

Meeting Minutes

**National Diabetes and Digestive and Kidney Diseases Advisory Council
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Department of Health and Human Services**

I. CALL TO ORDER

Dr. Rodgers

The NIDDK Director, Dr. Griffin P. Rodgers, called to order the 196th meeting of the National Diabetes and Digestive and Kidney Diseases Advisory Council at 8:30 a.m. on September 3, 2014, in Conference Room 10, Building 31 of the NIH campus in Bethesda, Maryland. Dr. Rodgers announced that there would be a re-ordering of agenda items to enable the Council to hear first from the NIH Director, Dr. Francis Collins.

A. ATTENDANCE – COUNCIL MEMBERS PRESENT

Dr. Domenico Accili
Dr. Sharon Anderson
Dr. David Brenner
Dr. Eugene Chang
Dr. Judy Cho
Dr. David Klurfeld
Ms. Ellen Leake
Ms. Robin Nwankwo

Dr. Jerry Palmer
Dr. Thomas Robinson
Dr. Jean Schaffer
Dr. Irving Smokler
Dr. Bruce Spiegelman
Dr. William Steers
Dr. Robert Vigersky
Mr. John Walsh

Also Present:

Dr. Francis Collins, Director, NIH
Dr. Griffin Rodgers, Director, NIDDK
Dr. Gregory Germino, Deputy Director, NIDDK
Dr. Brent Stanfield, Executive Secretary, NIDDK Advisory Council

B. NIDDK STAFF AND GUESTS

Abbott, Kevin - NIDDK
Abraham, Kristin - NIDDK
Agodoa, Lawrence - NIDDK
Akolkar, Beena - NIDDK
Barnard, Michele - NIDDK
Bavendam, Tamara - NIDDK
Begum, Najma - NIDDK
Best, Karen - American Urol. Assoc.

Bishop, Terry - NIDDK
Blondel, Olivier - NIDDK
Bourque, Sharon - NIDDK
Bremer, Andrew - NIDDK
Brown, Sherry - NIDDK
Buchanan, Sarah – Hlth. & Med.
Council of Washington
Byrd-Holt, Danita - NIDDK

Cadwalader, Erin - Lewis Burke
Calvo, Francisco - NIDDK
Camp, Dianne - NIDDK
Carrington, Jill - NIDDK
Castle, Arthur - NIDDK
Cerio, Rebecca - NIDDK
Chavez, Elizabeth - NIDDK
Cho, Jennifer - NIDDK
Curtis, Leslie - NIDDK
Dirks, Dale – Hlth. & Med.
Council of Washington
Doo, Ed - NIDDK
Doherty, Dee - NIDDK
Donohue, Patrick - NIDDK
Drew, Devon - NIDDK
Duggan, Emily - NIDDK
Fradkin, Judy - NIDDK
Gadbois, Ellen – NIH/OD
Gansheroff, Lisa - NIDDK
Gossett, Ben - NIDDK
Graves, Reed - CSR
Grey, Michael - NIDDK
Guo, Xiaodu - NIDDK
Haft, Carol - NIDDK
Hamilton, Frank - NIDDK
Hanlon, Mary - NIDDK
Hoffert, Jason - NIDDK
Hoofnagle, Jay - NIDDK
Hoover, Camille - NIDDK
Hoshizaki Deborah - NIDDK
Hunter, Christine - NIDDK
James, Stephen - NIDDK
Jenkins, Ann - NIDDK
Jones, Teresa - NIDDK
Karp, Robert - NIDDK
Ketchum, Christian - NIDDK
Kimmel, Paul - NIDDK
Kirkali, Ziya – NIDDK
Krause, Michael – NIDDK
Kuczmarski, Robert - NIDDK
Kusek, John - NIDDK
Laakso, Joseph - The Endocrine Society
Laughlin, Maren - NIDDK
Li, Yan - NIDDK

Love, Dona - NIDDK
Malik, Karl - NIDDK
Malozowski, Saul - NIDDK
Maruvada, Padma - NIDDK
Margolis, Ronald - NIDDK
Martey, Louis - NIDDK
Miller, David - NIDDK
Moxey-Mims Marva - NIDDK
Mullins, Christopher - NIDDK
Mullsteff, Clairisse - NIDDK
Narva, Andrew - NIDDK
Pawlyk, Aaron - NIDDK
Pellnitz, Lori - SRI International
Perrin, Peter - NIDDK
Perry-Jones, Aretina – NIDDK
Pike, Robert – NIDDK
Podskalny, Judith - NIDDK
Ramani, Rathna - NIDDK
Rankin, Tracy - NIDDK
Rasooly, Rebekah - NIDDK
Reiter, Amy - NIDDK
Roberts, Tibor - NIDDK
Rosenberg, Mary Kay - NIDDK
Rosendorf, Marilyn - NIDDK
Roy, Cindy - NIDDK
Sastry, Chandan - NIDDK
Savage, Peter - NIDDK
Sheard, Nancy - CSR
Sheet, Dana - NIDDK
Sherker, Averell - NIDDK
Shepherd, Aliecia - NIDDK
Silva, Corinne - NIDDK
Singh, Megan - NIDDK
Star, Robert - NIDDK
Stoeckel, Luke - NIDDK
Tatham, Thomas - NIDDK
Teff, Karen - NIDDK
Unalp-Arida, Aynur - NIDDK
Vassileva, Maria - Foundation for NIH
Vinson, Terra - NIDDK
Weiner, Jeff - NIDDK
Whitaker, Sanya - Foundation for NIH
Wu, Ping - CSR
Yang, Jian - NIDDK

II. A View from the NIH Director *Dr. Francis Collins*

Dr. Rodgers introduced Dr. Collins, who has been the NIH Director since 2009. Dr. Collins served as Director of the National Human Genome Research Institute from 1993-2008. He is well known for his leadership of the international Human Genome Project, and for his discoveries of disease genes as a physician-scientist. Before joining the NIH, Dr. Collins was a Howard Hughes Medical Institute investigator at the University of Michigan. An elected member of the Institute of Medicine and the National Academy of Sciences, Dr. Collins was awarded the Presidential Medal of Freedom in November 2007, and received the National Medal of Science in 2009.

In opening his remarks, Dr. Collins said that the NIDDK is a central part of the NIH. The Institute conducts and supports research across a wide variety of important areas to understand the underlying causes of major diseases affecting the public, and to discover ways to treat and prevent them. In these times of resource constraints, Dr. Collins said that NIH leaders need to be thoughtful, creative, and able to set and adhere to priorities. He complimented Dr. Rodgers on his leadership of the Institute, and also the work of his Deputy, Dr. Gregory Germino, and other members of the NIDDK.

Dr. Collins gave a brief update on NIH efforts to accelerate the development and testing of a vaccine to combat the Ebola virus. Early human testing of a vaccine candidate, co-developed by NIH and industry, began in early September 2014 at the NIH Clinical Center. Assessments are being made of its safety and ability to generate an immune response, and to determine whether it should be tested on a larger scale. In addition, other therapeutic approaches are being pursued, including a possible cocktail of monoclonal antibodies that shows promise in animal studies. Dr. Collins said that it will be essential to have the capacity to scale up production of therapies that are shown to be safe and efficacious. He noted that many HHS components and other organizations are collaborating to fight Ebola, including the Centers for Disease Control and Prevention (CDC) and the Departments of State and Defense.

Dr. Collins next turned to the three main topics of his presentation: 1) the NIH budget and workforce; 2) trans-NIH Programs; and 3) the Accelerating Medicines Partnership (AMP).

NIH Budget and Workforce

Dr. Collins presented inflation-adjusted data showing the real growth in the NIH budget from 1990 to the President's Budget request for FY 2015. He noted the relatively steady upward trend in funding until 1998, which marked the beginning of a five-year period of budget doubling. However, when the doubling ended in 2003, the NIH budget began a decline that continues to the present day--except for a two-year funding bolus from the American Recovery and Reinvestment Act of 2009. Recent measures to reduce the

nation's fiscal deficit have constrained funding for domestic discretionary programs such as the NIH. Dr. Collins pointed out that the NIH probably would have been better off with a stable 3.7 percent annual real growth since 1990, instead of the rapid growth of the budget doubling period followed by decline. He said that a steady, stable, predictable trajectory of real growth, on the order of four percent annually, would enable the NIH to better plan and balance its programs, support researchers across their career spans, and avoid the problems of a budget roller coaster ride.

Turning to the biomedical research workforce, Dr. Collins pointed to the downward trend in success rates since the end of the budget doubling in 2003. Prior to that time, annual success rates had typically ranged between 25 and 35 percent. In 2013, the success rate was 16 percent, which means that many excellent applications went unfunded. A low success rate limits the ability of the NIH to recruit and retain talented individuals in research careers, especially individuals from groups that have been traditionally under-represented in biomedical research.

The NIH has initiated several efforts to nurture science, and support a diverse, well-trained, highly creative workforce. For example, to increase diversity, the NIH is supporting the Building Infrastructure Leading to Diversity (BUILD) Program, the National Research Mentoring Network (NRMN), and the Broadening Experiences in Science Training (BEST) Program. To nurture young scientists, the NIH created Early-Career Investigator Awards, the NIH Director's Early Independence Award, and the NIH Pathway to Independence Award. To cultivate innovation, the NIH established the NIH Director's Pioneer Award, the New Innovator Award, and the Transformative Research Award.

Dr. Collins elaborated briefly on some of these programs. The BEST Program gives graduate students and post-doctoral scholars exposure to a variety of career paths, recognizing that only about 25 percent of them will end up in the tenure track at academic institutions. The Early Independence Award makes it possible for highly talented Ph.D. or M.D./Ph.D. students to move directly from completing their doctoral research into an independent research career with appropriate institutional support.

The Pioneer Award enables investigators to be funded without having to provide the extensive amount of preliminary data typically required for a regular research project grant (R01 grant). Applicants for Pioneer Awards describe a general vision for their research projects, but are not required to describe specific aims or details. Their applications must represent an entirely new research direction and should include novel, pioneering experimental approaches. Dr. Collins noted that a 10-year evaluation of Pioneer Awards concluded that research funded through that mechanism is more innovative and has a higher impact than research funded through R01s, and about equivalent on those parameters to research funded by the Howard Hughes Medical Institute (<http://commonfund.nih.gov/pioneer/evaluations>). As a result of these findings, several NIH Institutes are now exploring the creation of their own versions of the Pioneer

Award. Dr. Collins said that the productivity of the Pioneer Award argues for greater NIH investment in a flexible research model, through which investigators use their own creativity to generate valuable scientific knowledge.

Dr. Collins said that the recruitment and retention of physician-scientists in research careers remains of great concern. The NIH is acutely aware of the declining numbers of M.D.s who are engaging in full-time or majority-time research activities. Without abatement, this trend is likely to continue to the point that, in another 10 years, there may be virtually no M.D.s engaged in research. That prospect is especially troubling given the unique contributions that M.D.s make in exploiting the scientific opportunities now opening up in clinical and translational research.

The NIH established a Physician-Scientist Workforce Working Group under the auspices of the Advisory Committee to the Director NIH (ACD) to analyze the current composition and size of the physician-scientist biomedical workforce and make recommendations for NIH actions to help sustain and strengthen a robust and diverse workforce. The Working Group defined “physician-scientists” as scientists with professional degrees, who have training in clinical care and who are engaged in independent biomedical research. In June 2014, the Working Group presented a report to the ACD that made several recommendations including the establishment of a granting mechanism specifically for physician-scientists that would be similar to the NIH Pathway to Independence Award; expansion of loan repayment opportunities; support for pilot grant programs to test existing and novel approaches to improve and/or shorten research training; and intensified efforts to increase diversity in the physician-scientist workforce (http://www.acd.od.nih.gov/reports/PSW_Report_ACD_06042014.pdf).

Trans-NIH Programs

Dr. Collins described the origin of the statutory trans-NIH program known as the Common Fund. This program is the successor to the NIH Roadmap for Medical Research established administratively by former NIH Director Elias Zerhouni. The Common Fund is continuing in the path set by the NIH Roadmap as a mechanism for proactively supporting compelling research projects that would benefit the scientific community, but that do not fit neatly into the research portfolio of any single Institute. Prior to the Roadmap, such research was likely to go unfunded unless Institute Directors successfully garnered voluntary contributions for trans-NIH initiatives from other NIH components. In June 2014, the NIH celebrated the tenth anniversary of the NIH Roadmap/Common Fund with a scientific symposium and short videos prepared by investigators, some of which were posted on the NIH Director’s blog. An article in *Science* by Drs. Collins, Zerhouni and Wilder provided a retrospective view (<http://www.sciencemag.org/content/345/6194/274.full>).

Some major Common Fund efforts supported from FY 2004-2013 include programs on big data, high-risk/high-reward science, technologies and methods, research-team

capacity building, and clinical/translational research. Proposed Common Fund projects are vetted broadly, both within and outside the NIH, to determine whether they are appropriate for support. Over \$4 billion has been invested in Common Fund research projects since the Program's inception--all managed by multi-Institute teams of NIH program staff.

Dr. Collins noted that the NIDDK has made significant leadership and staffing contributions to Common Fund efforts. One example is the Metabolomics Initiative, which is spurring the development of this emerging field through technology development, standards synthesis, and data-sharing capabilities. Another example is the Human Microbiome Project, which has provided new knowledge about the role of microbes in health and disease, including some unexpected insights about diabetes and obesity. Dr. Collins noted the project on Human Health and Heredity in Africa, which is building research capacity in Sub-Saharan Africa for large-scale studies of genetic and environmental contributions to disease, including kidney disease. The NIH has undertaken this project in conjunction with the Wellcome Trust and the American Society of Human Genetics. In looking back at research efforts of the Common Fund to date, Dr. Collins said that the most successful projects have met not only the eligibility criteria for funding, but have also incorporated from their outset clear goals and benchmarks achievable within the maximum ten-year funding period. For 2014, the Common Fund has an appropriation of \$533 million, an amount equivalent to about 1.7 percent of the NIH budget, which is well below the five percent ceiling set in law by the Congress.

Accelerating Medicines Partnership (AMP)

Dr. Collins highlighted the origins and goals of the newly established Accelerating Medicines Partnership (AMP; <http://www.nih.gov/science/amp/index.htm>). This is a new collaboration involving the NIH, the Food and Drug Administration, ten biopharmaceutical companies, and several non-profit organizations. The aim is to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological targets of disease. The ultimate goal is to increase the number of new diagnostics and therapies for patients and to reduce the time and cost of developing them (<http://www.nih.gov/science/amp/index.htm>). The AMP is currently focused on spurring research through pilot projects in three disease areas: Alzheimer's disease, autoimmune disorders (specifically rheumatoid arthritis and lupus), and type 2 diabetes.

The concept for the AMP partnership emerged from meetings of the international Hever Group, which is composed of the heads of Research and Development for major pharmaceutical companies. The Group is named after Hever Castle in England, the site of the first of many meetings for sharing perspectives on science. Dr. Collins was invited to a Hever Group meeting in the U.S. at which participants recognized that great opportunities are emerging for drug development based on data from Genome Wide Association Studies (GWAS), proteomics, and other cutting-edge research. However,

they also recognized the lack of an efficient mechanism for sifting through the data to guide industry's substantial investments in drug development. This perceived need sparked consultations and workshops aimed at developing a collaborative framework to address the problem and move the science forward. The NIH requirements for a partnership included open access to any data produced, and equal cost-sharing among the government and industry partners. The industry participants felt that it was possible for them to engage in data-sharing, yet still remain competitive in developing and bringing drugs to market. A key issue for industry was to identify the most compelling areas of interest for support. The consensus was that at least four, and preferably five, of the industry partners would need to agree on a short list. In February 2014, these discussions culminated in the announcement of the AMP partnership, its scientific focus, and its integrated governance structure. Over five years, the partners will provide up to \$230 million in total funding for pilot projects. The Foundation for NIH is playing a critical role in accepting donations from the private sector.

Dr. Collins described the three pilot projects, which have milestones and deliverables. They will be guided by Steering Committees with government and private sector members.

Alzheimer's Disease: The AMP pilot project will focus on the inclusion of exploratory biomarkers in clinical trials to identify those that could be used to as indicators of disease progression and as surrogate endpoints. This work will capitalize on the ability to track deposition of the *tau* protein in patients' brains, and will pave the way to side-by-side comparisons of various interventions. Work will be coordinated with the Food and Drug Administration to ensure a clinical path forward for biomarkers. In more fundamental studies, researchers will use the tools of systems biology to understand the differences between Alzheimer's and normal brains. Based on that knowledge, they will seek to identify nodes and networks that might be targeted in developing the next generation of drug therapies.

Autoimmune Disorders - Rheumatoid Arthritis and Lupus: Building on GWAS studies, this pilot project will analyze tissue and blood samples from patients to pinpoint molecules and pathways involved at a single cell level. Modular, molecular analysis will be applied to identify differences and to make comparisons at various disease stages. The data obtained will be made available to the research community via a Knowledge Portal.

Type 2 Diabetes: To exploit findings from GWAS and other analyses, this pilot project will feature creation of a Knowledge Portal of comprehensive genotype/phenotype data on type 2 diabetes and its complications. Informatics will be used to identify predictors of risk and potential therapeutic targets. High-priority targets will undergo genetic sequencing/genotyping. Hypothesis-driven phenotyping will focus on high-priority genetic variants to validate potential targets. Dr. Collins

thanked Dr. Rodgers and Dr. Phil Smith for the work they have done to establish this project.

Dr. Collins said that several funding opportunity announcements in these areas have already been posted, but awards have not yet been made. He believes that the three initial pilot projects hold great promise for bringing public and private sectors together in an unprecedented way to understand the triggers of the diseases being addressed, and to develop the next generation of therapeutics. Going forward, he hopes that the AMP could be expanded to include other diseases such as schizophrenia. He encouraged the Council to check his blog to see updates on exciting science, the AMP, and other NIH activities. (www.directorsblog.nih.gov)

Dr. Collins emphasized the importance of broadly communicating the NIH story. Institute leaders and staff do this in various forums, but it is also vital for other members of the research community to share information and excitement about NIH programs and advances, funding opportunities for scientists, and issues that affect the research enterprise and its continued vitality.

Council Questions and Discussion

Council members thanked Dr. Collins for his leadership, vision, and stewardship of the NIH during difficult budgetary times.

***Ebola:** The Ebola crisis is an example of the need for a robust NIH. Will this realization lead to increased resources for the agency?* Dr. Collins replied that the NIH has been working on an Ebola vaccine since 2001 and is just beginning Phase 1 trials with the fifth version of the vaccine. Recent Ebola events illustrate the important role of the NIH and other agencies in fighting disease, and the need to support a strong national research enterprise.

***Team Science:** Is the NIH favoring team science as opposed to the independent investigator-initiated research for which the Pathway to Independence Program (K99/R00 award) prepares recipients?* Dr. Collins replied that investigators need to follow their scientific passions, and seek funding programs that will best support their goals. Depending on an investigator's discipline and the research questions he or she wants to answer, either team science or more independently conducted science may be more appropriate. Clearly, a great deal of exciting science is being done in teams, as evidenced by the many co-authors on published papers. Also, NIH Requests for Applications (RFAs) often solicit team science because the questions to be addressed may need an interdisciplinary approach. However, recipients of Pathway to Independence awards should be reassured that most of the budgetary resources for NIH research project grants are used to support individual, unsolicited R01 grants. Moreover, special nurturing is given to first-time applicants for R01 grants and early-stage

investigators. The NIH is not replacing investigator-initiated R01 grants with team science.

Potential for Capital Investments from Individuals: *Has the NIH considered efforts to acquire capital investments from individuals who don't have to work through the organizational constraints of boards and shareholders?* Dr. Collins said that all ideas for funding science need to be on the table, and that the NIH welcomes resource support from non-government sources. However, robust federal support has been responsible for the success of the U.S. biomedical research enterprise and will be needed for its continued success. Philanthropic support is extremely small when viewed as a percentage of the total NIH budget, which has lost about 25 percent in purchasing power since 2003, and is facing a sequestration of funds in FY 2016 absent congressional intervention. Currently, the growth rate for public funding of the NIH is lagging behind the growth rate of biomedical research funding in several other countries.

III. COUNCIL FORUM: The Accelerating Medicines Partnership (AMP) *Dr. Olivier Blondel, Dr. David Altschuler, Ms. Mary Carmichael*

Dr. Rodgers opened the Council Forum, which was focused on the Type 2 Diabetes Pilot Project of the Accelerating Medicines Partnership (AMP) described by Dr. Collins. The Pilot Project is intended to create a Knowledge Portal comprising data on DNA sequences, functional genomic and epigenomic information, and clinical data from studies of type 2 diabetes and its cardiac and renal complications. The data set and analytical tools of the Knowledge Portal would be accessible to academic and industry researchers for identifying and validating changes in DNA related to the onset of type 2 diabetes, disease severity, disease progression, and protective effects of genes and genetic variants.

A. *Dr. Olivier Blondel Program Director, Division of Diabetes, Endocrinology and Metabolic Diseases, NIDDK*

Dr. Blondel presented on behalf of the NIDDK team that is working on the AMP Type 2 Diabetes Pilot Project, including Dr. Phil Smith and Dr. Beena Akolkar. Dr. Blondel said that AMP partners have committed about \$50 million over the next five years to fund this project. Industry partners currently include Johnson and Johnson, Lilly, Merck, Pfizer, and Sanofi. Non-profit partners currently include the American Diabetes Association, the Juvenile Diabetes Research Foundation, and the Foundation for the NIH. Dr. Blondel expressed his hope that more partners will join the project in the future.

Dr. Blondel commented on the reasons that type 2 diabetes was selected to be an AMP Pilot Project. In addition to the huge impact of the disease on society, a trove of clues has been amassed regarding the pathways involved in this genetically complex disease. The intersection of public health need and research opportunity is compelling. Focusing on important targets in humans should accelerate the development of therapeutics with a very high probability of efficacy in humans. This approach is different from the

traditional drug discovery process in that it does not involve the use of non-human disease models that may poorly reflect human physiology.

The goals of the project are: to follow footprints of disease risk in genes and genetic variants to identify new pathways for therapeutic development; to increase the number of investigators who can contribute to target discovery and validation; to leverage all available resources to strengthen evidence for novel targets; and to support clinical studies on individuals with genotypes of particular interest for target validation.

The strategies envisioned to achieve these goals include the following:

- ***To build a Knowledge Portal to make genetic data and analytical tools available to the broad scientific community.*** This portal will enable academic and pharmaceutical researchers to access all available data from the international genetics community pertaining to genetic variants in type 2 diabetes, as well as phenotypic data. The user will be able to query and analyze the data, to link specific genetic variants with other sources of information, and to use a library of analytic tools to mine the data in creative ways.
- ***To expand available genetic and phenotypic data with broad representation across ethnic/racial groups.*** Data will continue to be aggregated from existing cohorts around the world, and will be augmented with additional sequence data on specific populations with the objective of target identification.
- ***To validate targets with in-depth physiological studies in individuals with defined variants.*** Clinical studies will be designed to provide further evidence that can support the development of actual compounds that modulate targets and newly identified disease pathways.

Dr. Blondel presented a timeline and milestones for the project from 2014 through 2018. He noted that, in later years of the project, it may be possible to include other aspects of type 2 diabetes, such as kidney and cardiovascular disease complications, and to provide a template for accelerating drug development for other diseases.

B. Dr. David Altshuler, Founding Core Member, Deputy Director, Chief Academic Officer, and Director of the Program in Medical and Population Genetics, the Broad Institute of Harvard and the Massachusetts Institute of Technology

Dr. Altschuler provided an overview of the discussions and reasoning that led to development of the conceptual framework for the AMP Type 2 Diabetes Pilot Project. The first awards have not yet been made, but are expected soon. The Project will feature a Knowledge Portal to enable investigators to access and analyze genetics data on type 2 diabetes with greater efficiency.

One compelling rationale for the AMP Pilot Project is that existing interventions for type 2 diabetes are only partially effective. The NIDDK-funded Diabetes Prevention Program was a landmark clinical trial that demonstrated the efficacy of lifestyle change in preventing type 2 diabetes in those at risk. However, a ten-year follow-up of participants in the study's lifestyle arm showed that 40 percent of them eventually developed type 2 diabetes. These findings underscore the need for better understanding and treatment of the disease.

Another rationale for the AMP Pilot Project is the need to improve pharmaceutical productivity, which has been relatively stagnant despite dramatic increases in investment. The pharmaceutical industry doubled its R&D investment from 1970 through 2005, but there was no corresponding increase in the number of FDA-approved compounds. Of the drug candidates that enter clinical trials, more than 95 percent fail, and more than half of those failures are because the drugs don't work. These failures play a significant role in the high cost of bringing a drug to market often cited by the pharmaceutical industry.

While different explanations have been offered for the high failure rate in drug development, Dr. Altshuler believes failures mainly occur when the initial therapeutic hypothesis is not connected to the physiology of the patients being studied in a particular clinical trial. In the same vein, successful drug development tends to incorporate insights about human physiology, such as genetic linkages of the target to the disease indication. Thus, prior to embarking on drug development, it is advisable to establish whether perturbation of the target in the context of human physiology results in a desired effect, without toxicity. This approach would be a more cost-effective means for the initial testing of a hypothesis in humans, rather than conducting costly clinical trials that are not grounded in human physiology. To illustrate this point, Dr. Alshuler gave some examples of clinical trial failures and successes with respect to coronary heart disease.

Turning to diabetes, Dr. Altshuler recounted the way that insights into human physiology provided the hypothesis for successful clinical trials. The *SLC30A8* gene was first shown to play a role in zinc transport in the insulin-producing beta cells of mice, thereby suggesting that it might play a similar role in humans. Subsequent clinical studies showed the existence of 12 different loss-of-function mutations in this gene, and that, in aggregate, inheriting any one of these mutations in just one copy of the gene reduced a person's risk of developing type 2 diabetes by 65 percent. Several pharmaceutical companies are now actively pursuing the therapeutic implications of these findings. (<http://www.nature.com/ng/journal/v46/n4/full/ng.2915.html>)

Dr. Altshuler noted that the *SCL30A8* research advance raises questions as to whether other protective mutations may exist among the many genetic variants already identified by Genome Wide Association Studies (GWAS). To answer this type of question has typically required years of finding, aggregating, cleaning, harmonizing, and analyzing data. Tailored data searches have been needed for each new question raised by an investigator, and few researchers have been able to access and analyze the data

themselves. However, the development of a Knowledge Portal through the AMP Type 2 Diabetes Pilot Project is expected to help remedy those problems.

C. Ms. Mary Carmichael, Member, Prototype Project Team

Dr. Altshuler introduced Ms. Mary Carmichael, a science journalist who demonstrated a Knowledge Portal prototype developed by the T2D-GENES Consortium. Ms. Carmichael said that the prototype was constructed with input from several sources, including interviews she conducted with some NIDDK Council members. The prototype contains only limited data at the present time; however, it could be populated by crowd-sourcing information.

Ms. Carmichael showed several ways the prototype could be used to assist investigators in accessing and analyzing genetics data. For example, an investigator could simply browse the data, or search by the name of a gene or genetic variant, or the title of a published paper. A curated summary of relevant information could thus be accessed, including the number of genome-wide significant hits on a genetic variant and any associated physiologic traits. Information could be accessed across multiple data sets to enable an investigator to dig deeply into genetic associations with disease, the frequency of genetic findings in different populations, and studies that replicate the findings of a particular paper. Annotations could be included about transcription effects, and the algorithms underlying analyses. It might be possible to add anonymized information about cohorts of patients who have participated in research studies. Thus, on a practical level, the investigator could efficiently narrow down the number of genetic variants he or she may wish to study further; understand their significance relative to human physiology; find clues about whether activating or deactivating a gene or genetic variant might increase or decrease associated disease risk; and use all this information to formulate research hypotheses that are data driven.

Concluding Remarks

Following Ms. Carmichael's live demonstration of the prototype, Dr. Altshuler closed with a few additional points. He underscored that the prototype is just an example of the kind of database and architecture that could be developed. It could be used to build upon and extend the work of existing genetics research consortia for type 2 diabetes, and existing approaches for data sharing such as the NIH Gene and Phenotype database (dbGaP). However, the ultimate utility of an expanded Knowledge Portal through the AMP Pilot Project on type 2 diabetes will largely depend on data contributions from the research community, whose members cannot be compelled to deposit data and must be incentivized to do so voluntarily. A cultural change will likely be needed among researchers who are not accustomed to disclosing their data outside of the traditional means of scientific publication. Going forward, a newly announced policy requiring data sharing in government-funded research will be an important step toward effecting that cultural change. Another incentive for the diabetes research community to deposit data

will be the growing appreciation of the broad benefits that would be derived for the entire field.

According to Dr. Altshuler, it is appropriate for the research community to take responsibility not only for generating data, but also for making that data broadly available for scientific progress, especially when the data have been accrued through large public investments in research. He also emphasized that the pioneering contributors to genetics consortia for type 2 diabetes--many of whom are in other countries--have a meaningful role to play in the new NIH AMP partnership with industry, and that their patient cohorts remain a valuable research resource.

Council Questions and Discussion

Rare Genetic Mutations: *Would it be possible to query the database for phenotypic traits associated with individual rare genetic mutations?* Dr. Altschuler said that the data for that type of query would need to be deposited in the Knowledge Portal. There are already genes of high interest, and a robust Knowledge Portal could enable researchers to do genetic sequencing on cohorts of study participants to narrow down the number of individuals who could then be called back for genotyping.

Reasons for a Genetic Variant's Associations with Type 2 Diabetes: *What would a user of the Knowledge Portal do if the reason for a genetic variant's association with type 2 diabetes is unclear from GWAS data? This is the case for most genetic variants associated with diabetes. Could data from the field of epigenetics or from studies using expression quantitative trait loci (eQTLs) help to provide answers?* Dr. Altschuler said that data helpful in answering that question are now available from the NIH Roadmap for Medical Research and through several active NIH projects, such as the 4D Nucleosome project of the NIH Common Fund. However, these data sets need to be made interoperable for efficiency of queries. Dr. Blondel added that data will continue to emerge from NIDDK-supported research on type 2 diabetes.

Usefulness of Knowledge Portal: *Will researchers beyond the genetics field be able to use a Knowledge Portal without a personal guide?* Dr. Altshuler responded that, if there is adequate resource support for a Knowledge Portal, then the appropriate infrastructure can be developed. One of the reasons for having curated summaries is to make the data understandable for researchers from different disciplines. The most useful type of support for the Knowledge Portal would be investments in the development of understandable data summaries and the creation of tutorials.

IV. CONSIDERATION OF SUMMARY MINUTES OF THE 195th COUNCIL MEETING

Dr. Rodgers

By voice vote, the Council approved the Summary Minutes of the 195th Council Meeting, which had been sent to them in advance for review.

V. FUTURE COUNCIL DATES

Dr. Rodgers

Dr. Rodgers drew the Council's attention to the schedule for upcoming meetings. He said that most meetings are expected to be a single day. However, Council members are asked to hold two days to ensure flexibility should a longer meeting be required.

2015

January 28-29 (Wednesday and Thursday)

May 13-14 (Wednesday and Thursday)

September 9-10 (Wednesday and Thursday)

Building 31, Conference Rooms 10, 6 and 7

2016

January 27-28 (Wednesday and Thursday)

May 18-19 (Wednesday and Thursday)

September 7-8 (Wednesday and Thursday)

Building 31, Conference Rooms 10, 6 and 7

VI. ANNOUNCEMENTS

Dr. Stanfield

Confidentiality

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

Conflict of Interest

Dr. Stanfield reminded the Council that advisors and consultants serving as members of public advisory committees, such as the NIDDK National Advisory Council, may not participate in situations in which any violation of conflict of interest laws and regulations may occur. Responsible NIDDK staff shall assist Council members to help ensure that a member does not participate in, and is not present during, the 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 Council member does not participate in the discussion of, nor vote on, an application in which he/she is in conflict, a written certification is required. A statement is provided for the signature of the member, and this statement becomes a part of the meeting file. Dr. Stanfield noted that each Council member's folder contained a statement regarding conflict of interest in his or her review of applications. He said that each Council member should read it carefully, sign it, and return it to the NIDDK before leaving the meeting.

Dr. Stanfield said 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. Stanfield said 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.

VII. REPORT FROM THE NIDDK DIRECTOR *Dr. Rodgers*

Dr. Rodgers made the following announcements.

Council Members Completing Their Terms of Service

Dr. Rodgers recognized the following six members who were completing their terms and rotating off the Council at the September 2014 meeting. He extended the NIDDK's appreciation for their service, and said that it had been a pleasure to work with each of them. He expressed his hope that the NIDDK could call upon them in the future.

▪ *Digestive Diseases and Nutrition Subcouncil*

Judy Cho, M.D., Professor; Vice-Chair Genetics and Genomics and Gastroenterology, Department of Genetics and Genomic Sciences, The Mount Sinai Medical Center: As an expert in genetics, Dr. Cho's service on the Council has been particularly valuable during a time when genetics and genomics have moved to the forefront of research on the widespread and costly diseases that are high priorities for NIDDK research. The leader of the NIDDK's Inflammatory Bowel Disease Genetics Consortium, Dr. Cho has provided many insights about the state-of-the-art and future directions in genetics research, and she has given the Institute helpful advice regarding complex peer review issues.

Thomas Robinson, M.D., M.P.H., The Irving Schulman, MD, Endowed Professor in Child Health, Department of Pediatrics and Medicine, General Pediatrics, Stanford Prevention Center, Stanford University Medical School: An exceptionally creative physician-scientist and pediatrician, Dr. Robinson has provided his expertise in pediatric obesity not only to the Council, but also to the NIDDK's Clinical Obesity Research Panel. The NIDDK has benefited from his experience in developing novel solutions for obesity prevention and treatment in children and adolescents in diverse populations. Dr. Robinson has brought to the Council a broad perspective derived from his service on three Institute of Medicine committees on childhood obesity prevention, and as the Principal Investigator on numerous NIH prevention and treatment studies.

▪ *Diabetes, Endocrinology, and Metabolic Diseases Subcouncil*

Domenico Accili, M.D., Professor of Medicine, Department of Medicine, Columbia University, College of Physicians and Surgeons: Dr. Accili's close ties with the NIDDK go back to his fellowship in the NIDDK Intramural Program, where he first delved into the pathogenesis of diabetes. During his time on the NIDDK Council, his research has generated major new insights into the mechanisms underlying progressive dysfunction of beta cells in type 2 diabetes and into strategies for their regeneration. In June, he received the Edwin B. Astwood Award from the Endocrine Society. He is also receiving the prestigious Claude Bernard Award at the European Association for the Study of Diabetes.

Robin Nwankwo, MPH, RD, CDE, Diabetes Educator, Department of Medical Education, University of Michigan Medical School: As a teacher and diabetes educator, Ms. Nwankwo has brought an important perspective to the Council and a passion for improving the lives of those with or at risk for diabetes. She has provided many insights about the patients who participate in clinical research and who make research progress possible. Her practical knowledge and understanding about the concerns of individuals, families and communities affected by diabetes have helped the NIDDK shape its clinical research programs. Ms. Nwankwo received the American Diabetes Association's Outstanding Educator in Diabetes Award while on the NIDDK Council in 2012.

▪ ***Kidney, Urologic and Hematologic Diseases Subcouncil***

William Steers, M.D., Professor and Chairman, Department of Urology, University of Virginia Health System: The NIDDK has benefited from Dr. Steers' wealth of clinical expertise derived from treating patients with urinary incontinence, neurogenic bladder, benign prostatic disorders, and erectile dysfunction. From his advice, the NIDDK has gained a deeper appreciation of the importance of investigator-initiated research grants and research training opportunities for investigators, especially new Principal Investigators. His service to the research community includes serving as Editor of the *Journal of Urology* since 2007, President of the American Board of Urology, member of the FDA's Reproductive Medicine Advisory Panel, and Chairman of the NIH's Clinical Trial Groups for urinary incontinence and interstitial cystitis. He has been recognized by the American Urological Association for his many achievements.

Mark Zeidel, M.D., Professor, Department of Medicine, Beth Israel Deaconess Medical Center: A widely recognized, highly productive clinician scientist, Dr. Zeidel has provided a broad range of experience and expertise to the NIDDK Council. He is well known for his pioneering research in the area of epithelial biology and water transport. Over the years, his research focus has expanded to include areas such as water movement in the bladder as a possible explanation for interstitial cystitis. His insightful research studies have received NIH funding support for over 20 years. While on the Council, Dr. Zeidel has informed many discussions about research training programs. He has vigorously supported programs that enhance the ability of research trainees to contribute to scientific progress.

"In Memoriam"

Dr. Rodgers informed the Council of the deaths of the following individuals who had contributed to the Institute's mission as members of the NIDDK community.

Dr. George Gilbert Ashwell was a long-standing NIDDK intramural researcher and former Chief of the Laboratory of Biochemistry and Metabolism. He was a pioneer in the field of glycobiology and is best known as a discoverer of the asialoglycoprotein receptor in the liver in the mid-1970s. Recently, this receptor was found to be important in mitigating the lethal coagulopathy of sepsis. After retirement from the NIDDK, Dr. Ashwell continued to be active as an emeritus scientist.

Dr. William G. Coleman had a long, distinguished career in the NIH Intramural Program. Most recently, he conducted innovative research at the NIDDK on *Helicobacter pylori*, which is associated with several clinical pathologies including gastritis, ulcers, and gastric cancers, and which affects millions of Americans, especially Mexican Americans and non-Hispanic blacks. Since January 2011, Dr. Coleman directed the Intramural Research Program of the National Institute on Minority Health and Health Disparities, with a focus on three areas of significant health disparities: cancer, cardiovascular

disease, and diabetes. A passionate advocate for research training, Dr. Coleman mentored a notable cadre of students, postdoctoral fellows, and science teachers.

Dr. Lois Lipsett had a long and productive career with the NIDDK Diabetes, Endocrinology and Metabolic Diseases Division, where she dedicated her efforts to advancing research training and research career development programs for scientists. She was also instrumental in establishing and leading the National Diabetes Information and Education Clearinghouse, and she contributed to enhancing other NIDDK health education programs.

Dr. Albert J. Stunkard received NIH research funding for five decades--primarily from the NIDDK and the National Institute of Mental Health. Dr. Stunkard produced pivotal findings on the genetic basis of obesity, obesity treatment strategies, binge eating disorders, and night eating syndrome. Among his many honors, Dr. Stunkard was an elected member of the Institute of Medicine of the National Academy of Sciences. The Obesity Society's Lifetime Achievement Award is named for Dr. Stunkard.

New Members of the NIDDK

Dr. Rodgers welcomed the following individuals to the Institute.

Dr. Kevin Abbott has joined the NIDDK's Division of Kidney, Urologic, and Hematologic Diseases as the Program Director for Kidney and Urology Epidemiology Programs. Dr. Abbott is board certified in internal medicine and nephrology and has authored more than 150 publications. He previously served as a staff nephrologist in the military, and has directly managed dialysis and transplant programs. He is a fellow within the American College of Physicians and is also a member of the American Society of Transplantation and the American Society of Nephrology. Dr. Abbott received his M.D. from the Medical College of Georgia, and completed his training in internal medicine and his fellowship in nephrology at the Brooke Army Medical Center, Fort Sam Houston, Texas. Dr. Abbott subsequently earned a Master's degree in Public Health with a concentration in Epidemiology/Biostatistics and Health Services Administration from the Uniformed Services University of the Health Sciences.

Dr. Dianne Camp is joining the NIDDK Review Branch, where she will contribute her extensive expertise and experience. She previously served at the NIH Center for Scientific Review as a Scientific Review Officer in the Endocrinology, Metabolism, Nutrition and Reproductive Sciences Integrated Review Group. Her earlier positions included work as a research scientist at the University of Michigan, and as a member of the bioscientific staff at Beaumont Research Institute in Royal Oak, Michigan. She has experience with the research areas of oxidative stress, inflammatory processes, adult stem cell therapy, and neurological conditions. Dr. Camp holds a Ph.D. in biopsychology from the University of Michigan, where she studied brain dopamine systems. Her postdoctoral

training was in the Department of Neurological Sciences at the University of British Columbia.

Dr. Daniel Gossett is a Presidential Management Fellow (PMF) who will gain experience in program management and the support of extramural research and translation from assignments with the NIDDK. Dr. Gossett's participation in the PMF program is enabling him to learn the workings of a federal agency, take on challenging projects, and start a career in public service. Dr. Gossett earned his Ph.D. in Biomedical Engineering at the University of California, Los Angeles. He then helped launch a company to commercialize one of the products of his graduate work.

Dr. Jason Hoffert is joining the NIDDK Review Branch, where he will contribute his extensive knowledge about the methods of proteomics; mass spectrometry, computational biology, and bioinformatics--especially as they apply to the study of kidney development and kidney disease progression. He earned his Ph.D. in biochemistry from the Johns Hopkins University School of Medicine in the laboratory of Nobel Prize winner Dr. Peter Agre. Following a post-doctoral fellowship, he worked as a Staff Scientist in the Epithelial Systems Biology Laboratory, where he studied the dynamics of vasopressin signaling in kidney collecting ducts using quantitative phosphoproteomics.

Dr. Chandan Sastry will serve as the NIDDK's new Information Technology Director and Chief Information Officer. For the past nine years, Dr. Sastry has helped to coordinate work in clinical informatics, bioinformatics, biovisualization, and core information technology at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). His earlier positions include serving as a Senior Consultant and Associate with Booz Allen Hamilton, and as a Research Assistant with Johns Hopkins University. Dr. Sastry is the recipient of the NIH Director's Honor Award, the NIH Director's Merit Award, and multiple NICHD awards for both excellence and collaboration. Dr. Sastry holds a B.S. in Operations Research from Cornell University, an M.S. in Biochemistry and Molecular Biology from George Washington University, and a Ph.D. in Environmental Health Engineering from Johns Hopkins University.

Dr. Luke Stoeckel has joined the NIDDK Division of Diabetes, Endocrinology, and Metabolic Diseases as Director of the Cognitive and Clinical Neuroscience of Obesity and Diabetes Program. He is a licensed clinical neuropsychologist and holds a doctorate in medical/clinical psychology. Previously, he was Director of Clinical Neuroscience at the Massachusetts General Hospital Center for Addiction Medicine, and Assistant Professor of Psychology at Harvard Medical School. Dr. Stoeckel's research includes the investigation of brain-behavior relationships. He has studied the neuropathophysiology of obesity and diabetes, and their intersection with neurological and psychiatric disorders, with the aim of identifying novel therapeutics.

Report on the NIDDK Intramural Research Program

Dr. Rodgers reminded Council members that the NIDDK Scientific Director would provide them with the annual report on the Institute's Division of Intramural Research in the closed session of the Council meeting.

VIII. SCIENTIFIC PRESENTATION:

“Sex Differences in Acute and Chronic Kidney Disease”

Dr. Sharon Anderson, Professor and Interim Chair, Department of Medicine, Division of Nephrology and Hypertension, Oregon Health and Science University (OHSU)

Dr. Rodgers introduced the presentation by Council Member Dr. Sharon Anderson, whose research interests include hypertension and the kidney, pathophysiology of the aging kidney, diabetic nephropathy, hormonal modulation of renal function, and the mechanisms of progressive glomerular injury. Dr. Anderson received her M.D. from Louisiana State University Medical Center. Following her internal medicine residency training at OHSU, she completed her clinical nephrology training at the Beth Israel Deaconess Medical Center, and her research training at the Brigham and Women's Hospital, Harvard Medical School.

IX. CONSIDERATION AND REVIEW OF GRANT APPLICATIONS AND OF THE DIVISION OF INTRAMURAL RESEARCH

In accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., and section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2) the following portions of the meeting were closed to the public:

In closed session a total of 1,188 grant applications (315 primary and 873 dual), requesting support of \$366,878,714 were reviewed for consideration at the September 3, 2014 meeting. An additional 493 Common Fund applications requesting \$274,349,352 were presented to Council. Funding for these applications was recommended at the Scientific Review Group recommended level. Prior to the Advisory Council meeting, 1045 applications requesting \$ 294,834,114 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 3, 2014 meeting.

Also in closed session, Dr. Michael Krause gave an overview of the NIDDK Division of Intramural Research (DIR) and reported the recommendations of the Board of Scientific Counselors, which were based on their review of specific DIR laboratories/branches during 2014.

X. ADJOURNMENT

Dr. Rodgers

Dr. Rodgers expressed appreciation on behalf of the NIDDK to the presenters and other participants. He thanked the Council members for their attendance and valuable input. There being no other business, the 196th meeting of the NIDDK Advisory Council was adjourned at 4:30 p.m. on September 3, 2014.

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

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

Griffin P. Rodgers, M.D., M.A.C.P.

Director, National Institute of Diabetes and Digestive and Kidney Diseases, and
Chairman, National Diabetes and Digestive and Kidney Diseases Advisory Council