Board, which was established under provisions of the NIH Reform Act of 2006. Comomposed of several Institute and Center Directors and external experts, the Board's purpose is to advise officials at the NIH and the Department on the use of certain organizational authorities. The Board is proposing two major organizational changes.

First, the Board proposes to integrate the organizations of the National Institute on Drug Abuse (NIDA) with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), along with the relevant research portfolios of other NIH Institutes and Centers. This integration will reflect recommendations to be generated by an internal NIH Task Force, which is also consulting with members of the scientific community. A detailed reorganization proposal for consideration by the NIH Director is expected from the Task Force in the summer of 2011, followed by the presentation of a plan to the Secretary in the fall. Because of budget formulation issues, definitive changes are unlikely to be made before Fiscal Year 2013.

Second, the Board is proposing to speed the development of biomedical discovery into treatment through the establishment of a new center for translational medicine and therapeutics, which would essentially replace the National Center for Research Resources (NCRR). The proposed center would include several ongoing translational entities, including the Clinical and Translational Science Award Program; the Molecular Libraries Program; the Therapeutics for Rare, Neglected Disease Program (TRND); the Rapid Access to Interventional Development Program (RAID); and an NIH/FDA regulatory science initiative. Also included would be the Cures Acceleration Network (CAN) called for in the Healthcare Reform law, but not yet funded. A straw model for the reorganization of NCRR's components is posted on the NIH web site for public comments (under the "Feedback NIH" section) and will be presented at an upcoming Board meeting. An NIH Task Force is guiding these efforts, and the NIH Director expects to present a detailed plan for the center to the Secretary in the summer of 2011.

Secretary Sebelius has informed the Chairs and Ranking Members of the congressional committees that oversee NIH of these proposed changes. The Congress has sent a list of questions to NIH to clarify related issues.

Appropriations

The proposed program funding level for NIH in the President's budget proposal for Fiscal Year 2012 is about $32 billion. This amount is about $745 million or 2.4 percent above the Fiscal Year 2010 level, which is the operating level under the current Continuing Resolution. It is not possible to compare the Fiscal Year 2012 proposed budget with Fiscal Year 2011, for which a final funding level has not yet been established. In the House, Government-wide reductions for Fiscal Year 2011 have been suggested on the order of $55, $60, or $100 billion, and even as much as $500 billion.

Dr. Rodgers had the pleasure to meet with the new Chair of the House appropriations subcommittee with jurisdiction over the NIH, Rep. Denny Rehberg (R-MT), and the new Ranking Member, Representative Rosa DeLauro (D-CT). Both of them had positive views of the NIH and the NIDDK. In terms of committee membership following the recent national election, the Democrats lost five seats on the House side, and the Republicans gained three seats. Subcommittee assignments have not been made on the Senate side. House and Senate appropriations hearings have not yet been scheduled for the NIH, but they tend to occur during the April-May period.

VI. THE DIABETES EDUCATION IN TRIBAL SCHOOLS (DETS) PROGRAM, AND THE DIABETES EDUCATION CURRICULUM K THROUGH 12 PROGRAM (DECK-12)

Dr. Lawrence Agodoa, Director, Office of Minority Health Research Coordination, NIDDK, and Dr. Doug Coulson, Partner, PS International, and Chair of the Evaluation Committee for the DETS Project

DETS Program Overview – Dr. Agodoa

Dr. Agodoa provided an update on the NIDDK's Diabetes Education in Tribal Schools Project (DETS). This project focuses on the development, testing and distribution of a kindergarten through 12th school curriculum. The goals of the curriculum are to increase American Indian/Alaska Native students' understanding of health, diabetes, and maintenance of life in balance; to further the students' understanding and application of scientific and community program knowledge; and to promote interest among the students in science and health professions.

Dr. Agodoa set the stage for his presentation with some data about the magnitude of the diabetes health problem in American Indians. In this population, diabetes is now one of the most common and most serious illnesses, which leads to morbidity and early death in the tribes. Once considered an adult disorder, type 2 diabetes is now emerging among youth. From 1990 to 2005, the tribes saw about a 149 percent increase in diabetes prevalence in the 25-34 age group; a 82 percent increase in the 20-24 age group; a 122 percent increase in the 15-19 age group; and a 57 percent increase in children under 15 years of age.

The DETS Project grew from a challenge that the Tribal Leaders Diabetes Committee posed to the NIH, particularly the NIDDK, to develop a curriculum to teach diabetes science in tribal schools. The response to this challenge brought together multiple partners, including the Tribal Colleges and Universities (TCUs) and several federal agencies. More specially, federal agency partners include the NIDDK, the Native Diabetes Wellness Program of the Centers for Disease Control and Prevention (CDC), the Division of Diabetes Treatment and Prevention of the Indian Health Service (IHS), and the NIH Office of Science Education. Eight TCUs were funded to lead the development of the curriculum: Cankdeska Cikana Community College, ND; Fort Peck Community College, MT; Haskell Indian Nations University, KS; Keweenaw Bay

Ojibwa Community College, MI; Leech Lake Community College, MN; Northwest Indian College, WA; Southwestern Indian Polytechnic Institute, NM; and Stone Child College, MT.

Represented by a circle, the DETS Project is named the "Health Is Life in Balance Curriculum." Components of the circle represent the physical, mental, emotional and spiritual aspects of the tribes. The curriculum design is based on inquiry learning; national education standards in the areas of science, health and social studies; teacher and student input; and traditional American Indian cultural knowledge.

Dr. Agodoa described the timeline for the project, which started with a November 2000 planning meeting with American Indian leaders, followed by a January 2001 meeting with the Tribal Leaders Diabetes Committee. The NIDDK National Advisory Council provided concept clearance for the initiative in February 2001. Planning grants (R21 grants) were awarded in September 2002, followed by Educational Program Grants for Curriculum Development (U25 grants) in September 2003. Several steps of curriculum testing ensued, including beta testing in January 2006, Field Test 1 in September 2006, and Field Test 2 in January 2007. Production of the curriculum commenced in January 2008. In November 2008, there was a National Launch of the program to begin recruitment of K-12 Tribal Schools. The National Launch occurred at the National Museum of the American Indian in Washington, D.C. Dr. Agodoa made copies of the curriculum available to Council members and attendees and noted that it can be downloaded from the NIDDK web site. He then introduced Dr. Coulson to discuss the recruitment efforts.

DETS Recruitment Report – Dr. Coulson

Dr. Coulson described efforts to recruit K-12 schools to use the DETS curriculum. The original 2009 recruitment plan linked to the eight TCUs and sister sites. Subsequently, recruitment efforts were expanded and the Indian Health Service distributed the curriculum nationally. Dr. Coulson has been working with the evaluation group to obtain, store, and track information on recruitment and distribution efforts through data obtained from over 1,200 zip codes and through other means. Over time, the number of zip codes in which schools were contacted on behalf of the DETS curriculum increased, reflecting the strong, continuing efforts of the eight TSUs.

Dr. Coulson showed that recruitment is widely distributed, ranging geographically from Hawaii, to Alaska, to New England. There is a considerable amount of detailed data backing up the national map. Means of recruiting schools included phone calls, e-mails, letters, school visits, information booths, and in-person contacts. The highest recruitment rates were typically generated from more personal contact activities including small presentations, professional development workshops, and the hosting of tables/booths at conferences.

The Indian Health Service (IHS) has the responsibility for storing and distributing the curriculum. The IHS receives requests for the curriculum through their web site and the

NIDDK website has links to the IHS page that advertises curriculum. Trend data from the IHS show strong increases in curriculum orders over time. There is a correlation between the distribution of the curriculum by the IHS and the recruitment of schools by the TCUs. Also, a voluntary teacher web survey produced highly positive comments regarding the ease of ordering the curriculum, ease of use, engagement of students, Native American content, and other attributes. Dr. Coulson also showed maps that indicate considerable use of the curriculum across the country.

Dr. Coulson said that a Novo Nordisk Design and Planning Grant was awarded to the evaluation group to look at the long-term impact of the DETS curriculum. Under this grant, the evaluation is being broadened to include community indicators, and perhaps an assessment that goes beyond effects on achievement and attitude to changes among participants in body mass index or glycemic index. Work under the grant is expected to be completed in December 2011. The planning grant will build on available resources, including the voluntary teacher survey, an online classroom evaluation, the results of a brainstorming session, and the findings of a 2008 implementation study that involved 1,500 students, a hundred teachers, and 60 schools. The existence of a mature TCU infrastructure will be very valuable. Evaluators are contemplating a translational design, with measurable inputs and outputs.

Next Phase of Diabetes Education Efforts - Dr. Agodoa

Looking ahead, Dr. Agodoa described a new diabetes education effort that will focus on Hispanic and African American youth and adolescents in grades K through 12. The project will be called the Diabetes Education Curriculum in K Through 12 Schools Initiative (DECK-12). Dr. Agodoa presented epidemiologic data that make this a compelling undertaking.

Among non-Hispanic black youth, 35.9 percent of those 2-19 years of age have a body mass index equal to or greater than the 85th percentile of all youth. They are almost eight times more at risk for diabetes than non-Hispanic white youth. The incidence rate for type 2 diabetes is about 19 per 100,000 for black youth 10-19 years old. Nearly one-third of the black youth older than 15 years with type 1 or type 2 diabetes had A1c values equal to or greater than 9.5.

Turning to Latino/Hispanic youth, Dr. Agodoa said that 38.2 percent of non-white Hispanic youth 2-19 years of age have a body mass index that is equal to or greater than the 85th percentile of youth overall. Type 2 diabetes is more common among females than males. Nearly one-third of the youth older than 15 years with type 1 or type 2 diabetes also had A1c values equal to or greater than 9.5.

The purpose of the DECK-12 initiative is to reduce the prevalence and incidence of type 2 diabetes and increase interest in science and health-related fields among African American and Hispanic youth in grades K through 12. To this end, the project will include developing, implementing, monitoring, and formally evaluating interdisciplinary

skills-based diabetes education supplemental curricula for K through 12 schools in a manner similar to the DETS project in American Indian schools.

The overall goals are to increase knowledge and awareness of diabetes and its complications, risk factors, and self-management principles; improve diabetes prevention and self-management behavior and skills; increase interest in science and health-related careers; and reduce risk factors for type 2 diabetes in the target population. The project has three phases. Phase 1 began in 2010. The Request for Proposals was issued and a contract was awarded to the Biological Sciences Curriculum Study (BSCS) in Colorado Springs, Colorado, for the development of the curriculum, which is expected to be completed by 2014. Phase 2 will feature an award through a Request for Applications to facilitate curriculum implementation. It is expected that Historically Black Colleges and Universities and Hispanic-Serving Institutions will be engaged in recruitment, implementation, and process evaluation. Phase 3 will focus on summative evaluation from 2014 through 2017.

Council Questions and Discussion

Is there an evaluation of the effects of the DETS curriculum in the timeline? Dr. Coulson responded that the measures for the implementation study, which was conducted in 2008, were educational measures. There were no health measures such as body mass index or glycemic index.

Is there an evaluation planned for the DECK-12 curriculum? Dr. Agodoa replied that the DECK-12 project has just begun. Following the Request for Proposals (RFP), a contract was awarded to BSCS only about two months ago. There will be an evaluation of the DECK-12 curriculum after it is developed.

Is consideration being given to curricula that have been developed and tested in other studies, such as the NIDDK-funded HEALTHY study, which was conducted in middle schools? Dr. Agodoa responded in the affirmative.

Do current DETS efforts focus exclusively on the curriculum or do they try to change other aspects of the school environment? Dr. Agodoa noted that moving beyond the curriculum would involve a long-term evaluation. The possible plans for such an evaluation have been discussed with the Indian Health Service and the NIDDK. Issues include determination of a lead agency and funding sources.

Are there any plans to use social networking to promote the DETS educational efforts or evaluate them? Dr. Coulson noted that issues of confidentiality would need to be worked out before social networking techniques could be used. There are also issues surrounding the participation of the Tribal Colleges and Universities and their access to the Internet. Social networking is an approach that continues to be discussed at meetings.

Will an effort be made to assess whether the use of the DETS curriculum resulted in positive changes, such as an increase in students' knowledge about diabetes? We need to

know the answer to this question because these types of programs represent major investments, and, if they are effective, they need to be aggressively deployed. Dr. Coulson replied that there is a qualitative component to the evaluation efforts in which the impact of the projects on students will be assessed through interviews and other means. Some data already exist along these lines on the DETS Project. Plans are under discussion to collect data on the DECK-12 Project.

Is a knowledge baseline being established, including not only students' attitudes but also their knowledge about the diabetes, so that later comparisons can be made to determine the impact of the educational materials? Dr. Coulson said that there is a pre/post evaluation design in which a pre-test determines the knowledge base.

VII. SCIENTIFIC PRESENTATION: "Hepatic Lipotoxicity"

Dr. Rodgers introduced Council Member Dr. Gregory J. Gores, Reuben R. Einsenberg Professor, Department of Medicine, the Mayo Clinic. Dr. Gore's laboratory-based research program is focused on mechanisms of liver cell death. An NIDDK grantee since 1989, Dr. Gores also develops and participates in clinical research protocols, especially protocols focused on the treatment of hepatobiliary neoplasia.

VIII. ADVISORY COUNCIL FORUM: Epigenomics, NIH, and NIDDK

In introducing the Council Forum, Dr. Rodgers provided context for the meeting attendees. He noted that epigenetics is an emerging frontier of science that involves the study of changes in the regulation of gene activity and expression that are not dependent on DNA sequence. Epigenetics refers to the study of single genes or sets of genes, whereas epigenomics refers to more global analyses of epigenetic changes across the entire genome. Diet and exposure to environmental chemicals throughout all stages of human development, among other factors, can cause epigenetic changes that may turn certain genes "on" or "off." These types of changes in the regulation of genes could make people more or less susceptible to developing a disease later in life. Because of the great potential for epigenomics research to enhance understanding of many basic biological processes and human health problems, the NIH established the Roadmap Epigenomics Project to pursue the many promising research opportunities in this area.

A. "The NIDDK Epigenomics Landscape"

Dr. Phil Smith, Co-Director of the Office of Obesity Research, and DeputyDirector, Division of Diabetes, Endocrinology, and Metabolic Diseases, NIDDK

Dr. Smith posed the question to as to whether NIDDK should take steps to spur the application of research in epigenetics and epigenomics to the understanding, treatment and prevention of diseases within the NIDDK mission. Dr. Smith presented trend data showing that the field of epigenetics has undergone an explosion of discovery, and that the new field of epigenomics, which builds upon it, is beginning to experience some exciting research activity. From 2000 to 2010, substantial growth occurred in the number

of publications entered into the National Library of Medicine's PubMed database involving the topic of epigenetics. These numbers have increased annually from just a few hundred in the year 2000 to over 3,000 in 2010. As for epigenomics, publications involving this topic were virtually non-existent from 2000-2004. Then, a slow upward trend began and continued through 2010, although numbers still remain below 500 per year. These publication trends are mirrored in the growth between 2000-2010 in the numbers of NIDDK grant applications and grant awards with respect to topics involving epigenetics and epigenomics. The epigenetics applications numbers began to show dramatic annual increases around 2006.

Dr. Smith noted that epigenetics mechanisms for the basis for translation of a single genome to a multicellular organism through progressive restriction of the expression of gene sets in various tissues. In this way, a liver cell develops and remains committed to being a liver cell, and a fat cell develops and remains committed to being a fat cell. The organism's environment can affect epigenetic mechanisms and influence gene expression--ultimately manifesting in the phenotypic characteristics of cells, organs, and tissues. The environmental factors that can lead to epigenetic changes may be internal to the organism--such as the metabolic or endocrine signals to which its cells and tissues are exposed--or they may be external, such as dietary factors, drugs or chemical toxins.

In eurokaryotic cells, genes can be expressed (activated or silenced) in different ways. One way involves the addition of a methyl group to the cytosine bases in the DNA itself--a process called methylation, which leaves chemical "marks" on the DNA. Another way is through the intricate regulatory mechanisms of chromatin--the complex of proteins and nucleic acid that dictates the organization of DNA within the nucleus. In the latter process, a critical role is played by histones--small, basic proteins most commonly found in association with DNA in the chromatin. Histones act like spools around which the DNA wraps. Chemical modifications of histones can alter the compactness of the wrapped DNA, and thus the availability of genes in the DNA to be activated. These effects can be short-term, long-term or permanent.

Dr. Smith introduced the scientific speakers for the Forum, and asked the Council members to think about the following questions during the presentations: Are there technologies or methods that need to be developed to study the role of epigenetic mechanisms in disease? Are there specific hurdles to overcome in applying these technologies to diseases of interest to the NIDDK? How can we share data generated by individual labs and ensure quality? Are there cohorts for which mapping makes sense? What can the NIDDK do to ensure that its grantees benefit from mapping expertise? What should the NIDDK do when the NIH Roadmap Epigenomics Program ends?

B. "The NIH Roadmap Epigenomics Mapping Consortium"
Dr. Bradley Bernstein, Associate Professor, Department of Pathology, Massachusetts General Hospital, Harvard Medical School

Dr. Bernstein provided his perspective on epigenomics/epigenomics research. Classically, epigenetics has been considered the study of lineage, that is, the way that

cells with the same genetic information acquire different phenotypes and maintain them stably. These functions relate to gene expression programs. Much of the current excitement in the research community pertains to discoveries about the different organization patterns of the genomic DNA and its variability across cell types. This research is crucially important for understanding disease states. Particularly exciting is new knowledge about mutations in a wide range of chromatin-modifying enzymes. Aberrant epigenetic landscapes may contribute to health problems such as cancer, as well as to neuropsychiatric, metabolic, and developmental disorders.

Although environmental influences can lead to disease-causing epigenetic changes, there is no clear view of how epigenetics is causing long-term changes in the genome to affect disease risk. For this reason, it is essential to continue support for basic research on epigenetic mechanisms. At the same time, there is an urgent need to build tool kits and a reference map of the human epigenome--similar to what was done for the human genome--in a technologically and statistically robust way. Then, it will be possible to increase understanding of the normal epigenome, learn about variations across individuals, and discover the way that factors such as the environment are altering the epigenome. Such knowledge will have very broad application as researchers learn about the way that genotype gives rise to phenotype in almost any disease and tissue.

Ongoing efforts to understand genetic variations include ENCODE, the NIH Roadmap Epigenomics Project, and international studies. It is currently known that DNA methylation impacts on the direct modification of cytosine bases in DNA, and that this process, in turn, affects the way that DNA base pairs are packaged into chromatin in terms of whether they're accessible or compacted. Histone modifications provide insights into the way that the packaging of elements is ordered across the genome. Many tools have transformed the ability of researchers to study this process, including genome-wide maps of epigenomic features, such as modifications of histones and other proteins. Epigenomics research has been transformed by next-generation sequencing techniques, including whole genome bisulfite sequencing, DNase-seq, and ChiP-seq. At the same time, many challenges remain. For example, better methods are needed for studies of single cells and tissues, *in vivo*.

Dr. Bernstein provided several vignettes from work conducted through the Roadmap Epigenomics Project with regard to methylomes of pluripotent stem cells. He noted that one of the first milestones was the production of whole methylomes for embryonic stem cells by the use of bisulfite sequencing. This type of sequencing has made it possible to look across the whole genome and map the methylation patterns. Another example of progress is the discovery of epigenomic defects in induced pluripotent stem cells (iPSCs). Dr. Bernstein's group has developed a metric for determination of the variability in methylation across many different cells. This variability is indicative of the developmental potential of the iPSCs or even of embryonic stem cells.

The Roadmap Epigenome Project has looked at different cell types, including pluripotent cells, blood cells, cultured cells, and islets. Using some statistical manipulations, scientists are trying to make an atlas of the epigenome. A reference now exists that other

researchers can build upon for disease-focused studies. An extremely interesting and important finding is that cells segregate according to cell type. Another significant finding is that repressive methylation marks are largely confined to gene promoters in pluripotent cells. In contrast, the spreading out of methylation marks tends to occur in cells that are not pluripotent. In culture, it is now possible to recreate this sort of repressive spreading effect, which is cell-specific and thus helps cells maintain fidelity/commitment to a specific lineage during the cell differentiation process.

In the next part of his presentation, Dr. Bernstein gave an example of research advances emerging from the NHGRI-supported ENCODE Consortium, which has focused in great depth on cell lines. A very large database has been assembled--a compendium of chromatin maps. These data can now be used to annotate the genome to locate not only genes, but also the non-coding elements in the so-called "dark matter," the gene enhancers, and other elements that are regulating genes at a distance. The result is a genome regulatory network. For example, using chromatin states as evidenced by methylation marks, researchers can identify known or possible gene promoters, cluster them by cell-type-specific patterns, and follow their regulation across different cell types to see when they are active or inactive. They can also validate gene enhancers and very important non-coding elements. Not surprisingly, gene promoters and enhancers are located near genes that they probably regulate. For example, gene enhancers that are active in immune cells are located near immune genes. Enhancers active in liver cells are near genes that control lipid metabolism. In a theoretical model, statistical metrics are now enabling researchers to use the variation in the cell-type-specific enhancers to link those enhancers to predicted target genes. Researchers are also working to develop models to learn how transcription factors activate gene enhancers.

Dr. Bernstein described the ways that research advances in epigenomics can guide clinical studies of human disease. Interestingly, the majority of disease-associated genetic variants identified through Genome Wide Association Studies (GWAS) appear to be in non-coding regions outside of the genes. Disease-associated variations in DNA are more likely to be in annotated enhancer elements. Moreover, there seems to be a meaningful correspondence between the disease-associated genetic variants and their related enhancers. For example, the variants associated with the autoimmune diseases rheumatoid arthritis and lupus are turning up in immune cells. These analyses might provide a way to triage genetic variants to cull those that are disease-causing from the many types found through GWAS.

In summary, Dr. Bernstein said that studies of chromatin dynamics have enabled researchers to define regulatory networks and make regulatory predictions based on GWAS. The ENCODE project has established hundreds of maps of chromatin marks, transcription factors, and RNAs. The NIH Epigenome Roadmap Project is now moving into work on *in vivo* tissues, where the clinical manifestations of genetic variants are likely to be found. The integration of all this work will provide a very rich resource for studies of human diseases.

Because of the enormous potential application of epigenomics to human health, it is critically important that the field be given guidance, impetus, and resources. For example, Dr. Bernstein said that there is an urgent need for more experimental models to move this research area forward. He illustrated the impressive results that can be realized. He described a genome-wide analysis of Wilm's tumor, a pediatric kidney cancer. This analysis revealed highly-active transcription factors that are basically the network of renal development. When these genes are knocked out in a mouse model, no kidneys are formed. Thus, this research revealed that a pediatric tumor is probably a relatively good reflection of a renal progenitor. As a result, there is an opportunity to look at early stages of kidney development through studies of this tumor. Dr. Bernstein recommended the encouragement and support of additional research of this kind in model systems. He noted that the research community can definitely benefit from the active support of the NIH in the development and application of tools and expertise for epigenomics research.

C. Epigenetic Mechanisms of Hematopoietic Transcription"

Dr. Gerd Blobel, Associate Professor, Department of Pediatrics, The Children's Hospital, Philadelphia, Pennsylvania

Dr. Blobel described some of the approaches his research team and colleagues are taking to pursue hypotheses or models generated by GWAS. Dr. Blobel underscored that gene expression patterns are maintained through multiple rounds of cell division. Although research to increase knowledge of the cell cycle is challenging, it can provide an opportunity to gain insights regarding the ways that transcription programs are maintained, and perhaps, may even be changed.

In studying eurokaryotic cells, two major challenges to understanding the cell cycle are: (1) to understand the phase in which the genome is duplicated (the S phase), and (2) to learn more about the subsequent mitotic phase--during which each cell splits into two distinct cells, often called "daughter cells." One question Dr. Blobel's laboratory is exploring is whether there are so-called "bookmarks" (epigenetic, genetic, or biochemical) that are involved in maintaining transcriptional programs during mitosis. To address this question, Dr. Blobel's team is studying MLL1 (a histone methyltransferase) and chromatin. MLL1 is one of the few modifiers of chromatin that has true epigenetic functions that can have genetic effects independent of DNA sequence. His team has found that MLL1 associates with chromatin during mitosis, the phase of the cell cycle when transcription does not occur. This is an unexpected finding given that previous studies showed that transcription factors globally dissociate from mitotic chromatin, and that MLL1 is known to mark active transcription. Thus, MLL1 seems to have a unique bookmarking function that emerges during the mitotic phase of the cell cycle.

These findings led the Blobel team to perform a genome-wide analysis of MLL1 immediately before and during mitosis. They found that there are several thousand genes that are occupied by MLL1 in these phases of the cell cycle. However, only about 1,000 of them are occupied by MLL1 exclusively during the mitotic phase. Several additional laboratory experiments have led the Blobel team to hypothesize that bookmarked genes may behave differently from non-bookmarked genes in the way that they are reactivated

following mitosis. MLL1 may associate with certain genes, chaperone them through mitosis, and then facilitate their reactivation following mitosis. Moreover, these functions of MLL1 appear to be independent of histone methylation, even though MLL1 is a known histone marker.

The research on MLL1 led the Blobel team to explore the existence of tissue-specific bookmarking proteins. They focused on GATA-1, which essentially regulates all erythroid-specific genes. Mutations in GATA-1 are associated with congenital anemia and some forms of leukemia, so GATA-1 affects the formation and development of red blood cells (hematopoiesis). The team found that the vast majority of GATA-1 dissociates from chromatin during mitosis, but some areas of chromatin retain GATA-1 at high concentrations. These findings suggest that GATA-1 may function as a bookmarking protein that maintains transcriptional programs in the mitotic phase of the cell cycle. After performing genome-wide studies, the team found that most of the genes that are marked by GATA-1 and mitosis are themselves key regulators of hematopoiesis, that is, they are transcription factors. In its bookmarking function, GATA-1 favored regulatory proteins that are critical determinants of the hematopoietic program. These results have led the team to ongoing studies aimed at answering the question: What is the function of mitotic GATA-1 retention in those genes?

Dr. Blobel presented another research vignette to illustrate how chromatin-remodeling complexes, although broadly distributed, may have some selective functions in the genome. He described the activity of a factor known as Friend of GATA (FOG), which can help or antagonize the activity of GATA-1. Through studies aimed at understanding how FOG interacts with chromatin, the team identified a protein complex called Nuclear Enzyme Remodeling and Histone Deacetylase (NuRD). When they disrupted the NuRD interaction in mice, they found that the mutant mice had anemia with enlarged spleens and other defects. In related work, the team also showed that the GATA-FOG-NuRD complex directly activates the development of erythroid-megakaryotoid cells, while repressing the development of an alternative lineage--destructive mast cells. The continuous presence of this complex appears to be necessary to prevent the cells from differentiating into other cell types.

Dr. Blobel noted that high-throughput technologies are being used to probe long-range chromatin architecture and interactions. Research has found that chromatin fibers are highly dynamic and flexible. They can permit the juxtaposition of genetic elements that have different functions and keep them from encroaching on each other. Many questions remain as to how interactions are established, which factors are involved, and how specificity of functions is established. In one line of research, Dr. Blobel's group is studying the way that chromatin can form distinct loops, which can turn off gene expression. Results suggest that it is possible for researchers to induce the formation of a chromatin loop and manipulate gene expression in laboratory studies. The research group intends to build on this work with genome-wide studies to address mechanisms and cause-and-effect relationships. Some of the questions they will pursue are: Can forced chromatin loops be used to silence genes? Can forced chromatin loops be used to

reprogram complex gene loci? Can this approach be used to move endogenous genes to distinct nuclear compartments to assess their role in gene expression?

D. Novel Mechanisms of Epigenetic Regulation of Gene Expression"
Dr. Gary Felsenfeld, Distinguished Scientist and Chief, Section on Physical Chemistry, Laboratory of Molecular Biology, NIDDK

Dr. Felsenfeld described a number of studies conducted by his research team and colleagues on the biology of chromatin. His laboratory is particularly interested in investigating the structure of condensed chromatin domains to learn how they are established and maintained. Condensed or compacted chromatin, called heterochromatin, has a silencing or repressive effect on gene expression. Dr. Felsenfeld noted that structural elements in eukaryotic cells can protect against the encroachment of condensed chromatin; protect against inappropriate gene activation signals; and stabilize functionally important long-range interactions. There is a growing appreciation that some of these structural elements can play a major role in epigenetic changes across the genome.

Dr. Felsenfeld's team has uncovered multiple DNA binding proteins with various activities that coordinate chromatin structure and gene expression. Using the chicken beta-globin genes as a model system, the researchers have made many discoveries. For example, they found a gene for an erythroid-specific folate receptor. They also found strong, positive enhancer-like regulatory elements, called Locus Control Region elements, adjacent to condensed chromatin. They have also illuminated the way that histones work.

A major focus of the team's research is DNA sequence elements that function as so-called "insulators." Insulators can act in two ways. They can serve as barriers to prevent the incursion of repressive heterochromatic signals into open areas of DNA. They can also serve as blockers of inappropriate contact between the enhancer of one gene and the promoter of another. Insulators act through diverse mechanisms. Barrier insulation is often associated with the ability to block the propagation of silencing histone modifications. Enhancer-blocking insulation is largely associated with the ability to stabilize the formation of chromatin loops within the cell's nucleus.

Dr. Felsenfeld's research team has learned a great deal about the action of insulators from studies based on their discovery and characterization of the first vertebrate insulator element located at the 5' boundary of the chicken beta-globin locus. For example, they showed that this region in erythroid cells is marked by activating histone modifications.

The research team eventually narrowed down the activity they were most interested in studying to a specific genetic fragment and used a technique called DNase footprinting to identify within that fragment five protein-binding regions or "footprints." Four of these proteins appear to be barrier insulators that protect open chromatin domains from being silenced by the spread of adjacent heterochromatic regions. The activity of one of these four proteins, the heterodimer USF-1/USF-2, involves the recruitment of positive histone-

modifying enzymes. This is the apparent barrier mechanism for halting the propagation of the heterochromatic structure. Three other footprinted regions bind different proteins, but have in common a protein named VezF1/BGP1. The deletion of any of the three footprints for this protein is a barrier to the advancement of silencing heterochromatin. The Felsenfeld team is continuing to explore these and other findings in order to gain a more complete understanding of the underlying mechanisms involved.

The fifth footprinted protein, CTCF, acts in a different way from the four barrier insulators. CTCF is an enhancer-blocking insulator, with remarkable functions. In vertebrates, CTCF provides a fundamental mechanism for dividing the genome into discrete domains and for keeping adjacent gene sites from interacting. CTCF also helps to explain the important phenomenon of genetic imprinting--that is, cases in which gene activity depends on the parent of origin (allele-specific expression). For example, CTCF controls the expression of a gene that codes for insulin-like growth factor 2 (*Igf2*) that is active in fetal development only if it is inherited from the father, not from the mother.

CTCF acts in different ways in different places; for example, it can either activate or silence transcription. Perhaps its most significant role is to stabilize long-range chromatin loop formation in vertebrates. In so doing, it can inhibit interactions between an enhancer and promoter, or between different regulatory elements. In vertebrates, CTCF plays a role in epigenetics/epigenomics by helping to establish long-range architecture important for large-scale genome organization that may be independent of gene expression levels. This activity facilitates interactions between distant regulatory elements that can further stabilize specific contacts, and can lead to stimulation of gene expression.

Dr. Felsenfeld's research team is now working to define the way that long-range interactions among structural elements may coordinate gene activation for specific biologic processes. Using a technique called Chromatin Conformation Capture (3C), the team has demonstrated that CTCF makes long-range contact with the gene *SYT8* and positively regulates its expression. Through a series of experiments, they showed that the *SYT8* gene is a major regulator of insulin secretion in human islets. Dr. Felsenfeld noted that the ability to carry out this work was largely dependent upon the NIDDK's support of a resource for the collection of donated human islets for research purposes.

As Dr. Felsenfeld's presentation emphasized, it has become increasingly clear that the genome is organized into discrete physical domains within the nucleus, and that some DNA sequence elements and their associated factors are important in establishing and maintaining these domains. The work of Dr. Felsenfeld's team in defining physical networks within the cell's nucleus is now leading to the identification of corresponding regulatory networks. The development of new knowledge about these networks will help to shed light on a wide range of genetic diseases.

Council Questions and Discussion

In a very short period of time, remarkable progress has been made in epigenetics and epigenomics. Although it is still not possible to "read" DNA, it is likely that the

necessary technologies to do so will be developed at some point in the future. It will then be possible to harness for clinical research purposes the wealth of fundamental knowledge being developed today about non-coding elements and other aspects of DNA--along with related biochemical and molecular discoveries. The work that is going on now is very impressive and encouraging, and the challenge, going forward, will be its clinical application.

There is a tidal wave of new technologies and knowledge that will enable researchers to crack the epigenetic/epigenomic code. For the NIDDK, the challenge is twofold: (1) to find ways to leverage advances to benefit the Institute's community of research investigators, and (2) to decide whether the cracking of the code will be useful for identifying drug targets.

Dr. Smith closed the Council Forum by noting that the epigenetics/epigenomics field needs informatics support, financial resources, and scientific expertise. He echoed Dr. Felsenfeld's comment that the work in human islets would not be possible without the islet resources that have been enabled by the Special Statutory Funding Program for Type 1 Diabetes Research. Similarly, very high grade reagents are required for many studies involving epigenetics and epigenomics. As the NIH Roadmap draws to a close, the fate of several initiatives that bear on epigenetics and epigenomics will need to be determined. This work includes not only the specific Roadmap Epigenomics Project, but also other relevant undertakings, such as the Molecular Libraries Program. Dr. Smith and Dr. Rodgers thanked Drs. Bernstein, Blobel, and Felsenfeld for their thought-provoking presentations.

IX. CONSIDERATION OF REVIEW OF GRANT APPLICATIONS

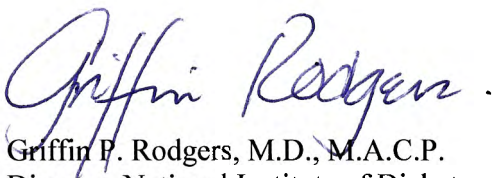
A total of 1,315 grant applications, requesting support of $334,760,137 were reviewed for consideration at the February 16, 2011 meeting. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 1,068 applications requesting $267,718,795 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 Feb 16, 2011 meeting.

X. ADJOURNMENT

Dr. Rodgers thanked the Council members for their attendance and valuable discussion. There being no other business, the 185th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m., February 16, 2011.

man, National Diabetes and Digestive and Kidney Diseases Advisory Council

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



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