NATIONAL ADVISORY COUNCIL FOR HUMAN GENOME RESEARCH
SUMMARY OF MEETING[1]
September 13, 2010

The Open Session of the National Advisory Council for Human Genome Research was convened for its sixtieth meeting at 8:32 A.M. on September 13, 2010 at the Fishers Lane Conference Center, Rockville, MD. Eric Green, Director of the National Human Genome Research Institute, called the meeting to order.

The meeting was open to the public from 8:32 A.M. until 4:10 P.M. on September 13, 2010. In accordance with the provisions of Public law 92-463, the meeting was closed to the public from P.M. on September 13, 2010 until adjournment for the review, discussion, and evaluation of grant applications.

Council members present:

Michael Boehnke
Eric Boerwinkle
Mark Chee
Rex Chisholm
Jorge Contreras Jr.
Richard Cooper
Claire Fraser-Liggett
Richard Gibbs
Geoffrey Ginsburg
Ross Hardison, *ad hoc*
Howard McLeod, *ad hoc*
Jill Mesirov, *ad hoc*
Richard Myers
Pearl O'Rourke
Pilar Ossorio
Pamela Sankar, *ad hoc*
David Valle
Richard Weinshilboum
David Williams, *ad hoc*
Richard Wilson, *ad hoc*

Council members absent:
none

Ex officio members absent:
None

[1] For the record, it is noted that to avoid a conflict of interest, Council members absent themselves from the meeting when the Council discusses applications from their respective institutions or in which a conflict of interest may occur. Members are asked to sign a statement to this effect. This does not apply to "en bloc".

Staff from the National Human Genome Research Institute:

Ajay, DER
Leslie Adams, DER
Alice Bailey, OD
Joan Bailey-Wilson, DIR
Maggie Bartlett, OD
Sanja Basaric, OD
Vivien Bonazzi, DER
Vence Bonham, OD
Ebony Bookman, OD
Joy Boyer, DER
Anita Brooks, DIR
Lisa Brooks, DER
Kyle Brown, OD
Comfort Browne, DER
Joseph Campbell, DER
Zieanna Chang, DER
Ernsley Charles, DER
Debbie Chen, DER
Shaila Chhibba, DER
Cheryl Chick, DER
Monika Christman, DER
Colleen Clark, DIR
Nicholas Clemm, DER
Christine Cutillo, DER
Camilla Day, DER
Corina Din-Lovinescu, DER
Gwen Dudley, DER
Elise Feingold, DER
Adam Felsenfeld, DER
Colin Fletcher, DER
Phyllis Frosst, OD
Jonathan Gitlin, OD
Peter Good, DER
Bettie Graham, DER
Eric Green, OD
Mark Guyer, DER
Lin Gyi, DER
Linda Hall, DER
Lucia Hindorff, OD
Trish Hylla, DIR
Heather Junkins, OD
Dan Kastner, DIR
Rongling Li, OD
Carson Loomis, DER
Rebecca Lowdon, DER
Teri Manolio, OD
Jean McEwen, DER
Keith McKenney, DER
Ray Messick, DER
Enrique Michelotti, DER
Ebony Mitchell, DER
Cathy Ng, DER
Ken Nakamura, DER
Susan Old, OD
Vivian Ota Wang, DER
Brad Ozenberger, DER
Jacqueline Palchik, DER
Dylan Perry, DER
Jane Peterson, DER
Rudy Pozzatti, DER
Erin Ramos, DER
Laura Rodriguez, OD
Ellen Rolfes, DER
Anna Rossoshek, DER
Jeff Schloss, DER
Geoff Spencer, OD
Jeff Struewing, DER
Carolyn Taylor, DER
Larry Thompson, OD
Elizabeth Thomson, DER
Susan Vasquez, DER
Simona Volpi, DER
Lu Wang, DER
Christopher Wellington, DER
Kris Wetterstrand, DER
Rosann Wise, OD
Julia Zhang, DER

Others present for all or a portion of the meeting:
Adam Berger, Institute of Medicine
Joann Boughman, American Society of Human Genetics
Francis Collins, Director, NIH
Jane Hammond, RTI International
Tabitha Hendershot, RTI International
Sharon Olsen, International Society of Nurses in Genetics
Sharon Terry, Genetic Alliance
JD Rench, RTI International
Marc Rigas, NIAAA
Rhonda Schonberg, National Society of Genetic Counselors
Rodney Howell, American College of Medical Genetics

INTRODUCTION OF NEW MEMBERS AND STAFF, LIASONS AND GUESTS

Dr. Guyer wished farewell to Council members Richard Weinshilboum, Richard Gibbs, and Jorge Contreras. whose terms are expiring.

Dr. Guyer noted that the new Council slate has been approved and six members are now full members. They are participating at this meeting as *ad hoc* Council Members: Ross Hardison, Howard McLeod, Jill Mesirov, Pamela Sankar, David Williams, Richard Wilson, and Deidre Meldrum (absent).

Dr. Guyer introduced new NHGRI staff: Ebony Mitchell, Administrative Program Analyst; Leslie Adams, Program Analyst; Zieanna Chang, Program Analyst; Shaila Chhibba, Program Analyst; Nicholas Klemm, Program Analyst; Cathy Ng, Program Analyst (all DER); and Kyle Brown, ASHG Policy Fellow, OD.

Dr. Guyer welcomed members of the press and liaisons from professional societies:
Joann Boughman, American Society of Human Genetics
Rodney Howell, American College of Medical Genetics
Sharon Olsen, International Society of Nurses in Genetics
Rhonda Schonberg, National Society of Genetic Counselors
Sharon Terry, Genetic Alliance

APPROVAL OF MINUTES

The minutes from the May 2010 Council meeting have not been submitted to the group. There will be an e-mail vote to approve them once they are finished.

FUTURE MEETING DATES

The following dates were proposed for future meetings: February 7-8, 2011; May 16-17, 2011; September 12-13, 2011; February 13-14, 2012; May 21-22, 2012; September 10-11, 2012

DIRECTOR'S REPORT

The slides for the Director's Report and associated supplemental material are available at http://www.genome.gov/directorsreport.

I. GENERAL NHGRI UPDATES

Scientific Director. Daniel Kastner, MD, PhD has been named the new Scientific Director, DIR. Dr. Kastner is currently the Clinical Director at the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS). He joined the NIH Intramural Program in 1985, and built a research program to study the genomics of arthritis. He has served as a Branch Chief and Laboratory Chief, and is currently the Clinical Director at NIAMS. He is a

member of the American Society of Clinical Investigators, the Association of American Physicians, and was elected to the National Academy of Sciences this year. Dr. Kastner's appointment as Scientific Director will begin on October 10, 2010.

Deputy Director Search. NHGRI has launched a search for a Deputy Director. An advertisement will appear in journals this week. It is hoped that Council members will provide recommendations for this position. Council asked Dr. Green to provide bullets summarizing the duties of the Deputy Director.

Strategic Planning Process Finale Meeting. As a finale to the planning process, NHGRI hosted a meeting at Airlie house to discuss a draft strategic plan. The meeting was attended by more than a hundred, including several Council members. The meeting was very successful and the Institute received a great deal of productive feedback on needed refinements in the plan, which is now in the final stages of revision.

There were several novel aspects to this meeting. The main sessions were videocast for invitees who were unable to attend and Institute staff who couldn't attend, as well as others invited specifically to join the meeting electronically. There were viewers from 28 states and China, with 261 unique IP addresses accessing the videocast. Second, a microblog was run during the meeting. There were 186 users of the microblog, almost 1500 comments, and four ad hoc groups created for smaller discussion. The microblog was widely viewed as a success and NHGRI will continue to use this device in other settings. More than 100 genomics trainees had also been invited to participate remotely by means of the videocast and microblog. A few weeks after the meeting, these trainees were given the opportunity to participate in a conference call with Dr. Green, Dr. Guyer, and others to discuss the planning process and to offer their comments about the strategic plan.

FY2009 PECASE Awardees. Four of the recently announced recipients of the Presidential Early Career Award for Scientists and Engineers for 2009 have NHGRI affiliations:

- Chuck Venditti, Intramural NHGRI investigator.
- Brian Brooks, Investigator at the National Eye Institute with an adjunct appointment at NHGRI..
- Manolis Kellis, NHGRI grantee, Associate Professor of Computer Science, MIT.
- Bradley Malin, NHGRI grantee, Assistant Professor of Biomedical Informatics, Vanderbilt.

NHGRI Budget. The FY2011 President's budget proposal includes a $1 billion increase (3.2%) to the NIH budget, which is equal to the rate of biomedical inflation. Not all Institutes were proposed to receive the same increase in funding; rather, the funding levels were partially dictated by the alignment of the Institute's with Francis Collins' five themes for NIH. The proposed increase for NHGRI is $534 million (3.5%), a slightly higher than average increase. It is projected that the budget may not be passed until January, leaving federal agencies operating under a continuing resolution (CR).

There has been a lot of discussion about budget cuts in 2012. The Administration recently asked all federal agencies to participate in an exercise to cut spending for 2012 by 5%. If the NIH budget were cut, it would presumably not be across the board but would also be based on alignment with the five themes.

II. GENERAL NIH UPDATES

Francis Collins. Dr. Collins recently completed his first year as NIH Director. His accomplishments during that time were discussed in a recent *Nature* article.

New Appointments

- **Lawrence Tabak, D.D.S., Ph.D. named Principal Deputy Director, NIH.** Dr. Tabak is currently the Acting Director of Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) and the Director of the National Institute of Dental and Craniofacial Research, meanwhile maintaining his own research program on glycoproteins.
- **Sally J. Rockey, Ph.D. appointed Deputy Director for Extramural Research, NIH.**
  Dr. Rockey was previously the Acting Deputy Director for Extramural Research. Her appointment was made permanent in August 2010.

- **James Anderson, M.D., Ph.D. named Director, DPCPSI.** The Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI), in the Office of the Director, NIH houses the Common Fund, previously known as Roadmap. Dr. Anderson came to the NIH from the University of North Carolina where he served as Chair of the Department of Cell and Molecular Physiology. Dr. Anderson has extensive clinical experience and is perceived as a top authority in the world on tight junctions and paracellular transport. The appointment of a Director for DPCPSI is important for NHGRI as the Institute has a disproportionate responsibility for managing Common Fund programs. Dr. Anderson will be asked to present to Council at a future meeting.
- **Robert Kaplan, Ph.D. appointed Associate Director, OBSSR.** Dr. Kaplan, will begin his post in early 2011. He is currently a Distinguished Professor in the Department of Health Services at the School of Public Health and the Department of Medicine at the University of California, Las Angeles. Dr. Kaplan is a member of Institute of Medicine.
- **Alan Guttmacher, M.D. named Director, NICHD.** Dr. Guttmacher, the Acting Director of NICHD, was appointed as Director. Dr. Guttmacher is the former Deputy Director and former Acting Director of NHGRI his appointment will allow new opportunities for interaction between the two Institutes.
- **Harold Varmus, M.D. sworn in as Director, NCI.** Returning to NIH, Dr. Varmus has expressed his support for TCGA and the importance of his relationship with NHGRI. Dr. Varmus' lab will be in the NHGRI intramural program.

White House Event to Release the Report on the American Recovery and Reinvestment Act of 2009. The NIH participated in an event with Vice President Biden on August 24, 2010. The White House made a major announcement regarding a report on the impact of ARRA funding in various sectors with emphasis on science. Mr. Biden specifically mentioned cancer genomics, the declining cost of genome sequencing, and the impact of genomics on disease prevention. Several NHGRI Program Directors and grantees attended the event.

NIH genetic testing registry. NIH announced plans to develop a genetic testing registry (www.ncbi.nlm.nih.gov/gtr/). At present, there are around 1,600 genetic tests that are available to patients and consumers, but there is no single resource to provide information on these tests. The registry will be a public database providing information about the validity and usefulness of tests, as well as other measures; the information will be submitted voluntarily by genetic test providers. Requests for comments have been posted in the Federal Register.

Therapeutics at NIH. Therapeutics is an area of active research at the NIH and the congressionally funded TRND (Therapeutics for Rare and Neglected Diseases) program is an example (http://www.genome.gov/27531965). The Cures Acceleration Network (CAN), which is intended to turn medical research into cures, was incorporated into the recent health care reform bill. TRND, the Chemical Genomics Center and the CAN Initiative are all currently within the NHGRI portfolio.

III. Genomics Updates

Media coverage of the 10th anniversary of the draft sequence of the Human Genome
June 26, 2010 marked the 10th anniversary of announcement of the first draft of the human genome sequence. This received a lot of media attention; articles appeared in *Nature*, *New England Journal of Medicine*, *New York Times*, *Der Speigel*, and others, and Charlie Rose dedicated a segment to the topic with guests Francis Collins and Eric Lander. February 2011 is the 10th anniversary of the publication of the draft human genome sequence, and there will be additional events to mark that occasion.

Economist Special Report. *The Economist* published a multi-part series entitled "Biology 2.0" outlining the impacts of the human genome project on biological sciences.

NHGRI Science Writers Workshop. The NHGRI Communications Branch held a science writers workshop in June to provide education and background information for stories about the 10th anniversary of the draft human genome sequence. The workshop was attended by journalists from 25 media outlets and there were another 25 attendees from Government communications offices, including the NIH, CDC, and others. All presentations are available online through YouTube. One of the writers attending the workshop wrote an article in *USA Today*.

Pending Legislation: H.R. 5440 – Genomics and Personalized Medicine Act of 2010.
H.R. 5440 is a reformed version of a previous bill, sponsored by Congressman Kennedy (D-R.I). Francis Collins Testified at the House Energy and Commerce Subcommittee on Health in a hearing entitled "NIH in the 21st Century: The Director's Perspective." In his testimony, Dr. Collins discussed his five themes, conflict of interest issues that have recently gained the attention of Congress, and the Gulf Oil spill, among other topics.

Other interactions with Congress. Eric Green has been to Capital Hill several times since his appointment as NHGRI Director. Of note, Dr. Green had two meetings with Congresswoman Louise Slaughter of NY, a supporter of NHGRI; spoke with Congressman Jim Langevin of RI, a supporter of stem cell and other biomedical research; and met with Congressman Michael Burgess of TX, who has a strong interest in personal genomics.

Personal Genomics regulation. There is growing concern in the government over the unregulated nature of the direct-to-consumer (DTC) genetic testing industry. Questions are being asked about whether the industry should be regulated and if so, who should regulate it.
The FDA contacted 21 DTC genomics companies to ask about the lack of premarket approval for their genetic tests. Congressional hearings were held, centering on high profile errors. All companies said they welcomed the FDA in setting standards for the industry, but several said they would not halt marketing and distribution of products until the standards are set. The Government Accountability Office (GAO) performed "secret shopper" investigations on DTC genomics companies. The GAO found that results were misleading and not useful; the same donor had different results from different DTCs more often than not. The report further exposed deceptive marketing, questionable practices, and misleading claims. The FDA held a two-day meeting on the development of regulations for lab-developed tests. Some concerns were raised about excessive regulatory burden and there were calls to avoid duplicative efforts. Further, the groups will need to address software analysis tools.

Personal Genomes and Universities. Stanford University Medical School will offer a course that gives students the option of studying their own genotype data. UC Berkley had previously announced a similar course, but it had to modify its plans due to lack of involvement of CLIA-approved laboratories.

Training pathology residents in genomics and personalized medicine. A recent article in the *American Journal of Clinical Pathology* called for pathologists to get involved in genomics and personalized medicine, and urged a wide-spread curriculum change in pathology training programs.

Celebrity Genomes. Researchers in Copenhagen have obtained consent from Sitting Bull's descendents to perform whole genome sequencing from a lock of his hair. Sitting Bull will be the first ancient non-frozen Native American genome sequenced.

CSHL Personal Genomes Meeting. The third Personal Genomes meeting concluded on September 12. The meeting was co-chaired by Council member Richard Gibbs, and several other Council members attended. The NHGRI strategic plan is integrating several of the issues that this meeting brings to the forefront, such as analysis of individual genomes and concerns about CLIA laboratory settings.

II. NHGRI – EXTRAMURAL PROGRAM

Large-scale Sequencing. The International Pea Aphid Consortium recently published the genome of the pea aphid, a major agricultural pest that is also a model for insect/plant interactions. Washington University researchers recently published the first sequence of the western clawed frog (*Xenopus tropocalis*), which is commonly used as a model organism for vertebrate development, and the transcriptome of the canine hookworm (*Ancylostoma caninum)*. Hookworm infection is the leading cause of maternal and child morbidity in developing countries and is considered a rare and neglected tropical disease. NIH-funded researchers recently used whole exome sequencing to discover the MLL2 gene mutation that causes Kabuki syndrome.

The Cancer Genome Atlas (TCGA). This month, TCGA submitted the ovarian cancer manuscript, which includes characterization of nearly 500 tumors and complete exomes on 315 tumors. TCGA data are available for acute myeloid leukemia (AML), colon, rectal, breast, and kidney cancers, and additional data are made available on an on-going basis.

HapMap 3 Publication. HapMap recently published a third generation map of human genetic variation, adding data from 7 populations.

1000 Genomes Project Data Release. 1000 Genomes released pilot project data and submitted a paper which will be published in early November. The FTP site has more than 10 Gb of sequence data for 624 samples.

Wellcome Trust. The Wellcome Trust and Sanger Institute announced the UK 10K project, with plans to sequence complete genomes from 4000 well-phenotyped individuals and an additional 6000 exomes from individuals with particular disorders.

DNA Sequencing Technology. A press release was issued today announcing10 new and continuing awards for the $1000 genome sequencing technology develop program. Grantees have already published about 50 papers this year describing work funded by this program. Several new RFAs were published, with receipt dates scheduled for October 2010, 2011, and 2012.

ENCODE and modENCODE. The ENCODE Analysis Working Group met in Barcelona in July of this year and focused on writing an integrative analysis paper. The Mouse ENCODE project, which was funded by ARRA, has begun submitting data.

Centers of Excellence in Genome Science (CEGS). NHGRI supports 10 CEGS; the most recent award was made to George Church last year. A revised program announcement was released last year; responsive applications will be considered at February Council meeting. Two of the CEGS will reach the end of funding by next year. There is a CEGS meeting planned for next month at Arizona State University. There was a discussion about a cap on the number of CEGS, which is currently not determined by number but rather by funding, with a cap at $2 million (DC) each.

ELSI Program. NHGRI received $1.8 million from the NIH OD to support three ELSI grants and a supplement. There will be a triennial ELSI research meeting at the University of North Carolina in April 2011.

Knockout Mouse Program (KOMP). KOMP is on target to achieve its goals by the end of the project in Fall 2011. NHGRI is expanding the program to KOMP^2, which will include phenotype data. RFAs were recently published for KOMP^2.

Informatics and Computational Biology. Vivien Bonazzi has been named as the official NHGRI liaison to NCBI. Kris Wetterstrand will work with her to improve coordination and communication. There are several upcoming informatics meetings that NHGRI staff will attend, including 'Beyond the Genome,' a cloud computing workshop, and Petascale Computing and Personalized Medicine Workshop.

IV. COMMON FUND PROGRAMS

Human Microbiome Project (HMP). HMP is a common fund program, for which NHGRI has major leadership responsibility. The Consortium published a paper in May describing the first HMP collection of human microbial genome sequences. There was an HMP meeting in St. Louis at the end of August with 450 attendees. HMP recently issued a press release announcing awards in three areas – eight demonstration projections (UH3s), five technology development awards, and six computational tools awards.

Genotype-Tissue Expression (GTEx). GTEx is a Common Fund project co-led by NHGRI and NIMH. GTEx has pilot funding for 2.5 years to show the feasibility of collecting multiple tissues from 160 deceased donors for eQTL analyses. Awards were made to The Broad Institute for the laboratory, data analysis, and coordinating center, and to the University of Miami for the Brain Bank. Awards for three to four Biospecimen Source Sites will be made soon. The inaugural GETx kick-off meeting will be held at end of September. At the request of Dr. Green and the NHGRI Council, recruitment for the External Scientific Panel is underway, which will serve to provide guidance about the overall direction and success of the project.

Library of Integrated Network-based Cellular Signatures (LINCS). LINCS is a Common Fund project co-led by NHGRI and NHLBI. The goal of the pilot is to facilitate a mechanistic understanding of disease in support of

drug and biomarker development, create a library of perturbation-induced cellular signals that will relate cellular responses to genetic variation, environmental exposures, and clinical phenotypes and develop computational tools and approaches to analyze cellular signatures and new technology for generating novel signatures. U54 awards were made to the Broad Institute (Todd Golub, P.I.) and Harvard Medical School (Tim Mitchison, P.I.) as the primary analysis centers. Several RFAs have been released for other aspects of phase I of the initiative.

Protein Capture Reagents. NHGRI co-leads this project. The goal is to generate a renewable community resource of high-quality affinity reagents for all human proteins. The applications for the resource could include ChIP, protein-protein interactions, immunostaining, arrays, and others. The program will initially prioritize monclonals, starting with human transcription factors and immunoprecipitation applications. Challenges include issues of scalability and IP concerns.

Human Heredity and Health in Africa (H3Africa). H3Africa is a new NIH Common Fund initiative that will be a joint venture with the Wellcome Trust with a goal of enhancing the capability of African scientists to pursue genomics research on the continent. NIH has pledged $25 million over five years, and the Wellcome Trust is contributing an additional $12 million. The project was announced at a joint press event in London in June. H3Africa has two working groups, the majority of whose members are African scientists, which are developing a proposal for the initiative. The working groups met in Oxford in August.

V. NHGRI OFFICE OF THE DIRECTOR

***New England Journal of Medicine* Perspective Series on Genomic Medicine.** *NEJM* initiated a new series on genomic medicine, which is edited by Alan Guttmacher and Greg Feero. There will be a total of 13 articles, which will be released every six weeks. Three articles have been released so far, and all of the articles in the series will be made freely available.

NHGRI Scientists Present Genomic Advances to Visiting Judges. The NHGRI Communications Branch coordinated a continuing education program for 60 senior-level judges from around the country titled *Genomics, Medicine, and Discrimination*. The successful four-day program included a tour of a sequencing center and several speakers from NHGRI and academia.

Summer Workshop in Genomics. NHGRI held the Summer Workshop in Genomics in August. The six-day course included 35 participants from 18 colleges and universities, several of which serve minorities. This workshop is a new collaboration with the NIH Office of Intramural Training and Education and is centered faculty mentoring.

Sickle Cell Disease. In April, the NCAA approved mandatory testing of athletes for sickle cell carrier status. NHGRI researchers Vence Bonham and Larry Brody collaborated with George Dover to publish a perspective on the ethical and social issues surrounding the testing of student athletes.

2010 marks the 100th anniversary of the publication of first characterization of sickle cell disease in Western medical research. This event will be commemorated by a symposium at NIH which is co-sponsored by NHGRI.

Newborn screening. With new sequencing technologies widely available, there is an opportunity to stimulate interaction between newborn screening and genomics. NICHD and NHGRI will be holding a workshop in December 2010 to frame a research agenda.

Electronic Health Records. There will be a two-day workshop in Spring 2011 on electronic health records and genomic information to explore the issues and challenges of integrating genomic information into clinical electronic health records. At the strategic planning process Finale Meeting, there was a spirited debate on the topic, with some participants saying that the problems have been solved, and others saying this remains a huge problem. This is also a topic of interest for the Obama administration. NHGRI will be increasingly called in to provide input on genomics aspects of such systems, and the purpose of the workshop will be to try and improve education on this topic. In addition some Council members may be asked to participate.

USA Science & Engineering Festival. The first USA Science and Engineering Festival will take place in October on the National Mall. NIH was asked to participate in this event and NHGRI is involved in six activities.

NIH to launch Gulf oil spill health study. NIH/NIEHS committed $28 Million for a five year study of oil spill clean-up workers to follow for 10 – 20 years. The focus will be on clean-up workers as there have been few long-term studies of such exposures and this will provide an opportunity to examine genotoxic effects. The study will include vulnerable populations, such as pregnant women and children. Teri Manolio has been asked to step in and co-lead this effort along with Harold Jaffe from CDC. It is hoped that future genetic studies could be created from this study. Also related to the oil spill, the Chemical Genomics Center has been asked to study some of the dispersants used in the clean-up effort.

VI. NHGRI – Intramural Program

Undiagnosed Diseases Program (UDP). Council received an update on the UDP last September. In brief, physicians can submit requests for consideration for patients who do not have a diagnosis for their condition. This is an NIH-wide program and studies occur at the NIH Clinical Center. The UDP is led by William Gahl and hosted by NHGRI. Medical records from 1200 patients have been received, and of these, 280 patients have or will be participants in the UDP. There will likely be a few papers in the next six months describing instances in which rare disease genes or rare variants were identified through exome sequencing at the UDP. The UDP receives regular media coverage, including in *People*, CNN, and others.

Recent Intramural publications

- Colleen McBride presented data in a one-day symposium in Detroit entitled *The Multiplex Initiative: Implications for Personalized Medicine.*
- Yingzi Yang's research identified a trigger for the cell's internal compass (*Nature*, June 20, 2010).
- Elaine Ostrander had publications on the Alaskan sled dog (*BCM Genetics*, July 22, 2010) and on the simple genetic architecture that underlies the diversity of canine traits (*PLoS Biology, August 10, 2010)*.

CONCEPT CLEARANCES

It was noted that two of the concept clearances (presented by Dr. Susan Old and Dr. Joan Bailey-Wilson) are for NHGRI intramural programs. These concept clearances are being presented to the NACHGR because of timing issues, as the usual processes would not have provided clearance in time. As a rule, there must be clearance of concepts for funding opportunities by a public body before RFAs can be issued.

Therapeutics for Rare and Neglected Disease (TRND) Dr. Susan Old presented a concept clearance proposal for the TRND program. TRND is congressionally mandated, with oversight by the NIH Office of Rare Diseases Research (ORDR); it is currently administered by NHGRI TRND is intended to address the area of therapeutics for rare and neglected diseases that are not currently being developed by the pharmaceutical industry.

At present, the NIH Molecular Libraries Program (MLP) works in the development of chemical probes, including those developed with assays relevant to rare and neglected diseases. TRND will pick up in the drug development pipeline where the MLP ends and move promising compounds through the pre-clinical trial phase, bridging the translational research gap by providing medicinal chemistry, toxicology, and proof of concept in human studies. Once a probe reaches the clinical trial stage, it should be picked up by a pharmaceutical or biotechnology company. TRND is disease-agnostic. It will also be trying to develop the science of clinical development. While 99.8 % of compounds in drug development fail at some point in the process, pharmaceutical companies do not investigate why these fail. TRND will attempt to understand the process and increase its efficiency.

TRND began in May 2009. It received $24 million in funding in each of the last two years. In Fiscal Year 2011 the President's budget calls for the funding to increase to $50 million. To date, TRND has taken on five pilots to test its ability to move a candidate through the drug development pipeline and to find out where the problems lie in implementing the process within the government setting.

TRND plans to start funding projects in April and must be fully operational by that point. A call for proposals will be released in the next few weeks. Proposals submitted to TRND will be reviewed by a technical evaluation panel. The TRND leadership will set programmatic priorities, and which will be reviewed at the second level by a trans-NIH advisory group.

NIH currently lacks the complete intramural facilities for TRND, and has been actively renovating to create the labs and acquire the necessary equipment. Until this construction is complete, TRND will function by working with Contract Research Organizations (CROs). The concept being presented to Council for clearance is for the necessary contract solicitations. To facilitate Council discussion, NHGRI convened a small expert working group to make a recommendation to the Council. There were few concerns raised in the working group's report, other than the need to diligently monitor the CRO contracts.

Council asked how the go no-go decisions would be made as molecules move through the program, compared to the process in Pharma. Dr. Old relied that TRND is now developing its governance process, putting together project plans, milestones, and criteria for go no-go decision points to establish a continuous evaluation process. TRND will be have its own Board of Scientific Councilors separate from the DIR Board of Scientific Advisors. The members of the TRND BSC will include experts in drug development, and experts in rare and neglected diseases. One way in which the oversight of the TRND process will be different from that in the pharmaceutical industry is that TRND decisions will not be profit-driven in the same way that industry decisions are. However, TRND will have to be very selective in its project selection because its current budget will only be enough for a few projects. Council also asked whether Pharma was interested in facilitating follow-up studies by TRND on failed compounds. Dr. Old noted that TRND has had many meetings with representatives of both the pharmaceutical and biotechnology industries, and there is a lot of interest. TRND is also negotiating the possibility of testing currently approved drugs from Pharma through its drug development system for rare and neglected disease indications. Council asked what would happen if one of the drug candidates proved to be successful. The specific answer will depend on several factors, including where the drug candidate had entered the TRND pipeline, and whether inventorship occurred at the NIH, an academic center, the private sector, or elsewhere. The NIH Technology Transfer Office will help facilitate these discussions. Council stressed the need for an exit strategy, as this program will not do phase III, marketing, and beyond. Council inquired how to move forward with non-profits who are increasingly interested in rare and neglected diseases. Dr. Old replied that TRND has met with several such organizations and has proposed a collaborative model. TRND can only do a small number of projects per year, maybe 3, and there are 6000 rare and neglected diseases, underscoring the importance of collaboration. There was a question about the cost premium for using the CROs. The NIH labs will be less expensive, even though the CROs are quite efficient. But the primary value of conducting the research intramurally will come from the opportunity to investigate the science of drug development. Council asked about NIH getting more involved in clinical studies. There are NIH clinical disease networks that could be tapped into for this. Council asked to what extent outsourcing will help set up the research, and Dr. Old responded that it would be mostly in process development.

Council unanimously approved the concept.

Ethical, Legal and Social Implications Program (ELSI) Dr. Jean McEwen presented the concept clearance for the ELSI RFAs.

The ELSI program is proposing two RFAs, R01 and R21, focused on issues around the question of return of individual results to participants in genomic and genetic research studies. This is an active topic of discussion in the field, and both IRBs and researchers are struggling with it. Opinions range from the position that it is overly paternalistic to withhold information where there is clinical significance and an intervention to the position that it is unethical to release these results because researchers often do not know what the results mean, the meaning may change, and doing so may burden people with information, causing more distress than good.

There have been some early attempts to evaluate these questions. However, these studies have generally been in the form of surveys, focus groups and other ways to collect information from hypotheticals. There is actually little data on how individuals actually react in research settings.
There is also a need for research on the legal and normative aspects of the question.

To stimulate such research, NHGRI proposes to issue two RFAs. One will solicit applications for R01 grants for behavioral and social research studies, giving priority to those collaborating with genomics researchers already in these situations. The other will solicit applications for smaller, exploratory legal or normative studies, or other, more limited, exploratory behavioral or social science questions. NGHRI proposes to commit about $1 million per year for the R01s and $500,000 for the R21s. NHGRI hopes to get other NIH Institutes to participate; increased participation would allow an increase in the number of awards that could be made.
Council members had several comments: These issues are also relevant for tissue banks, where samples may have been collected 10 years ago. The questions are also important to consider in the context of the electronic medical records. Data to support decision-making in this area would be very useful. It will be important to attend to putting what subjects want into a context of their understanding and knowledge. It will be important to do this research in a practical way, using real world examples, to avoid endless cycles of theoretical consideration
There are logistical burdens involved, especially with a biobank, to keeping track of many subjects and promising to return results, which may result in a legal liability if the researchers are actually not able to follow through. The real polarization of this issue is between those who consider return of results permissible, but not obligatory, and those who consider it obligatory. If return of results is obligatory, there will need to be a lot of structure put in place. Proper consent would be an issue, in that it is difficult to inform people about results that might not be uncovered until 10 years in the future. Consideration of time span is atypical for any other research, posing a distinctive challenge for this type of research. Council asked that a consideration be made for children. Council noted that another aspect of legal research that was not included in this RFA, but perhaps should be, is IP constraints that patent holders put on what can be done by researchers. It is not clear to what extent patent considerations are preventing researchers from sharing results.

Council unanimously approved the concept.

Intramural Contract Dr. Joan Bailey-Wilson, an NHGRI intramural scientist, presented a concept clearance for an intramural contract. As this is an intramural project, it would normally be presented to intramural program's Board of Scientific Counselors. However, the Board is not meeting until late November, and waiting for that meeting would keep Dr. Bailey-Wilson's group from getting the contract in place on time.

Dr. Bailey-Wilson's lab works on the genetics of lung cancer, the most common cause of cancer death in the US. Tobacco smoke is the main, but not the only, risk factor, and after adjusting for smoking, there are data showing a strong genetic. The contract for which Dr. Bailey-Wilson is seeking approval is to support a rapid ascertainment network for lung cancer patients and their families for linkage, GWAS, and sequencing studies. Collection will be at a single site, Louisiana State University; Dr. Bailey-Wilson established this site when she was a faculty member at the University. The reason that concept clearance is required for this contract is that it is being proposed for Other than Full and Open Competition. Dr. Bailey-Wilson explained that it is very difficult to do these types of studies with lung cancer, and that the current contractors have 15 years of experience and an existing network of 37 hospitals, and their questionnaires are well-tested. Introducing a new contractor would cause an estimated two-year delay. Another complication would be that the IRB rules would not allow a different contractor to re-contact the families who are already enrolled for follow-up studies.

The funding for this project is from Dr. Bailey-Wilson's lab and from DIR central research funds. The contract can be terminated at any point.

In answer to a question from Council, Dr. Bailey-Wilson said that so far, 20 families that are good for linkage studies have been enrolled, with many more families that are biospecimen-limited. Therefore, an additional 10 to 15 families from the contract would represent a substantial increment. As for the availability of the samples, they are available for anyone to use, if they receive IRB approval and fulfill the other requirements. The group recently received ARRA funding to re-consent the families for dbGaP, and most of them agreed to that. The GWAS data are widely available, with linkage evidence that there may be several key genes. Council thought that it was important to note why a chartered committee was required for a contract with other than full and open competition. Some members were concerned that there may be other groups in the country with experience in this type of collection, and did not think that the IRB rationale was sufficient in light of the fact the group recently re-consented many of the families to enter their data into dbGaP, and so presumably could be re-contacted and re-consented for another contract. Dr. Bailey-Wilson noted that the families could be re-consented, but it would cause a time delay. Council questioned whether this approach was the best way to move forward, given the

available technologies. Dr. Bailey-Wilson stated that these studies are valuable in allowing an understanding of which mutations are segregating with the disease, with advantages beyond linkage analysis. She agreed that perhaps additional families would not be needed in large numbers if the genetics of the disease turned out to be relatively simple, but nevertheless the addition of 10 to 15 more families would greatly increase the analysis power.

Council voted to approve the concept, with one member abstaining.

PROJECT UPDATE

Human Microbiome Project (HMP) Dr. Jane Peterson gave the update on recent developments in the HMP.

The HMP is a Common Fund initiative to characterize the microbes that inhabit the human body and to examine whether changes in the microbiome can be related to health and disease. The HMP has funded efforts to characterize the normal microbiome, Demonstration Projects to investigate the relationship between changes in microbiome characteristics and disease, computational tool development, technology development, a data analysis and coordination center, reference data set generation, and ELSI studies.

Four genome centers are funded to characterize the normal microbiome. Two (Baylor and Washington University) recruit subjects for the characterization of the normal microbiome, and all four perform both 16S and whole genome shotgun metagenomic sequencing. To date, the target of 300 subjects have been recruited and sampled at least once (some repeat visits are ongoing). Samples have been taken from the oral cavity, skin, nasal cavity, gut (stool), and in females, the vagina. Microbial DNA yields have been adequate at most sites, although yields from the skin samples have been low in some cases..

The Centers are also sequencing microbial reference genomes to aid in the analysis of the metagenomic data. Recently, cost decreases and evidence of the utility of these sequences have led to increasing the target number of reference genomes to 3000 from the original 1000.

The time burden to analyze this large number of samples has lead to the development of

HMP has organized a Data Analysis Working Group (DAWG) that has about 80 members, from both the funded projects and from outside. The DAWG has sub-groups working on the analysis of 16S or shotgun data, as well as other specific tasks. New software tools have had to be developed for the analysis of the complex metagenomic data. There have also been advances in filtering out human sequence data to allowing the microbial to be deposited in an open access resource.

The Demonstration Projects have been going very well. HMP was able to fund the ramp-up of 8, and ICs continued funding several others. Several examples of early results were described. In the case of a study of the infant microbiome and necrotizing enterocolitis, for example, increased transcription in one type of bacteria was found to occur few days before the onset of the medical crisis that often leads to death in the affected babies, raising hope that this observation could lead to early diagnosis.

Council asked a number of questions. In response to one, Dr. Peterson noted that blood was being collected and stored for potential use in the future but host genotyping was not currently being done. With respect to the possible role of diet, she noted that, given the tremendous amount of detail that would be needed to make these data useful, the HMP does not collect data on participant diet. With respect to the analysis of bacterial species that have not been cultured, Dr. Peterson stated that the majority of the bacteria in the human microbiome are not culturable, and the technology development projects are addressing new culture techniques or the sequencing of bacteria without culturing.

PRESENTATION BY THE NIH DIRECTOR, Dr. Francis Collins.

Dr. Collins discussed the five themes he articulated shortly after starting as NIH Director. These are based on areas he considers to have exceptional opportunities for research. The first theme is heavily based on genomics, but the other four also have genomic components.

He then spoke about the recent controversial court decision regarding human embryonic stem cell (hESC) research. He noted that the remaining uncertainty about the case is causing young scientists to reconsider continuing to work in stem cell research or to think about moving their research efforts to other countries. While induced pluripotent stem cells appear to show a lot of promise, there is growing evidence that they do not behave identically to stem cells. It is very important that there be an opportunity to make the necessary comparisons.

Advances in DNA sequencing continue dramatically reduce costs and to expand opportunities. Recent large-scale sequencing efforts have been able to track down molecular basis of rare disorders, such as Kabuki syndrome, with whole exome sequencing. NHGRI is increasingly becoming involved in translational efforts and to move basic discoveries into therapeutic pipelines. Some examples include the high throughput screening activities at NCGC, the Molecular Libraries Project's movement of research probes into therapeutic practice, TRND, and RAID. New NIH initiatives involve new interactions with Pharma, CTSAs, the NIH Clinical Center, and the biotechnology industry. The NIH recently announced a new partnership with the FDA, with a joint leadership council to meet next month. NIH will support research to provide new methods to handle innovative clinical trial ideas and rare disease protocols.

The Health Care Reform Act has been very exciting for the NIH. President Obama is very knowledgeable about science and has a lot of interest in scientific research. A recent development has been the Cures Acceleration Network, which was originally proposed by Arlen Spector and has passed. This program is intended to accelerate the pathway through the so-called "valley of death" for new drug candidates. It also provides some flexible funding mechanisms and a new set of opportunities to speed up the process of passing a drug through clinical trials.

There is increasing need for diversity in science and medicine in the US, and the NIH continues to look for innovative ways to increase the diversity of those entering these fields. A new development is the Path Finder award from Stimulus funding.

The end of the two-year ARRA funding period is coming to a close. Of the $10 billion in Stimulus funds for NIH, $9.3 billion has already been awarded, and over 2,000 positions have been funded. There is, however, concern about the post-ARRA drop-off which, even with the Administration's proposed increase in the NIH budget, will still be $4 billion. It isn't clear how this will affect success rates for those applying for NIH funding. It is possible that the number of applications will increase, as newly funded institutions will re-apply. This is likely to stress the system for grantees, reviewers, Councils, and others. It will require re-considering what research has been supported, and facing up to the fact that some things that have been supported are now of lower priority than some new innovations. The best way to move science forward is to innovate, do new things, and generate excitement about biomedical research. This is an exciting moment in NIH history.

Council asked how the number of young people entering the field has been affected by funding. Dr. Collins noted that the former NIH Director, Elias Zerhouni, developed innovator programs to help new investigators. The NIH OD is preparing to announce another new program, this one for to support talented PhD graduates who are able to move directly into independent positions. However, it is not just new investigators who are of concern; another group is those who are trying to renew their grants for the first time. There is a fine line that needs to be walked between advocating for the fact that research is under-supported and scaring away new investigators. Council raised a concern about how the current fiscal climate might affect the distribution of funding, with the institutions with the greatest funding able to increase their funding, at the expense of programs currently receiving less support. There was also a comment about how the reliance of investigators on soft money for salaries hurts biomedical research, as investigators are increasingly spending more of their time applying for funding. With respect to overall NIH funding levels, Council noted that there is an economic argument for increasing the NIH budget, as research funds are exceptionally well spent and analyses have shown that biomedical research has saved money over time. All recognized, however, that there is increasing concern about the deficit. It was also

noted that the competitiveness of U.S. science has diminished, giving further reason for Congress to increase the NIH budget. Dr. Collins recent prepared a report on this topic, and said that he would distributed it to the Council members. On another topic, one Council member wondered whether Congress may object to NIH opening the pipeline from drug development to the clinical setting due to real or perceived conflicts of interest. This led to a discussion of the difficulties in managing expectations for translational medicine while still acknowledging the many instances where this is already happening. Dr. Collins noted that, after reading one of the negative pieces written on the occasion of the 10th anniversary of the Human Genome Project, he easily made a list of 29 clear accomplishments due to the HGP. He offered this as an example of how NIH could be more proactive in communicating its success stories to the general public and to policy/stakeholder groups. To that end, the NIH has created a brochure making the case for NIH, which has been provided to Congress. Dr. Collins suggested that Council members and other scientists could also contribute by educating their congresspersons about the excitement and relevance of biomedical research in their home state. Finally, Council asked about the recent FDA collaborations. Secretary Sibelius is working to strengthen ties with other HHS branches, including the FDA, ARC, CDC, Indian Health, and hopefully the CMS in the near future.

TRAINING PROGRAMS

In response to a previous Council request, Dr. Bettie Graham discussed the NHGRI T32 grants. The data she presented come from the responses to a questionnaire that was sent to T32 Program Directors over the summer.

NHGRI funds 12 pre-doctoral and 8 post-doctoral T-32 programs. Many have had the same program director since funding began. A variety of departments are involved, most commonly deapr departments are biology, statistics, genetics/genome sciences, computer science/bioinformatics and microbiology. Other participating departments, with fewer trainees, include clinical sciences, biochemistry, chemistry, ecology, pharmacology, bioengineering, social science, and physics.

The responses to the questionnaire pertained to 454 pre-doctoral trainees who have been supported on a training grant. 38% are female and 62% male. 13% are under-represented minorities (URMs). Dr. Graham noted that the percentage of URMs in the computer sciences/bioinformatics discipline was 21%, higher than the overall average in that discipline. . 59% of past trainees are in academia (11% are in faculty positions, 19% are research associates, 4% are post-doctoral students, 20% are graduate students, 4% are medical students, and less than 1% are veterinary students). 13% of trainees are in for-profit institutions, 1% are in government or non-profit, and data were not known for 27% of trainees.

Responses also pertained to 145 post-doctoral trainees. 32% are female and 68% male. 9% of post-doctoral trainees are URMs. Dr. Graham noted concern that there were no URMs in the computer science/bioinformatics discipline. Currently, 69% of post-doctoral trainees are in academia (28% are faculty, 32% are research associates, 9% are post-doctoral students, and 1% are graduate students). 18% are in for-profit institutions, 1% are in government or non-profit, and data were not known for 12%.

Dr. Graham also presented the average number of refereed publications for all trainees. For pre-doctoral students, average publications per trainee were 3.3 and ranged from 2.3 to 4.7 for all trainees; for URMS, the average was 2.8 and ranged from 1.3 to 6.3. For post-doctoral trainees, average publications per trainee was 3.0 and ranged from 2.0 to 15.6; for URMS, the average was 4.8 and ranged from 2.5 to 6. It was noted that the 15.6 statistic may have been a reporting error.

11.5% of pre-doctoral trainees and 1.4% of post-doctoral trainees did not complete the program, for various reasons. The average pre-doctoral appointment was 2.2 years, and the average post-doctoral appointment was 1.7 years.

NHGRI does not fund a formal training program for ELSI, but does support 35 trainees through the CEERS program..

Council member Michael Boehnke is the Program Director for the University of Michigan NHGRI T32, which was one of the first the NHGRI funded, and is now in its 16th year. The goal of this program is to train students at the

interface of genetics, genomics, and mathematical sciences. There are several participating departments. This program had 8 slots for students in years past, but it has been increased to 13 this year. Most of the trainees are pre-doctoral students. Dr. Boehnke noted that there are more qualified students that could be accepted if the number of available slots were greater. He also commented on the need for more trainees in the quantitative sciences. The Minority Action Program (MAP) has helped his program in recruitment and retention of URMs. Two areas where he would like to see changes are funding for foreign students and for Master's level students.

Council member Rick Myers is the former Program Director for the Stanford NHGRI T32, where he ran the training program for 14 years. Genomics has been a popular area at Stanford, with 11 departments participating in the training program. The program has emphasized computational biology from its inception. Last year, the program had 26 pre-doctoral and 4 post-doctoral positions available. Dr. Myers echoed Dr. Boehnke's comments that a greater number of trainees are needed, and that the flexibility of this program has been very helpful. The Stanford program has strived to increase diversity from the beginning.

Janet Sinsheimer and Kenneth Lange of the UCLA were invited to describe their T32 program via teleconference. UCLA's T32 has 11 slots from 7 departments, with a number of sub-specialties. The UCLA T-32 began without URMs, but after Drs. Sinsheimer and Lange began attending the MAP meetings, they became involved in that program and have been able to increase the number to 8 URMs out of 36 students. This has been achieved partly by looking at the potential of applicants as scientists, rather than simply considering GRE scores. There have been recent efforts to reach out to URMs; some URMs from the program have gone back to recruit at their former institutions and at other universities with a strong minority presence. UCLA has also coordinated several programs at a local middle school with a large minority percentage to build interest in genomics. Recently, the program received a minority supplement, allowing them to fund a recruiter to focus on this population and to add tutors.

There was a discussion on the burden placed on program directors of T32s, both at NHGRI and at other NIH institutes, in collecting data for the MAP program. It has been a full-time administrative job to gather the statistics, and the process dissuades people from applying for training grants. While some of the data are valuable, many of the statistics are not as informative and do not get carefully reviewed. It was suggested that the NHGRI Council issue a statement regarding the administrative burden of T32s to the NIH. It was noted that recently Washington University was awarded a grant to support a data coordination center for this program. The goal is to keep a record on each student, and allow the program to update its information on a yearly basis.

Council voiced concern about the non-response of one institution to the survey. Council also cautioned against over-interpretation of these statistics; due to the small number of trainees, a difference of one student can make a large change in the percentage.

COUNCIL-INITIATED DISCUSSION

Rick Myers would like to discuss human subjects issues at an upcoming Council meeting. As these issues are changing frequently, it would be good for the group to be informed on this topic. In particular, issues that about children in biomedical research, best practices for research activities, variations between IRBS, federal laws and regulation, and others. It was suggested a panel discussion may be the best way to cover this topic.

Staff had suggested including a discussion of the CEGS program at the next Council meeting. Two of the CEGS are coming into their 10th and final year. Council would like to hear about the accomplishments in those CEGS, as well as the others.

There was also a request to cover gene and lifestyle interactions, and how the interplay between these plays out in issues of smoking and lung cancer, and other related topics.

Potential agenda items for the February 2011 Council:

1. **Human subjects issues**
2. **CEGS**
3. **Gene and lifestyle interactions**

4. **How software proposals are reviewed, issues around grants supporting software.**

ANNOUNCEMENTS AND ITEMS OF INTEREST

Dr. Guyer directed Council to the Council folders containing items of interest.

CONFLICT OF INTEREST

Dr. Guyer read the Conflict of Interest policy to Council and asked them to sign the forms provided.

REVIEW OF APPLICATIONS

In closed session, the Council reviewed 151 applications, requesting $97,692,481. The applications included 97 research projects, 20 ELSI grants, 2 RFAs, 9 research center grants, 5 conference grants, 7 SBIR Phase I grants, 2 SBIR Phase II grants, 6 individual training grants, 1 education project award, and 2 mentored quantitative research center awards. A total of 96 applications totaling $42,144,796 were recommended.

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

_____ _____

Date Mark Guyer, Ph.D.
Executive Secretary
National Advisory Council for Human Genome Research

_____ _____

Date Eric Green, M.D, Ph.D.
Chairman
National Advisory Council for Human Genome Research