Meeting Minutes
Department of Health and Human Services
National Institutes of Health
National Diabetes and Digestive and Kidney Diseases Advisory Council
September 22, 2010

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 184th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m., Wednesday, September 22, 2010, in Building 31, C. Wing, 6th floor, Conference Room 10.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. David Altshuler
Ms. LaVarne Burton
Dr. Charles Elson, III
Dr. Robert Flanigan
Dr. Christopher Glass
Dr. Gregory Gores
Ms. Jane Holt
Ms. Judy Hunt
Dr. Francine Kaufman
Dr. David Klurfeld
Dr. Mark Magnuson
Dr. William Mitch
Dr. Anil Rustgi
Dr. Anthony Schaeffer
Dr. John Sedor
Dr. Patrick Tso

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

B. NIDDK STAFF AND GUESTS

Abankwah, Dora – NIDDK
Akolkar, Beena – NIDDK
Ameen, Vanessa – NIDDK
Appel, Michael – NIDDK
Arreaza-Rubin, Guillermo – NIDDK
Austin, Christopher – NHGRI
Barnard, Michele – NIDDK
Bethea, Gina-NIDDK
Beverly, Kevin – Soc. Sci. Sys.
Bishop, Terry – NIDDK
Blondel, Olivier – NIDDK
Bloom-Davila, Maria – NIDDK
Carrington, Jill – NIDDK
Castle, Arthur – NIDDK
Chianchiano, Dolph – Natl. Kid. Found.
Connaughton, John – NIDDK
Copeland, Randy – NIDDK
Curtis, Leslie – NIDDK
Dayal, Sandeep – NIDDK
Donohue, Patrick – NIDDK
Doo, Edward – NIDDK
Eggerman, Thomas – NIDDK
Eggers, Paul – NIDDK
Evans, Mary – NIDDK
Flessner, Michael – NIDDK
Fonville, Olaf – NIDDK

Fradkin, Judith – NIDDK
Gallivan, Joanne – NIDDK
Gansheroff, Lisa – NIDDK
Garfield, Sanford – NIDDK
Garofalo, Robert – NIDDK
Greene, Lucy – NIDDK
Grey, Michael – NIDDK
Grooves, Reed – CSR
Guo, Xiaodu – NIDDK
Haft Renfrew, Carol – NIDDK
Hamilton, Frank – NIDDK
Hanlon, Mary – NIDDK
Harris, Mary – NIDDK
Hilliard, Trude – NIDDK
Hoofnagle, Jay – NIDDK
Horlick, Mary – NIDDK
Hoshizaki, Deborah – NIDDK
Hunter, Van – NIDDK
Hyde, James – NIDDK
James, Stephen – NIDDK
Jerkins, Ann – NIDDK
Jolly, Julie – Lewis-Burke Assoc.
Jones, Teresa – NIDDK
Karp, Robert – NIDDK
Ketchum, Christian – NIDDK
Kim, Sooja – CSR
Kimmel, Paul – NIDDK
Kochis, Doriel – Amer. Soc. of Neph.
Kranzfelder, Kathy – NIDDK
Kuczmarski, Robert – NIDDK
Kusek, John – NIDDK
Lescheck, Ellen – NIDDK
Linder, Barbara – NIDDK
Malik, Karl – NIDDK
Malozowski, Saul – NIDDK
Manouelian, Denise – NIDDK
Margolis, Ronald – NIDDK
May, Ken – NIDDK
McKeon, Catherine – NIDDK
Miles, Carolyn – NIDDK
Miller, David – NIDDK
Miller, Megan – NIDDK
Moxey-Mims, Marva – NIDDK
Mullins, Christopher – NIDDK
Nicholson, Katherine – NIDDK
Nixon, Ralph – Nathan Kline Inst.
Nurik, Jody – NIDDK
Ostell, James – NLM/NCBI
Patel, D.G. – NIDDK
Pike, Robert – NIDDK
Podskalny, Judith – NIDDK
Polglase, William – NIDDK
Pope, Sharon – NIDDK
Rada, Beth – XOMA
Rankin, Tracy – NIDDK
Rasooly, Rebekah – NIDDK
Reiter, Amy – NIDDK
Roberts, Tibor – NIDDK
Robuck, Patricia – NIDDK
Rodrigues, Michelle – SRI Inter.
Rushing, Paul – NIDDK
Rys-Sikora, Krystyna – NIDDK
Sahai, Atul – CSR
Salaita, Christine – NIDDK
Sankaran, Lakshmanan – NIDDK
Sato, Sheryl – NIDDK
Savage, Peter – NIDDK
Sekis, Bronka – Soc. Sci. Sys.
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, Rebecca – NIDDK
Wallace, Julie – NIDDK
Wellner, Robert – NIDDK
Woynarowska, Barbara – NIDDK
Yanovski, Susan – NIDDK
Zeidner, Rita – NIDDK

C. ANNOUNCEMENTS

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

Events Celebrating NIDDK's 60th Anniversary

Dr. Rodgers noted that celebration of the NIDDK's 60th Anniversary in 2010 has included events at over a dozen professional and scientific meetings. In addition, the Institute organized a scientific symposium featuring research advances supported by NIDDK and a celebratory dinner on September 21, 2010. He thanked the Council members who were able to attend those events.

In June 2010, Rep. Frank Pallone, Jr. (D-N.J.), a senior member of the House Energy and Commerce Committee and chair of the Subcommittee on Health, introduced House Resolution 1444, recognizing the Institute's 60th anniversary. Later that month, a Congressional breakfast attended by Representatives Nita Lowey, Diana DeGette, Zack Space and Gene Green was held in honor of the anniversary. The event, sponsored by patient advocacy and professional groups, included honoring four scientists who made major contributions toward advancing NIDDK research. Drs. Phillip Gorden, David Nathan and Jeffrey Gordon received NIDDK Distinguished Scientist awards and Dr. Theo Heller received an NIDDK Early Career Investigator Award.

Members Retiring from the Council

Dr. Rodgers acknowledged the service of five Council members who have fulfilled their terms and will rotate off the Council.

Departing from the Diabetes, Endocrinology and Metabolic Diseases Subcouncil:

- *Dr. Mark Magnuson, M.D., the Earl W. Sutherland Jr. Professor of Molecular Physiology and Biophysics, Professor of Cell and Developmental Biology, and Professor of Medicine at Vanderbilt University, Nashville, Tennessee.* A former member of the NIDDK Intramural Program, Dr. Magnuson's advice has been greatly appreciated as the NIDDK has considered approaches to foster multi-disciplinary research and scientific collaboration. As the leader of the NIDDK Beta Cell Biology Consortium (BCBC), he has pioneered novel approaches to attract new talent and encourage collaborative bridging projects across the Consortium, which is being used by some other Institutes as a model for collaborative research. In a presentation to the Council, he described strategies he used successfully to build trust needed for sharing unpublished results and for creating incentives for collaboration. These lessons learned from the BCBC have assisted the NIDDK in strengthening other efforts. Dr. Magnuson has also been very helpful to the NIDDK in its efforts to enhance the effectiveness of its centers programs.

Departing from the Digestive Diseases and Nutrition Subcouncil:

- *Dr. Charles Elson, III., Professor, Department of Medicine, University of Alabama, Birmingham, where he holds the Basil I. Hirschowitz Chair in Gastroenterology.* For nearly 30 years, the NIDDK has supported Dr. Elson's research on the regulation of mucosal immune responses. He has shown how such regulation relates to maintenance of normal homeostasis and contributes to states of chronic intestinal inflammation. Dr. Elson has provided the NIDDK with especially thoughtful and keen observations about the changing field of Inflammatory Bowel Disease research, and provided the Council with an excellent presentation on the immunoregulatory role of IgA in intestinal homeostasis. As a previous Training Director, he has also contributed important insights about the need to keep physician-scientists engaged in research to maintain a robust NIDDK research portfolio in the future.

- *Dr. Patrick Tso is Professor of Pathology and Laboratory Medicine, University of Cincinnati, and Associate Director of the Obesity Research Center at the University's Genome Research Institute, where he leads the lipid research group.* For more than 25 years, the NIDDK has supported Dr. Tso's research on the regulation and physiological consequences of intestinal lipid absorption. While serving on Council, Dr. Tso gave an excellent presentation: "How Does Apolipoprotein AIV Regulate Food Intake and Body Weight?" He also helped to organize the NIDDK workshop on "Lymphatics in the Digestive System, Physiology, Health and Disease." His efforts contributed to an outstanding workshop to stimulate research in this under-studied area. Dr. Tso has also served as the Council's liaison to the NIDDK Clinical Obesity Research Panel.

Departing from the Kidney, Urologic, and Hematologic Diseases Subcouncil:

- *Drs. William Mitch, the Gordon A. Cain Professor of Medicine and Director of the Division of Nephrology at Baylor College of Medicine, Houston, Texas.* Dr. Mitch is a long-term NIDDK grantee whose cross-cutting research has been supported by two Divisions. His research interests include the study of metabolic abnormalities associated with kidney disease, the mechanism controlling the loss of muscle mass, and the treatment of patients with chronic renal disease, including methods for delaying loss of kidney function. Dr. Mitch is a recognized expert on the care of patients with hypertension and chronic kidney disease and on the use of dietary methods to protect the kidney. He has offered the NIDDK thoughtful input on research questions and priorities, and has been a strong advocate for investigator-initiated grants and training opportunities for new Principal Investigators. Dr. Mitch has also demonstrated a keen sense of future opportunities and trends in research.

- *Dr. Anthony Schaeffer, the Herman L. Kretschmer Professor, and Chairman of the Department of Urology at the Feinberg School of Medicine, Northwestern University, Chicago, Illinois.* Dr. Schaeffer has used his vast expertise in urology to help enhance the NIDDK urology program, especially by advocating for new and expansive training opportunities for Principal Investigators. During his time on the Council, he also

served as Chair of the Research Council for the American Urological Association, and he worked diligently to strengthen interactions between the NIDDK and the urology community. Dr. Schaeffer has been a major supporter of new programs, including the Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP study) and new research centers programs. A vigorous proponent of interdisciplinary research, he has offered insightful ideas for several cross-cutting initiatives.

Awards

- *Dr. Jeffrey M. Friedman, Howard Hughes Institute Investigator, Rockefeller University, New York.* The 2010 Albert Lasker Basic Medical Research Award honors NIDDK grantee and Howard Hughes Institute Investigator, Dr. Jeffrey Friedman, and his colleague, Dr. Douglas Coleman of the Jackson Laboratory for their discovery of leptin, a hormone that regulates appetite and body weight. Dr. Friedman isolated the gene that encodes leptin and showed that fat cells release it. With their work, Dr. Friedman and Dr. Coleman have demonstrated that many overweight people suffer not from lack of willpower, but from metabolic disruptions.

- *Dr. Muneesh Tewari, Assistant Professor, University of Washington, School of Medicine, and an Assistant Member, Fred Hutchinson Cancer Research Center, Seattle, Washington.*

  Dr. Martin Zanni, Associate Professor in the Department of Chemistry at the University of Wisconsin, Madison, Wisconsin.

  These NIDDK grantees were two of the 20 recipients of the recently announced 2009 Presidential Early Career Award for Scientists and Engineers (PECASE). This is the highest honor bestowed by the U.S. government to outstanding scientists and engineers who are beginning their independent careers. Each year, the White House confers the awards--which honor and support the awardees--based on recommendations from eleven participating federal agencies.

  Dr. Tewari discovered that micro RNAs are released by cancer cells and circulate in the blood in both mice and humans. These micro RNAs are stable in blood and can be detected in smaller quantities than proteins. This seminal work was published in 2008 in *The Proceedings of the National Academy of Sciences.* Dr. Tewari's transformative R01 award upon which his PECASE nomination was based will investigate the role of these circulating micro RNAs as potential hormone-like substances that are released from one site in the body, circulate in the blood and then are potentially taken up by distant tissues, thereby regulating transcription. If his hypothesis is confirmed, these studies will have a tremendous impact on potential therapeutic strategies related to a number of metabolic diseases including diabetes and obesity.

  Dr. Zanni was honored at the NIDDK 60th Anniversary Scientific Symposium with an NIDDK Early Career Investigator Award. Dr. Zanni is an outstanding young investigator at the forefront of developing novel spectroscopy methodologies for

studying the molecular mechanisms by which biomolecules cause disease. In particular, he is well known for his accomplishment in applying two-dimensional infrared (2D-IR) spectroscopy to uncover key details about amylin toxicity in type 2 diabetes.

- *Dr. Reed Larsen, Professor of Medicine, Brigham and Women's Hospital, and Chief of the Division of Endocrinology, Diabetes and Hypertension, Harvard University.* A long-term NIDDK grantee, Dr. Larsen is the recipient of the prestigious Sheikh Hamdan bin Rashid Al Maktoum Award for Medical Sciences. This award was established with the primary aim of rewarding excellence in biomedical research. Dr. Larsen was selected in recognition of his many contributions to the field of thyroid physiology, pathophysiology and disease. He will travel to Dubai in December to receive the award at the Emirates Endocrine Conference.

In Memoriam

- *Dr. Steven Elbein, M.D., Professor of Internal Medicine, and Chief of the Section on Endocrinology and Metabolism, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina.* A former NIDDK grantee, Dr. Elbein died unexpectedly in June. He joined Wake Forest just eleven months before his death. Earlier in his career, Dr. Elbein held positions at the University of Utah and the University of Arkansas. Dr. Elbein's work on polymorphisms that contribute to the risk of diabetes, especially Type 2 diabetes, broke new ground in the field and helped to elucidate previously unappreciated concepts in the pathophysiology and genetic susceptibility of the disease. He served as a regular member of the Diabetes, Endocrinology and Metabolic Diseases B Study Section from 2003 to 2007 and then as Chair of the Study Section for two years. The NIDDK expresses its condolences to Dr. Elbein's family and colleagues.

Appointments at the National Institutes of Health

- *Dr. James Anderson, Professor and Chair, Department of Cell and Molecular Physiology, School of Medicine, University of North Carolina, Chapel Hill.* A long-standing NIDDK grantee, Dr. Anderson has been appointed to a senior NIH leadership position as Director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives. Prior to his appointment at Chapel Hill, Dr. Anderson was Professor of Medicine and Cell Biology, and Chief, Section of Digestive Diseases, Yale School of Medicine. He has extensive clinical experience in both internal medicine and hepatology, and is considered among the top authorities in the world in his primary research field of tight junctions and paracellular transport. With experience in clinical medicine, academic research, and administration, he has a broad understanding of the biomedical research spectrum that will serve him and the NIH well in his new position as Director of a Division whose mission includes identifying emerging scientific opportunities, rising public health challenges, and scientific knowledge gaps that merit further research. The Division he will lead is responsible for planning and implementing trans-NIH initiatives supported by the Common Fund and

for coordinating research related to AIDS, behavioral and social sciences, women's health, and disease prevention.

Retirements of NIDDK Staff Members

- *Dr. Carolyn Miles, Director, Clinical Obesity and Nutrition Program, and Project Scientist for the Longitudinal Assessment of Bariatric Surgery (LABS), Division of Digestive Diseases and Nutrition.* Dr. Miles has also served as the Project Scientist for a Phase III clinical trial on the use of glutamine in parenteral nutrition for surgical intensive care patients. She has represented the NIDDK on the NIH Nutrition Coordinating Committee and has chaired several Clinical Studies Working Group Committees, including the committee to develop a U34/U01 clinical studies mechanism, and a committee on development of ancillary study guidelines and a data sharing policy for multi-center clinical studies.

- *Dr. Ken May, Director, Gastoenterlogy Neuroendocrinology, Transport and Absorption, and Nutrient Metabolism Programs, Division of Digestive Diseases and Nutrition.* Dr. May also has also served as Budget Coordinator for the Division. He previously served in the NIDDK Review Branch as a Scientific Review Officer and then later as Deputy Chief. Dr. May has received a number of honors and awards since joining NIDDK. Most recently, he received the 2010 Research Service Award from the American Gastroenterological Association for his efforts in advancing gastroenterological science and research.

II. CONSIDERATION OF SUMMARY MINUTES OF THE 183RD COUNCIL MEETING

A motion was made, seconded, and passed by the Council to accept the minutes of the 183rd Council meeting.

III. FUTURE COUNCIL DATES

Dr. Rodgers called the Council's attention to the following future meeting dates. Although NIDDK expects that each meeting will be one day, Council members were asked to reserve two days to ensure flexibility should the need arise for a longer meeting.

2011
February 16-17 (Wednesday and Thursday)
May 11-12 (Wednesday and Thursday)
September 7-8 (Wednesday and Thursday)

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

IV. ANNOUNCEMENTS
Dr. Stanfield

Confidentiality

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

Conflict of Interest

Council members were reminded 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.

Dr. Stanfield 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.

Dr. Stanfield noted procedures regarding Council members with positions at multi-campus institutions of higher education. An employee may participate in any particular matter affecting one campus of a multi-campus institution of higher education, if the employee's financial interest is solely employment in a position at a separate campus of the same multi-campus institution, and the employee has no multi-campus responsibilities.

To ensure that a member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. A statement is provided for the signature of the member, and this statement becomes a part of the meeting file. Dr. Stanfield directed each Council member to his or her folder containing a statement regarding the conflict of interest in his or her review of applications. He asked each Council member to read the statement carefully, sign it, and return it to NIDDK prior to leaving the meeting.

V. REPORT FROM THE NIDDK DIRECTOR
Dr. Rodgers

Dr. Rodgers reviewed the status of two strategic plans and expressed his gratitude to the many scientists, voluntary groups, patient advocates, and members of the public who are providing input to these important planning processes.

Strategic Plan for NIH Obesity Research

Dr. Rodgers updated the Council on the development of a new Strategic Plan for NIH Obesity Research. A draft developed by the NIH Obesity Research Task Force is now available on the NIH website for a one-month public comment period. The draft reflects rapid progress in obesity research and new scientific opportunities that have emerged in the years since NIH published the first Obesity Research Strategic Plan in 2004. The new Plan will serve as a guide to accelerate a broad spectrum of research toward developing new and more effective approaches to address the tremendous burden of obesity, so that people can look forward to healthier lives. To gather external input, the NIH sent an initial draft in the spring to scientists in obesity research-related fields, as well as to voluntary and professional health organizations. Dr. Tso and Dr. Kaufman of the Council provided input during that review. The draft was subsequently revised, based on the feedback received, before posting on the NIH website. Research challenges and opportunities identified at meetings and workshops have also helped shape the draft and will continue to inform the NIH obesity research planning process. Dr. Rodgers encouraged the Council members to review and provide input to the current draft. (http://www.obesityresearch.nih.gov)

Strategic Plan for Diabetes Research

As the leader of the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC), the NIDDK has been spearheading the compilation of research advances and emerging opportunities in diabetes research for inclusion in a strategic planning report currently being prepared under the auspices of that Committee. Several past and present Council members have assisted with the development of this plan over the past 18 months. A broad array of opportunities has been identified ranging from pursuing very fundamental research on diabetes genes to finding ways to translate more effectively clinical findings into practice for the benefit all Americans with diabetes or at risk of developing it. This plan is expected to serve as a guidepost for federally-supported diabetes research at NIH and other agencies for the next decade. The document is in the final stages of review by the Coordinating Committee and the NIH, and will subsequently be posted on the NIDDK website for public comment. Dr. Rodgers acknowledged the efforts of Dr. Judy Fradkin, Director of the NIDDK Division of Diabetes, Endocrinology and Metabolic Diseases, in leading this effort.

Follow-up from Council Forum on Informatics

In follow-up to the discussion at the previous Council meeting regarding NIDDK's plans to develop the Consortium Interconnectivity Network (DKCOIN), Dr. Rodgers reported that a version of this resource is now live and accessible on the NIDDK website (http://www.dkcoin.org). The goal of DKCOIN is to interconnect the data from four NIDDK basic science consortia to enable individuals to search for and retrieve information with ease. DKCOIN represents a proof-of-principle experiment in developing a broader NIDDK informatics effort that can serve the wider NIDDK community of investigators and provide information regarding mission-specific questions. The NIDDK Working Group largely responsible for bringing this resource to life included NIDDK staff members Kristin Abraham, Olivier Blondel, Art Castle, and Ron Margolis. Extramural members included Mark Magnuson, and J.P. Catelier, both at Vanderbilt; Rick Macondo at the Medical College of Georgia; and David Steffen and Neo McKenna both at Baylor's College of Medicine.

Dr. Rodgers noted that the NIDDK carefully considered the comments provided by the Council when this topic was discussed at the last meeting. He underscored that the NIDDK is not attempting to replicate the caBIG initiative of the National Cancer Institute. Rather, by integrating and coordinating four existing NIDDK databases and resources, DKCOIN will provide an important portal for the investigative community.

Fiscal Year 2011 Budget

As reported previously, the House and Senate Appropriations Subcommittees for NIH held hearings this spring and subsequently passed their respective versions of an appropriations bill for the Departments of Labor, Health and Human Services, Education, and Related Agencies. Both versions included a 3.2 percent increase (a $1 billion increase) for NIH over the Fiscal Year 2010 level--the same amount as the President's budget request. On July 29, the full Senate Committee passed its bill, which allocated a 2.8 percent increase to NIDDK. The full House committee has not taken action on the House Subcommittee mark. At this point, the NIDDK is preparing to start the new fiscal year on October 1, 2010, under a Continuing Resolution, most likely at the Fiscal Year 2010 funding level. The expectation is that there will be an omnibus spending bill enacted at some point in the future.

Dr. Rodgers brought to the Council's attention an important provision in the Senate appropriations bill that would transfer $50 million from the NIH Institutes and Centers to the Office of the NIH Director to initiate and launch the CURES Acceleration Network (CAN). This Network is established in law as part of the President's Healthcare Reform effort. The Network will provide a new mechanism at the NIH for making awards to accelerate the development of high-need cures. These cures are defined as drugs, biological products, or devices that are a priority to diagnose, mitigate, prevent, or treat the harm from any disease or condition for which the incentives for commercial markets are unlikely to result in any adequate or timely development. Awards are expected to be made quickly to further the rapid movement of discoveries from the laboratory bench,

through the development, testing, and regulatory review process, and into the hands of the patients who need them. This initiative is viewed as an important step forward in bridging the ever-widening gap between basic and clinical research--often referred to as the "Valley of Death," where many promising new ideas languish for various reasons.

VI. ADVISORY COUNCIL FORUM: The Molecular Libraries Initiative

Dr. Rodgers introduced the Forum by providing a brief overview about the importance of small molecules. In research, small molecules have proven to be an extremely valuable means of exploring biological functions at the molecular and cellular levels, and *in vitro* and *in vivo* studies. In medicine, many new pharmaceuticals for treating diseases have arisen from the discovery of small molecules and compounds. In the high-throughput screening (HTS) process, existing or newly developed assays are used to rapidly screen tens or hundreds of thousands of small molecules and compounds to identify those that demonstrate desired properties as chemical probes. Such probes can be used to advance knowledge about a biological target (such as a gene, cell, protein, or pathway), to identify new targets, or to serve as pre-therapeutic leads for drug development. The capacity for HTS for drug development had been built up within the pharmaceutical and biotechnology sectors for many years, but not in the public sector. With the advent of the resources provided by the NIH Molecular Libraries Initiative, public sector scientists were given access to centralized HTS and related technology for small molecule discovery. Dr. Rodgers said that the Forum would include three presentations: (1) a historical perspective on the NIH Molecular Libraries Initiative, (2) an overview of one of the current Centers in this large-scale NIH initiative, and (3) a perspective on small molecule discovery conducted in one academic laboratory.

A. "The Molecular Libraries Program: An Integrated Approach to Chemical Biology"

Dr. Ron Margolis, Molecular and Endocrinology Senior Advisor, NIDDK, and NIDDK Representative to the NIH Molecular Libraries Program

Dr. Margolis described the Molecular Libraries Initiative--one of the first signature NIH Roadmap programs, which has grown into a fully developed program of chemical genomics (http://www.mli.nih.gov). As a research tool, chemical genomics is an important adjunct to biochemistry and molecular biology studies funded by the NIH both intramurally and extramurally.

Historical Background

Dr. Margolis provided historical background relative to the establishment of the Molecular Libraries Initiative. He presented data showing that, from 1994-2007 the number of new drugs entering the U.S. market trended downward, despite substantial annual increases in the U.S. investment in Research and Development. On the positive side, completion of the Human Genome Project in 2003 offered exciting prospects for both expanding the science base and for exploiting newly revealed, unprecedented therapeutic targets for drug development. Other technological advances also bolstered

research capabilities. The daunting challenge was to find ways to translate these enormous research opportunities into biological insights and new therapies.

Small molecules have long been of interest as possible chemical probes for research purposes and for the development of new drugs. In 2003-2004, the pharmaceutical industry focused on perhaps 500 such molecules/compounds for potential drug development--many of which were G-protein-coupled receptors. With the completion of the Human Genome Project, investigators were soon able to study many more potentially novel targets, including transcription factors. There was a growing appreciation that small molecules offered an important means of uncovering new biological knowledge, revealing disease mechanisms, and possibly opening the door to new drug development. At that time, there were about 20 academic efforts under way on small molecule discovery, mostly supported by NIH through regular research grants (R01 grants). The academic researchers involved were engaging in assay development, screening, chemistry, and technology development. However, these publicly supported scientists did not have access to the tools available to pharmaceutical researchers. No centralized, publicly supported screening process or repository for small molecule research existed to further this type of research in academia or government.

Inception of Molecular Libraries Initiative

Against this backdrop, the NIH launched the Molecular Libraries Initiative in 2004. The overarching goal was to provide research resources for the scientific community. These resources would promote the discovery and development of small molecule chemical probes as research tools, and enable the creation of comprehensive, publicly available datasets for broad-based mining of the resulting data. When possible, emphasis would be placed on new paradigms for assay development, screening, and instrumentation; new chemistry approaches; unprecedented targets and rare or neglected diseases; and enhancement of translational progress toward improvements in human health.

To realize these goals, a pilot phase was launched featuring:

- Establishment of a Small Molecule Repository for the deposit, maintenance and enrichment of a library of highly diverse compounds. The molecules that were proposed for inclusion in the Repository by academia, industry, or government were required to pass a rigorous series of tests for quality control prior to acceptance.

- Formation of a network of screening centers comprising a chemical biology program designed to develop small molecule compound probes.

- Creation of a comprehensive public database of chemical structures and their biological activities.

The pilot phase also included a series of technology development initiatives, as well as some other pilot studies involving development of tools such as chemical informatics.

Initially, there was an imaging component; however, imaging functions were later placed under the purview of the National Institute of Biomedical Imaging and Bioengineering.

By 2008, the pilot phase had been completed and the production phase had begun. The initial screening centers network of the pilot phase was succeeded by the Molecular Libraries Probe Production Centers Network.

Since inception of the Molecular Libraries Initiative, 17 of the 27 NIH Institutes and Centers of the NIH have become involved in the Program. Leadership has been provided by the National Human Genome Research Institute and the National Institute of Mental Health, but representatives from many other Institutes, including the NIDDK, have contributed to this effort.

Funding for the Molecular Libraries Initiative has transitioned over time from the NIH Roadmap to the NIH Director's Common Fund. Beginning in 2012, funding is slated to transition out of the Common Fund to other sources yet to be determined.

Interface of Molecular Libraries Initiative with the Drug Development Process

Dr. Margolis presented a continuum showing the interface of the Molecular Libraries Initiative with the drug development process. Until 2003-2004, public-sector science support for small molecule discovery was focused mainly on the first step of the process--the identification of genetic, cellular or molecular targets or pathways. However, the establishment of the Molecular Libraries Initiative expanded public sector support to encompass additional early steps, such as assay development, high-throughput screening, and the development of chemical probes based on the matches made during the screening process ("hit-to-probe"). Public investments in these areas seemed reasonable, given that the probability of success and the cumulative costs of this type of research were relatively favorable early in the process. Later in the process, the scientific and regulatory challenges of bringing a new drug to market militated against success and caused costs to balloon. It was generally agreed that public support should transition to other sources of support whenever small molecules identified for research purposes also showed potential for drug development. Such molecules (drug "leads") would then move from public sector support into a privately funded process that included: optimization of the promising molecule(s) through medicinal chemistry and other means--followed by phased clinical trials, regulatory review, and additional safety monitoring.

Current Activities of the Molecular Libraries Probe Production Centers Network

The Network currently comprises nine centers funded through a cooperative agreement grant mechanism. The main objective of the Centers Network is to develop 40 to 50 high-quality small molecule chemical probes per year, and also to maintain and expand the diverse chemical library in the NIH Small Molecule Repository. Complementing the Network are studies performed in about 60 academic sites that are engaged in small molecule discovery with project funding from a variety of sources, including project-based grant support from the NIH and private foundations. Data from both the Centers

Network and the academic efforts feed into an NIH-funded central, publicly accessible data repository, PubChem, through a partnership of the Molecular Libraries Initiative and the National Library of Medicine's National Center for Biotechnology Information (http://pubchem.ncbi.nlm.nih.gov).

Dr. Margolis described the structure and operations of the Centers Network, which comprises comprehensive centers, specialized screening centers, and chemistry centers. There are four comprehensive centers, which have comprehensive screening capabilities, informatics components, and chemistry resources. The specialized centers have very specific capabilities--for example, a focus on ion channels or multiplex assays. There are also specialized chemistry centers that support the entire Network with both synthetic and medicinal chemistry capabilities. Of the nine centers in the Network, one is located at the NIH--the NIH Chemical Genomics Center (NCGC). The NCGC is a comprehensive center that optimizes biochemical, cellular and model organism-based assays submitted by the biomedical research community; conducts automated high-throughput screening (HTS); and performs chemistry optimization on confirmed matches ("hits") resulting from the screening process. Its objective is to produce chemical probes for dissemination to the research community for the study of protein and cell functions, and the investigation of biological processes relevant to physiology and disease.

In general, researchers propose assays to the Centers Network for testing against chemical entities in the Small Molecule Repository through a series of initiatives that include research grants (R21, R03 and R01), as well as a fast-track mechanism. When a proposed assay is accepted by the Network for study, a standard form (Material Transfer Agreement) is executed to protect the assay, the assay provider, and the Center that will do the research with respect to intellectual property rights. The assay is transferred to a relevant center, where it may undergo some pre-screening adaptation, miniaturization, and informatics before it is used to screen compounds in the Small Molecule Repository. Once the screening process produces and validates an activity match ("hit") between the assay and a small molecule or compound, a decision is made as to whether the chemistry of that particular compound renders itself amenable to further manipulation and perhaps optimization. If so, chemistry resources are applied. More often than not, the project results in a successful compound that represents a significant improvement to the current state of the art. The results of the process are placed in PubChem two weeks after validation.

In essence, the Network is a multidisciplinary team effort involving the assay provider, the NIH, and NIH-funded scientists in the Centers Network. The output of the Network is in the form of the chemical probes and related data that are disseminated through PubChem, probe reports, publications, and the NCBI Bookshelf—a compilation of probe reports readily available online (http://www.ncbi.nlm.nih.gov/books/NBK47352/). The objective is to increase the availability of high-quality chemical probes that represent a significant improvement on those currently available. All products of the Network are freely available to the public throughout the world.

The Network's track record over the last five years has been strong, with numerous assays that have turned into one or more probe projects. These are the biological tools for target validation and drug discovery. This work has engaged the breadth and depth of expertise in the research community, including such fields as the neurology, virology, oncology, nephrology, endocrinology, and metabolism, and, importantly, it has underscored the importance of integrating biology and chemistry. The projects are relevant to the missions of many of the NIH Institutes and Centers. For the NIH, this is a performance-based project, i.e., the resources provided to the Centers is a function of their productivity.

The productivity of the Molecular Libraries Initiative from 2005-2010 is noteworthy. During that time period, the research that was conducted involved 375 primary assays, 451 probe projects, and 386 targets--resulting in 169 chemical probes from which 95 drug leads were developed. Dr. Margolis noted that a chemical probe development project usually takes about 18 months of pre-clinical development, and that numerous probes have been produced relevant to NIDDK mission areas.

PubChem

Dr. Margolis elaborated on the value of PubChem, which he considers to be one of the most important tools developed through the Molecular Libraries Initiative. PubChem is an on-line service that permits an individual to search for information by assay, compound, or chemical substance. The importance of PubChem as a research tool is evidenced by its use. The database is accessed between 50,000 and 60,000 times a day. PubChem has continued to evolve--providing more capabilities for the user. One module, the Bioactivity Analysis, summarizes information across millions of substances and compounds and thousands of assay records. The data can be searched and mined in many different ways. Another tool is the Selected Records Tool. If a researcher has identified a set of compound records, he can immediately identify the subsets for which there are some bioactivity experiments and further annotation. The search can be performed by assay and by specific compound.

Differences Between Molecular Libraries Initiative and Academic Laboratories

Dr. Margolis noted that the Molecular Libraries Initiative and academic laboratories--which engage in small molecule discovery through the regular NIH grant-making process--are distinct, complementary, and sometimes intersecting in their interests. Both approaches foster opportunities for greater collaboration among government, academia, and private interests.

Some of the differences between the Molecular Libraries effort and the academic laboratories relate to intellectual property issues. The NIH must meet public-policy needs for disclosure, whereas academic institutions may have an interest in developing proprietary outputs. Of course, once the NIH makes a chemical probe publicly available, the assay provider can develop intellectual property rights around subsequent work.

Differences in scope are also apparent. The NIH has deliberately sought great breadth and diversity in its Small Molecule Repository. As of July 2010, there were just under 390,000 compounds in that diverse collection. In contrast, most academic laboratories focus on libraries that are perhaps a little less diverse, tailored to specific interests, and generally include 50-150,000 compounds. Differences between the two approaches can also be found in the breadth and diversity of the assay screening technologies employed.

Future Directions

Looking toward the future, Dr. Margolis said that the output from the Molecular Libraries Initiative is expected to continue--with articles in the literature, PubChem listings, public availability of new chemical probes, and the identification of new targets and pre-therapeutic leads. Discussions are already under way across the NIH about the potential roles the Institutes may play in the transition phase in funding slated for the Program in 2012, and whether some of the current activities may become smaller and more focused. Dr. Margolis offered his belief that the defining legacy will be in PubChem, the Small Molecule Repository, and the appreciation of chemical genomics as an important tool in discovery.

Council Questions and Discussion

This Program seems to be a great resource for the research community. What is the transition between the dissemination of knowledge about a new chemical probe and its actual use by the broad research community? Can researchers buy a probe commercially or will the Program develop quantities of a small molecule and make them available? Dr. Margolis said that, when a probe is declared and a project ended, 50 mgs. of the small molecule are maintained--half for entry into the Small Molecule Repository and half for distribution to researchers upon request. The probe's structure is also published, so that chemists can synthesize it. In addition, some of the large chemical supply houses market probes of particular interest.

The logic of this Program, which appears well-founded, is that it can enable academia to pursue meritorious ideas that, for whatever reasons, would not be pursued by industry. However, one problem is that academics may want to repeat experiments, or do experiments that interest industry. If so, the value added by the Program would be questionable. From the experience to date, what has been the level of innovation of the actual work proposed compared to ideas that might have arisen in any event from the literature and from other knowledge commonly shared by scientists in academia and industry? How is innovation evaluated? Dr. Margolis replied that the NIH has been wrestling with this issue. Most of the assays proposed for testing in the Molecular Libraries process are submitted to NIH through the peer review system, which provides a conservative evaluation--and of those submitted, many are novel. The NIH Molecular Libraries Initiative's Project Team tries to identify and move forward those that have novel approaches, new potential targets not being addressed elsewhere, and reasonable peer review scores.

Has the NIH considered or planned to have a meeting with industry, in a pre-competitive way, to compare the screening experience of the Molecular Libraries Program with that of industry in order to learn how NIH might maximize the unique contributions of the publicly funded enterprise? Dr. Margolis replied that there is no formal meeting planned; however, the Molecular Libraries Initiative has an external evaluation committee. About two-thirds of its representatives are from the pharmaceutical industry. Thus, there is a continuing interaction and dialogue with industry about the Program. In many instances, industry has offered assays for screening, and in some cases, compounds. Some companies seem to be moving away from their former operational models because they now believe that the public sector is better suited to conducting the early stages of small molecule discovery, and that industry is better suited for the later drug-development stages. This transition could result in more compounds being identified as pre-therapeutic leads that industry might pursue.

Given the apparent success of this Program, why might it be downsized in the future? Are there components that haven't worked so well? Why would NIH dismantle parts of the terrific infrastructure it has built, particularly if NIH wants publicly funded researchers to be the early screeners? Dr. Margolis replied that this Program is subject to the procedures of the Common Fund, which provides its financial support. The Common Fund supports projects for a defined funding period, at which point projects must transition to other funding sources. For the Molecular Libraries Program, that transition is slated for 2012. Detailed discussions have not yet fully begun about alternative funding sources. There may be potential interest by individual Institutes, or a consortium of NIH components, in funding one or more Molecular Library Centers that focus on mission-relevant scientific disciples or disease areas.

How can this Program be shared with the larger public, particularly advocacy groups and patients? How can patients who are affected by diseases, and the advocacy groups that represent them, understand the impact of this Program in terms of new treatments? Dr. Margolis said that the public face of the Program is essentially PubChem. Background information is also available on the Molecular Libraries Initiative website (http://www.mli.nih.gov). Because the Molecular Libraries Program is engaged in early-stage small molecule discovery for research purposes, the chemical probes it produces require considerable additional research by others to determine whether they have relevance to one or more diseases and/or potential uses as pre-therapeutic agents. Dr. Margolis noted that the CURES Network Dr. Rodgers mentioned may ultimately help to fill in the gap between small molecule discovery research and its clinical application.

B. "The NIH Chemical Genomics Center and Molecular Libraries: Creating Tools for Discovery"
Dr. Chris Austin, Director, NIH Chemical Genomics Center, and Senior Advisor for Translational Research, Office of the Director, National Human Genome Research Institute

Dr. Austin founded the NIH Chemical Genomics Center (NCGC) in 2003, and has built it into one of the leading centers for high-throughput screening, chemical probe

development, and chemical genomics. A developmental neurogeneticist by training, Dr. Austin came to the National Human Genome Research Institute (NHGRI) in 2002 from the private sector, where his work focused on genome-based discovery of novel targets and drugs. As NHGRI's Senior Advisor for Translational Research, Dr. Austin is responsible for initiation of programs to determine gene function and therapeutic potential across the genome. In this role, he spearheaded the Knockout Mouse Project (KOMP), a large-scale transcriptome study of mouse tissues, and the Molecular Libraries Roadmap Initiative, of which NCGC is a part.

Dr. Austin pointed out that the NIH Chemical Genomics Center (NCGC) was the first component of the NIH Molecular Libraries Initiative to produce innovative chemical tools for use in biological research and in drug development (www.NCGC.nih.gov).

The inception of the NCGC dates to 2004, when a pilot phase addressed early administrative and scientific issues. About a year later the full-scale Center was established. Administratively, the NCGC is an intramural activity within the National Human Genome Research Institute (NHGRI); however, functionally, it is a trans-NIH effort, with funding from the NIH Common Fund. About 90 percent of collaborations involve extramural scientists. When the Molecular Libraries Screening Centers Pilot phase began NCGC competed for one of the slots and was accepted as member of the consortium.

Overview: Purpose, Scope, Staffing

The overarching purpose of the NCGC is to connect sophisticated high-throughput technologies with unmet research and medical needs. Projects are mutually-dependent collaborations between NCGC staff and other scientists. The NCGC provides expertise in areas such as high-throughput screening, medicinal chemistry, informatics, and **early** aspects of drug development. The scientists external to NCGC provide expertise in disease areas, targets (e.g., genes, cells, protein, pathways), and experimental systems, such as animal models. Emphasis is placed on projects that involve novel targets, and rare or neglected diseases.

The primary focus of the collaborations is to develop chemical probes that can be used in screening small molecules or compounds to identify those that may be useful in either basic research or for drug development. For this work, the NCGC directs considerable effort to research on the development of new technologies, not simply the application of existing ones. Such technology development efforts are expensive and have a high failure rate.

The Center's scope of work encompasses the universe of diseases and targets exclusive of those already being pursued by the pharmaceutical industry. In a sense, the scope can be characterized as: "one minus P*h*arma." Applicants must present a convincing rationale for the proposed work, and demonstrate, to the satisfaction of peer reviewers, that the current state of the art is not sufficient to address the biological questions

involved. If tools and compounds already exist to do the work, then the project will not be accepted for study.

From a staffing perspective, the NCGC seems similar to a biotechnology company in that about one-third of the scientists are biologists, one-third are medicinal chemists, and one third are either informatics scientists or specialists in robotics automation. About 80 percent of the staff members are recruited from the biotechnology and pharmaceutical industries because that is where the needed expertise resides. To be hired, applicants should have compelling ideas about how to improve the drug development process, which currently has a greater than 99 percent failure rate, and, when successful, requires an investment of 15 years and as much as $1.5 billion to bring a new drug to market.

Operations

Projects usually begin with an e-mail or phone call to the Center from scientists who want to identify a small molecule in order to modulate a genetic target, cellular phenotype, or pathway. It can take between three months and three years for NCGC to work with these scientists to develop a robust, reproducible, automation-friendly assay for screening small molecules. Assays generally must pass a peer review test in order to be accepted into the NCGC pipeline. Once a chemical probe is developed from the screening process, it is evaluated against a number of qualitative criteria such as potency, solubility, and selectivity--properties that the NCGC has worked out with the requesting scientists before starting the project.

The degree to which a probe meets the pre-defined criteria will determine the next steps to be taken. About one-third of the time, probes can be refined with additional biological work and analytical chemistry, but they do not require optimization chemistry. About two-thirds of the time probes need to undergo several rounds of optimization and medicinal chemistry to enhance their properties so that they meet the agreed-upon probe criteria. The objective is not to produce a laundry list of results, but rather, to produce results of scientific value, which will be demonstrated by publications. To reduce costs and increase efficiency in this process, the NCGC minimizes reagents and maximizes the use of robotics and miniaturization in as many procedures as possible.

Dr. Austin described details of the probe-development process and the key role played by robots, each of which can be the size of large conference rooms at the NIH and are key to the rapid and comprehensive screens that are the result. He also described the extensive and diverse collections of compounds now available in molecular libraries for testing. He said that his research group once calculated that the work they do on an experiment in one week would take a graduate student eight hours a day, seven days a week, for 12 years.

In principle, the process is one of reductionism. The complexity of physiology is reduced to the greatest extent possible without eliminating physiological relevance. Image-based technologies such as High Content Screening enable the study of phenotypes; fluorescent substances such as luciferase aid the study of pathways; and enzyme readouts provide

insights into proteins. After scientists have taken the protein out of the pathway, the pathway out of the cell, and the cell out of the organism for research purposes, their findings then need to be assessed for their relevance to the whole organism.

Dr. Austin pointed to some of the advantages of the NCGC screening process. First, NCGC does not screen all compounds to a single concentration. Instead, NCGC's quantitative high-throughput screening paradigm produces pharmacology on every compound in the primary screen. [*Proc Nat Acad Sci U.S.A.* 2006; 103(31): 11473-11478.] For example, when NCGC researchers screen 400,000 compounds, they get 400,000 dose-response curves and activity profiles. This type of analysis rapidly produces a wealth of rich data regarding potency and efficacy of compounds, and also reduces the probability of false-positive or false-negative results. On average, the NCGC saves about four-to-six months of work by using this approach. Secondly, the NCGC has developed a relational browser that enables researchers to look across hundreds of targets and compounds to see their relative interactions. This browser can cluster compounds biologically, structurally, or in a relational way. Dr. Austin said that this browser should be available on the NCGC website very soon. Thirdly, NCGC promotes synergism among research fields. For example, many researchers are studying the same pathway, such as the DNA repair pathway, but in different contexts or diseases. NCGC-produced data on pathways of shared interest among scientists can spur collaborative endeavors. The NCGC process can yield results with widespread application to fields such as cancer, aging, metabolism, human development, and environmental toxicology--to name just a few.

Examples of Work Relevant to NIDDK Research Areas

Dr. Austin provided the following examples of NCGC work relevant to NIDDK research areas.

- Basic research conducted in collaboration with Brian Oliver of the NIDDK Intramural Program and Mattias Beller of the Max Planck Institutes resulted in the identification of a small molecule involved in the regulation lipid homeostasis. This finding then led to the ongoing search for novel, more specific compounds that can eliminate lipid storage without killing cells. [Beller M, et al. COPI Complex Is a Regulator of Lipid Storage. *PLoS Biology* 2008, Nov; 6(11): 2530-2548.]

- Research findings that emerged from a collaborative project with Ellen Sidransky, National Human Genome Research Institute, will permit medicinal chemistry work to move forward on small molecules that may be able to bind to and correct the misfolded protein (glucocerebrosidase) involved in Gaucher disease, and chaperone it to the lysosome where it can exert its catalytic activity. [Zheng W, et al. Three classes of glucocerebrosidase inhibitors identified by quantitative high-throughput screening are chaperone leads for Gaucher disease. *Proc Natl Acad Sci U.S.A.* 2007 August 7; 104(32): 13192-13197.]

- Collaborative work with Marvin Gershengorn of the NIDDK Intramural Program identified the first TSHR agonists and inverse agonists based a huge screen, extensive medicinal chemistry, and follow-up assays. [Neumann S, et al. Small-molecule agonists for the thyrotropin receptor stimulate thyroid function in human thyrocytes and mice. *Proc Natl Acad Sci U.S.A.* 2009 July 28; 106(30): 12471-12476.]

- Collaborations with Theodore Holman, University of California, Santa Cruz, and Jerry Nadler, Eastern Virginia Medical School, have led to the identification of compounds that can inhibit 12hLO, which is thought to be involved in the inflammatory process that leads to the death of insulin-producing cells in a mouse model of type 1 diabetes. Researchers are now building on these findings in studies with human islets. In addition to being relevant to type 1 diabetes, 12hLO is also involved in thrombosis and in multiple forms of cancer. Hence, the development of 12hLO inhibitors offers therapeutic promise for several diseases.

Disseminating Research Results

Like genome-sequencing work, screening experiments produce a wealth of data that may be valuable to the broad research community, not just the scientists involved in a specific project. To make this information widely available NCGC, as a member of the MLPCN, contributes screening data and structures of probes to the NIH data repository, PubChem, one of the databases maintained by the National Center for Biomedical Information, National Library of Medicine. (http://pubchem.ncbi.nlm.nih.gov/).

The NCGC has entered nearly 500 assays into PubChem. The NCGC also generates probe reports, which are available on the website for the Molecular Libraries Initiative (http://mli.nih.gov/mli/mlp-probes/). A probe report can provide details about a compound such as its structure, characteristics, and activities. As part of its educational and outreach initiatives to assist the research community, the NCGC has also developed an Assay Guidance Manual based on a model freely provided by the Eli Lilly Company. To date, this manual, which is available electronically on the NCGC website, has been accessed about a million times (http://assay.nih.gov/).

Council Questions and Discussion

Has the NIH run into any resistance from the pharmaceutical industry because of intellectual property issues? Dr. Austin responded that, initially, there was some resistance. At a 2005 meeting with the heads of Research and Development at major pharmaceutical companies, the NIH was urged to stop the program because companies had apprehensions about competition. However, the project continued to move forward. Now, pharmaceutical companies seem pleased that the NIH has the capability to do this type of high-throughput screening and is providing a crucial resource for the research community. Through this work, the NIH is occupying an important part on the continuum of research that ranges from early fundamental discoveries to clinical practice--thus bridging a translational gap.

Are there any competitive issues that arise once the NIH work is in the public domain? To avoid that type of issue, Dr. Austin noted that the NIH made a conscious decision not to travel too far along the drug-development continuum. He emphasized that the last thing the NIH wants to do is to poison patent space by putting into the public domain research findings that could be considered "prior art." Dr. Austin said that the pharmaceutical companies know that chemistry work is not within original patent space.

If the NCGC operates with such a high degree of efficiency, why do the costs of drug development continue to rise? According to Dr. Austin, existing data show that the costs of the work the NIH does to contribute to drug development are less than the costs that the pharmaceutical industry would expend to do the same work. However, there are high costs associated with other parts of the research continuum in which the NIH is not presently involved. The hope is that, over time, total drug development costs may be curtailed because the NIH is making its chemical probe and molecular library resources widely available. Therefore, there should be no reason for scientists to repeat experiments to obtain the data the NIH has already accrued and made freely available worldwide.

The largest drug-development costs appear to be associated with answering the key question: Is there any likelihood that a small molecule is going to help a patient? Often that question cannot be answered without conducting very costly Phase 3 clinical trials, whose ultimate results may turn out to be negative. Dr. Austin agreed and noted that, in that context, it is very important to consider that furthering drug development is not the primary purpose of the NCGC and other components of the Molecular Libraries Initiative. Rather, the chief purpose is to understand how proteins, cells and pathways work by developing chemical probes that can help identify and validate novel targets. If effective clinical interventions are subsequently developed as a result of this work, that is a welcome outcome; however, even if that does not happen, the NIH has contributed to the development of extremely valuable and broadly applicable research tools.

How do the NCGC and Molecular Library activities interact with the companies that synthesize compounds? Dr. Austin said that the primary means of interaction is through the NIH Small Molecule Repository. The NIH assembled a group of experts to make suggestions regarding how to design a gold-standard, diverse chemical library of about a half million compounds. Based on those suggestions, the NIH procured compounds from commercial companies and academic investigators. On a medicinal chemistry level, the NIH also uses contracts to obtain expertise from those companies when it is not available through in-house NIH staff.

Does the Molecular Libraries Initiative have the potential to characterize a compound quickly and thereby influence its period of patent protection, if the compound ever reaches patentability? Dr. Austin responded in the affirmative.

C. "Small Molecule Discovery in an Academic Setting"

Dr. Alan Verkman, Professor of Medicine and Physiology, and Director, Cystic Fibrosis Research Development Program, University of California, San Francisco

Dr. Verkman has a very active and diverse research program. The research activities of his laboratory are in three principal areas: mechanisms of water transport across cell membranes; biophysics of molecular diffusion and interactions in living cells; and drug discovery and lung disease mechanisms in cystic fibrosis. Dr. Verkman presently has R01 grant support from NIDDK, the National Heart, Lung and Blood Institute (NHLBI), and the National Eye Institute (NEI). He also has MERIT awards from the National Institute of Biomedical Imaging and Bioengineering (NIBIB).

Dr. Verkman thanked the NIDDK for the opportunity to describe the process of small molecule discovery from the perspective of a research laboratory in an academic setting.

Overview: Drug Development Paradigm

Dr. Verkman presented his view of the academic paradigm for drug discovery--an inverted triangle that starts at the top with over 100,000 chemicals and ends at the bottom with a single drug. The intermediate points in the process are the identification of 10-100 candidate molecules (hits) from the 100,000 chemicals screened, and the further reduction of that number to 5-10 validated hits, moving further to fewer than five leads, and finally, 3 developed drug leads, culminating in one drug. Preclinical development efforts cost about $3-5 million, whereas clinical development, including studies with an FDA-approved investigational new drug, requires an additional investment of over $500 million. The process takes many years.

Dr. Verkman pointed out that the goals of NIH and academic research organizations differ. The pharmaceutical industry is concerned about monetary value, i.e., maximizing profitability, securing intellectual property rights, and maintaining the perceived value of the company. In contrast, NIH goals include furthering support for research programs, developing and applying research tools, and facilitating drug development for rare and neglected diseases. A small academic laboratory is interested in the identification and development of novel targets and screening approaches, specifically to develop research reagents and, if everything goes well, candidate drugs. The output for such a laboratory is scientific publications and research grants.

Difficulties and Successes in Small Molecule Discovery and Validation

Dr. Verkman described the way his laboratory implements the academic paradigm. The research team selects a target, does a screen, performs the usual optimization need to transform a "hit" into a "lead," obtains biological data, and hopes, at that point, to have a useful research tool. If the resulting compound is a candidate for drug development, the lab will secure intellectual property rights early on by obtaining a provisional patent without disclosing its findings. The lab will then approach industry, foundations and

others for additional sources of support to develop the drug candidate. To do its work, the Verkman lab has accumulated a fairly large collection of synthetic, drug-like small molecules; proprietary, commercially-available compounds; and smaller collections of drugs and purified natural products. The lab has also acquired robotics and other equipment for high-throughput screening. With funding from the Cystic Fibrosis Foundation and continuing support from the NIH, the lab began to assemble these resources well before the NIH Roadmap Initiative began.

Dr. Verkman asked the Council to consider an ideal drug discovery project as a context for discussion. A target should be highly significant, disease relevant, and conceptually novel. A screen should be easy, target-specific, simple, and inexpensive. Hits emerging from the screens should be in multiple chemical classes with a good structure-activity relationship. They should also have the following characteristics: low nanomolar potency, target-specific, non-toxic, orally bioavailability, metabolic stability, stable in storage, and capable of straight-forward synthesis. A small molecule or compound should have high efficacy in a disease-relevant animal model, as well as in a brief, simple, definitive clinical trial. It is also interesting to think in advance about the probability of success of a small molecule screening project. The lowest probability of success would probably attach to an activator of wild type enzyme that is already fully active. From there, increasing probabilities of success might attach to the following, in ascending order: (1) transcription modulator, (2) stem cell differentiation regulator or disruptor of protein-protein interaction, and (3) corrector of misfolded mutant protein. The highest levels of success might be expected for an ion transport inhibitor, enzyme inhibitor, or receptor agonist/antagonist.

In this context, Dr. Verkman presented several concrete examples of projects chosen from his own research interests: urea transport inhibitors for diuretic-refractory edema; CFTR chloride channel inhibitors for polycystic kidney disease and secretory diarrhea; calcium-activated chloride channel modulators for diarrheas, cystic fibrosis and dry mouth; and auto-antibody inhibitors for an aquaporin autoimmune disease, neuormyelitis optica. Through these examples, he demonstrated some of the difficulties and successes of screen development and target validation--including how researchers progress from a small molecule "hit" to a drug "lead," and from *in vitro* to *in vivo* studies.

- *Urea Transport Project:* Based on existing knowledge, Dr. Verkman's lab tested the hypothesis that urea transport inhibitors might be effective in diuretic-refractory edema. If so, there would be a new class of diuretics, which they called "ureareticS," with the potential of treating water-retaining states. To pursue this idea, they found a method to overcome the analytic impediment that urea transport is extremely fast. Then, from an initial screen, and with minimal medicinal chemistry, they developed a novel inhibitor of urea transport that had a million times better potency than previously existing inhibitors, and also had good selectivity. However, the drawbacks for drug development were that the compound was not very stable and it did not work well in an animal model. The researchers filed a patent, and several pharmaceutical companies approached them--recognizing the merits of the project: first-in-its-class, novel target, excellent potency, and large potential market.

Nevertheless, the key weakness for drug development was the lack of efficacy data in animals. The researchers therefore screened 100,000 compounds against mouse red blood cells. One promising class of molecules emerged with the potential for inhibiting urea transport in both mice and humans. Unfortunately, its activity was not detectable in mice. Currently, the lab is working on ways to modify the class of compounds for further testing in mice. [Levin MH, et al. Urearetics: a small molecule screen yields nanomolar potency inhibitors of urea transporter UT-B. *The FASEB Journal* 2007; 21: 551-563.]

- *CFTR Chloride Channel Inhibitors for Polycystic Kidney Disease:* Dr. Verkman's lab has conducted extensive research on the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) in cystic fibrosis and other diseases. The lab has built on existing knowledge that cyst expansion in polycystic kidney disease (PKD) involves progressive fluid accumulation, which is believed to require CFTR, as well as epithelial cell proliferation. Using high-throughput screening, the lab found that two classes of small-molecule CFTR inhibitors slow cyst expansion in both *in vitro* and *in vivo* models of PKD. These results implicate CFTR in renal cyst growth and suggest that CFTR inhibitors may hold therapeutic potential to reduce cyst growth in PKD. The lab is continuing to improve these inhibitors through medicinal chemistry, and is currently selecting lead compounds for testing in mice. A key to this work was the lab's previous development of a good assay, which is now used very widely for multiple chloride channel targets. [Yang B, et al. Small-molecule CFTR inhibitors slow cyst growth in polycystic kidney disease. *J Am Soc Nephrol* 2008 19: 1300-1310.]

- *CFTR Inhibitors for the Secretory Diarrhea of Cholera:* Dr. Verkman pointed out that, when overactivated, CFTR can also cause diarrhea. Nearly a decade ago, Dr. Verkman and colleagues identified a CFTR inhibitor ($CFTR_{inh}$-172), which was about 500 times better than other CFTR inhibitors at that time, and has since been a very good research tool. It has good selectivity, potency, and metabolic stability--along with minimal toxicity. However, the lab has continued to seek even further improvements in CFTR inhibitors through the use of medicinal chemistry. For example, by combining chemicals that had desirable properties, they produced a compound that was non-absorbable, and that inhibited CFTR completely and rapidly. However, one remaining concern was that the compound could be easily washed out of the body during episodes of diarrhea. The lab therefore developed a strategy to make the compound sticky by combining it with lectins--and also to further improve its potency. The result is a group of CFTR inhibitors that has multiple excellent properties, and that has been shown to cause intestinal retention and to improve survival in a suckling mouse model of cholera. [Sonawane ND, et al. Lectin conjugates as potent, non-absorbable CFTR inhibitors for reducing intestinal fluid secretion in cholera. *Gastroenterology* 2007 Apr; 132(4): 1234-44.]

- *Calcium-Activated Chloride Channel (CaCC) Modulators*--Modulators of calcium-activated chloride channels have the potential to treat health problems such as diarrhea, cystic fibrosis, hypertension, and dry mouth. In 2008, several published

studies pointed to a critical membrane protein (TMEM16A) as being associated with calcium-dependent chloride channel activity. Dr. Verkman's research team sought to clarify the function of this protein by developing an assay to identify small molecules that inhibit or activate it. The researchers then performed laboratory studies to determine the effects of the molecules on cells. The conclusion from pharmacology studies was that the TMEM16A protein is a major calcium-activated chloride channel in salivary gland tissue, but not in airways or intestinal tissue. The challenge now is to optimize the inhibitors and activators of the protein and test them in mouse models of salivary gland dysfunction, as well as in cell and airway models of human cystic fibrosis. Dr. Verkman noted that, in related work, the lab also screened drug and natural product libraries and found that tannic acid completely inhibits calcium-activated chloride channels. Because tannic acid analogs, such as gallotannins, are major constituents of red wines and green teas, the team decided to test those products. Remarkably, the researchers found that a 1,000 fold dilution of red wine inhibited calcium-activated choride channels by more than 50 percent. Moreover, other laboratory studies in *ex vivo* models showed that gallotannins block intestinal fluid secretion and smooth muscle contraction. The Gates Foundation is now funding the lab to test gallotannins in models of diarrhea. [Namkung W, et al. Small-molecule activators and inhibitors of calcium-activated chloride channel, TMEM16A. *Pediatric Pulmonology* (Meeting Abstract) 2009; Supplement 32: 288. Namkung W, et al. Inhibition of calcium-activated chloride channels by gallotannins as a possible molecular basis for health benefits of red wine and green tea. *The FASEB Journal* 2010 Nov; 24(11): 4178-86.]

- *Inhibiting a Cell-Killing Antibody in Neuoromyelitis Optica.* Dr. Verkman described his lab's work on neuromyelitis optica (NMO), an inflammatory demyelinating disease that selectively affects optic nerve and spinal cord and is considered a variant of multiple sclerosis. This work built on a collaboration with V.A. Lennon at the Mayo Clinic, who made the incredible discovery that patients with this disease have a circulating antibody that targets a membrane water channel (aquaporin 4). It was subsequently shown, in collaboration with a European group, that direct injection of the purified antibody (NMO-IgG) will produce the characteristic lesions of the disease in the laboratory. Therefore, the best possible therapy might be to block the antibody directly with a small molecule--an approach that would represent a new way of treating an autoimmune disease. By use of a simple assay and screening techniques, the researchers found a promising compound, Arbidol, which blocks the binding of the cell-killing antibody in a dose-dependent manner in laboratory studies. Because this compound is already in use, there is no need to invest in development of a new chemical entity to achieve these effects. Remaining challenges are to obtain a therapeutic concentration of the blocking agent for testing, and to address the lack of a good animal model and clinical trials. The team is moving forward with this work with support from the Guthy-Jackson Charitable Foundation. [Lennon VA, et al. IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *Journal of Experimental Medicine*, The Rockefeller University Press 2005 Aug; 202(4): 473-477.]

Observations and Recommendations

In summary, Dr. Verkman said that a key question is: What makes a discovery project meritorious? In his view, the target and functions should be significant and novel whether the goal is to develop a research reagent or a drug candidate. The primary screen needs to be feasible, with an *a priori* likelihood of success via a rigorous method. The "hit" should be specific and verifiable, and the proposal should have good follow-on plans. For a research tool, plans should include documentation of the mechanism of action and specificity of the identified molecule. For a drug candidate, efficacy and various pharmacology studies should be planned.

Dr. Verkman next raised the issue of the relative advantages and disadvantages of small molecule screening done by an academic laboratory *versus* a large, centralized screening operation. He noted that Dr. Austin made a beautiful case for minimizing duplication of effort and attaining research success through centralized expertise, instrumentation, and compounds. However, from Dr. Verkman's experience, success is less likely and efforts are less cost-effective in large centralized facilities that separate biologists and screeners, and that may have activation barriers to use of the facilities. According to Dr. Verkman, the rate-limiting step in small molecule drug discovery is not the high-throughput screening, which is easy to learn and perform, and not overly costly. In fact, small molecule discovery is rapidly becoming a standard lab tool/approach, much as molecular biology was in the 1980s, confocal microscopy was in the 1990s, and super-resolution imaging is now.

In light of these observations, Dr. Verkman's recommendation to the NIDDK is to focus on biology more than methodology, and consider screening as a research tool for use by academic research laboratories through existing grant mechanisms--with some modifications, such as relaxation of the preference for hypothesis-driven research at the peer-review level.

Dr. Verkman thanked the NIDDK for its generous support of his research over the years, along with the Cystic Fibrosis Foundation and other sources of support.

Council Questions and Discussion

What is known about the cause of NMO antibodies, which were presented as 100 percent specific and disease-causing? Dr. Verkman replied that their cause is unknown, and there appears to be no genetic basis for them. The onset of NMO symptoms seems to correlate with some immune event, such as serve gastroenteritis. Some patients are positive to the antibodies years before they develop the disease. More research is needed to understand the reasons that the antibodies form and the way that they enter the central nervous system to cause disease.

While most of us would agree that barriers between biologists and technology experts are generally inhibitory, the proposed combination of both biological and screening expertise in academic labs may also pose challenges. For example, is good training in

high-throughput screening technology readily available for small labs? Would resources be wisely spent to provide such training and to scale small molecule discovery down from a centralized level to a laboratory level? Also, does the NIH peer review system have the metrics to evaluate whether proposals for small molecule discovery from small labs provide the necessary expertise and equipment for the intended studies? Dr. Verkman agreed that the education of screeners is necessary, but maintained that, in his experience, it is easy to teach the skills of small molecule discovery and related functions to people entering the lab without that expertise. He said that he is not certain about the best way to implement his proposal; however, scientific meetings and workshops could be a means of discussing with the research community, including peer reviewers, the idea of downsizing the small molecule discovery process to the scale of the academic laboratory.

VII. SCIENTIFIC PRESENTATION

Chronic Pelvic Pain: Opening the Black Box

Dr. Anthony Schaeffer, the Herman L. Kretschmer Professor, and Chairman of the Department of Urology, Northwestern University

NIDDK Council member, Dr. Shaeffer, is known for his pioneering work in basic and clinical research on urinary tract infections and prostatitis. He has also made major contributions to management of post-prostatectomy incontinence. Dr. Schaeffer earned his M.D. at the Feinberg School of Medicine at Northwestern University. He then did his Internship at Chicago Wesley Memorial Hospital, a Surgery Residency at McGaw Medical Center at Northwestern, and a Urology residency at Stanford University Medical Center. Dr. Schaeffer has had NIH support for his research for the past 30 years, including support for more than 20 years from the NIDDK.

VIII. CONSIDERATION OF REVIEW OF GRANT APPLICTIONS

A total of 1,460 grant applications, requesting support of $370,840,911 were reviewed for consideration at the September 22, 2010 meeting. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, an additional 1,145 applications requesting $294,064,026 received second-level review through expedited concurrence. All of the expedited concurrence applications were recommended for funding at the Scientific Review Group recommended level. The expedited concurrence actions were reported to the full Advisory Council at the September 22, 2010 meeting.

IX. ADJOURNMENT

Dr. Rodgers thanked the Council members for their attendance and valuable discussion. There being no other business, the 184th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m.

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

Griffin P. Rodgers, M.D., M.A.C.P.
Director, National Institute of Diabetes and Digestive and Kidney Diseases
Chairman, National Diabetes and Digestive and Kidney Diseases Advisory Council