NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL

MEETING MINUTES
June 13, 2006

I. CALL TO ORDER AND OPENING REMARKS - Dr. Elizabeth G. Nabel

Dr. Elizabeth Nabel, Director of the National Heart, Lung, and Blood Institute (NHLBI), welcomed members to the 222nd meeting of the National Heart, Lung, and Blood Advisory Council (NHLBAC).

Member Updates:

Dr. Nabel introduced four new Council members:

- Victor J. Dzau, M.D., Chancellor for Health Affairs, School of Medicine, Duke University
- Helen H. Hobbs, M.D., Professor, Department of Molecular Genetics, University of Texas Southwestern Medical Center
- Joseph Loscalzo, M.D., Ph.D., Chairman, Department of Medicine, Brigham and Women's Hospital
- Jennie R. Joe, Ph.D., M.P.H., Director, Native American Research and Training Center, College of Medicine, University of Arizona

Dr. Nabel also introduced three new NHLBI staff members:

- Dr. Susan Shurin as Deputy Director of the NHLBI. Dr. Shurin is highly talented and experienced in academic medicine, university leadership, and management of complex organizations. She was Professor of Pediatrics and Oncology at Case Western Reserve University and Chief of Pediatric Hematology/Oncology at Rainbow Babies & Children's Hospital in Cleveland. Dr. Shurin is currently leading Institute efforts to enhance the clinical research program.
- Dr. Charles Friedman as Director of the new NHLBI Center for Research Informatics and Information Technology (CRIIT). Dr. Friedman comes to the NHLBI from the University of Pittsburgh where he was Founding Director for the Center for Bioinformatics. He will establish an NHLBI-wide informatics program and will oversee NHLBI information technology resources.
- Dr. Christopher O'Donnell as Senior Advisor to the Director for Genome Research. Dr. O'Donnell will continue to serve in his current position as Associate Director of the NHLBI-supported Framingham Heart Study in addition to assuming his new duties with the Institute.

An additional staff appointment, pending administrative clearances, is expected to be finalized soon:

- Dr. Alan Michelson as Associate Director for Basic Research. Dr. Michelson comes to the NIH from the Division of Genetics in the Department of Medicine at the Brigham and Women's Hospital.

Guest Speakers:

- Dr. Toni Scarpa , Director, Center for Scientific Review
- Dr. Peter Savage, Director, Division of Epidemiology and Clinical Applications
- Dr. Elias A. Zerhouni, Director, National Institutes of Health

[Top of Page]

II. REVIEW OF CONFIDENTIALITY AND CONFLICT OF INTEREST - Dr. Elizabeth G. Nabel

The Council was reminded that according to Public Law 92-463, the Federal Advisory Committee Act, the meeting of the NHLBAC would be open to the public except during consideration of grant applications. A notice of this meeting was published in the *Federal Register* indicating that it would start at 8:30 a.m. and remain open until approximately 12:00 p.m. Dr.Nabel also reminded the Council members that they are Special Government Employees and are subject to Departmental conduct regulations.

[Top of Page]

III. REPORT OF THE DIRECTOR - Dr. Elizabeth G. Nabel

Dr. Nabel highlighted several items of interest included in the materials distributed to the Council members:

- The NHLBI Legislative update on the 109th Congress.
- Recent scientific articles published by NHLBI grantees, including several articles published by investigators from NHLBI's pulmonary networks.
- Recent NHBLI press releases.
- NIH Fact Sheets being developed as part of an effort by Dr. Zerhou n m i Zerhoumi to educate the Congress and the public about NIH extramural funding policies and research areas of interest. The NHLBI has developed Fact Sheets on Heart Disease and Sickle Cell Disease.
- Recently released NHLBI initiatives.

Strategic Plan

The NHLBI began Level 1 of its strategic planning process in April 2006. Each NHLBI extramural Division has established a series of Level 1 meetings to identify scientific areas in which the NHBLI is well positioned to make major contributions and to evaluate Institute business and operational policies. The Level 1 phase, which will end in September 2006, will be community-based, incorporating input from approximately 500 investigators. In October 2006, a Level 2 meeting will be held to aggregate the recommendations received during the Level 1. The Council and members of the NHLBI Board of Extramural Advisors will participate in the Level 2 meeting. A final strategic plan is expected in Spring 2007.

Budget Report

Dr. Nabel reviewed the recent budget history of the Institute. The proposed FY 2007 President’s Budget for the

NHLBI is $2,865.9 million, a 1.0 percent decrease from the Institute's FY 2006 appropriation. The NHLBI payline for research project grants has been increased from the 14.0 percentile to the 15.0 percentile (20.0 percentile for new investigators). Grants between the 14.0 and 15.0 percentile that were not funded earlier in the year can now be funded. Dr. Nabel noted that the current NHLBI payline is one of the highest among the NIH Institutes and Centers. Dr. Nabel also indicated that despite the current austere financial climate, the NHLBI remains committed to its core values of support for investigator-initiated research and for new investigators. Dr. Nabel also noted that there will be fewer noncompeteing grants in FY 2007, making more funds available to fund competing grants.

[Top of Page]

IV. CONDUCT OF NHLBI-SPONSORED CLINICAL TRIALS – Dr. Susan Shurin

Dr. Susan Shurin, Deputy Director of the NHLBI presented an overview of the conduct of NHLBI-sponsored clinical trials and described recent efforts to enhance clinical trial efficiency and effectiveness. Dr. Shurin noted that clinical research is an important part of Dr. Nabel's vision for the future of the NHLBI. Business operations related to clinical trials will be examined carefully during the NHLBI strategic planning process.

The NHLBI recently established two new entities devoted to clinical research:

- a Clinical Studies Coordinating Committee to facilitate trans-NHLBI coordination of clinical trial policies and procedures across the extramural Divisions;
- an Office for Clinical Research that will work with the extramural Divisions and with information technology staff to streamline clinical trial reporting, tracking, and oversight and develop training programs for Division staff.

The Institute is considering several possible approaches for enhancing output of existing studies, partnering with other funding entities to reduce duplication of infrastructure resources, creating new networks for multicenter trials, and creating Centers that incorporate both basic and clinical research. Dr. Shurin invited the Council to provide feedback and advice on the proposed approaches and on setting priorities for investment in clinical trials, selecting metrics, benchmarks, and outcome measures for trials, and balancing competing priorities.

Council members were supportive of NHLBI efforts to enhance clinical trials. They noted that the increasing costs of clinical research discourage some institutions from participating in clinical studies. They also were supportive of NHLBI efforts to work with regulatory agencies to standardize reporting. Council members also offered suggestions regarding management of patient accrual into trials. Further suggestions from Council members are welcome.

[Top of Page]

V. NIH AT THE CROSSROADS – Dr. Elias Zerhouni

Dr. Elias Zerhouni, Director of the National Institutes of Health, discussed the NIH budget and presented his vision for the future of the NIH. The NIH currently is facing a difficult budgetary climate, so it is important for researchers to be unified in their efforts to educate the public about the value of investment in biomedical research and the need for a sustained commitment to the investment. Dr. Zerhouni presented data showing that three factors, large scale capacity building and increases in the number of new faculty, Congressional appropriations below inflation since the end of the NIH budget doubling, and the budget cycling phenomenon

have contributed to lower paylines. The data indicate that demand for grants took off just as the doubling of the NIH budget was ending, creating an imbalance between the demand and available funds. Dr. Zerhouni emphasized the importance of protecting the NIH's key principles, including discovery of new knowledge and support for new investigators, during tough budgetary times. To support new investigators, the NIH has recently established a Pathway to Independence Award that would allow up to two years of funding support for mentored post-doctoral fellows and up to three additional years of funding once fellows transition to an independent research position. Finally, Dr. Zerhouni shared his vision of reducing the cost of health care by moving from a paradigm of curative therapy to one of predictive, personalized, preemptive care.

The Council thanked Dr. Zerhouni for his testimony to Congress and presentations to the public about the tremendous return the United States receives on its investment in biomedical research and the importance of biomedical research to the Nation's health and economic competitiveness.

[Top of Page]

VI. CHALLENGES AND OPPORTUNITIES OF NIH PEER REVIEW – Dr. Toni Scarpa

Dr. Toni Scarpa, Director of the NIH Center for Scientific Review (CSR), discussed new challenges and opportunities facing the NIH peer review system. Dr. Scarpa noted that the system has produced an effective partnership between the federal government and research institutions, has protected the NIH against outside influence, and has contributed to the excellence of biomedical research in the United States. Now, efforts are underway to make the system even better by increasing communication, transparency, uniformity, and efficiency. Specific goals include shortening the review cycle, addressing the concern that clinical research is not properly evaluated, improving the assessment of innovative, high-risk, high-reward research, and recruiting and retaining more high-quality reviewers. The CSR is currently transitioning to a system of electronic grants submission to help streamline the submission process. The CSR also has begun testing the use of knowledge management tools including Collexis and other software to assign applications to study sections and select reviewers with appropriate expertise. A new pilot program is underway to determine the feasibility of expedited review for grant resubmissions by new investigators. The CSR also is exploring the use of electronic platforms for study sections.

The Council commended the CSR's efforts and emphasized the importance of ensuring adequate expertise and experience of reviewers.

[Top of Page]

VII. PRESENTATION OF BEA INITIATIVES – Dr. Peter Savage

NHLBI staff presented 18 new initiatives, 17 of which were reviewed in April by the Board of Extramural Advisors (BEA). Dr. Peter Savage, Director, Division of Epidemiology and Clinical Applications, explained that an additional initiative, which is being developed with the National Human Genome Research Institute to study genotype-guided dosing of warfarin, was not reviewed by the BEA.

The Council was supportive of the initiatives but made a number of specific recommendations for consideration prior to their release. Dr. Nabel will consider the recommendations of the BEA and the Council and other budgetary and programmatic issues in determining which of the proposed initiatives, if any, to implement.

Ancillary Studies in Clinical Trials **, RFA**

Purpose: to To solicit research grant applications to conduct time-sensitive ancillary studies in conjunction with ongoing Phase II and III clinical trials related to heart, lung, and blood diseases and sleep disorders.

Council recommended this initiative.

A Resource for Blood and Marrow Transplant Clinical Research **, NOT**

Purpose: to To provide continuing support for the Center for International Blood and Marrow Transplantation Research (CIBMTR) Statistical Center to collect and analyze outcome data from recipients of hematopoietic stem cell transplants (HSCT).

Council recommended this initiative.

Basic and Translation Research in Lung Transplantation **, RFA**

Purpose: to To support basic and translational clinical research on preventing and/or reducing complications associated with lung transplantation.

Council recommended this initiative.

Biology of Venous and Lymphatic Diseases **, RFA**

Purpose: to To support basic and translational research on venous and lymphatic biology, and the investigation of disease mechanisms in these two closely allied components of the circulation. Collaborative studies that may allow improved diagnosis, new therapeutic options, and prevention of venous and lymphatic disorders are encouraged.

Council considered these areas of research to be very important and recommended that there be two separate initiatives to address them.

Building Research Capacity and Collaborations through Unique Institutional Partnerships in Genomics and Proteomics **, RFA**

Purpose: to establish mutually beneficial and long-lasting collaborations to conduct heart, lung, blood, and sleep (HLBS) disease research in genetics, genomics, proteomics, or other –omics areas, between investigators at research-intensive institutions (RII) and minority-serving institutions (MSI). Essential to the success of these collaborations are career development and training in –omics research.

Council recommended this initiative.

Cancer and Cardiovascular Disease Research Network (CCRN)

Purpose: to expand the NCI's HMO (Health Maintenance Organization) Cancer Research Network (CRN) into a joint NCI and NHLBI Clinical Research Network (CCRN) to:

- Provide more robust cardiovascular disease (CVD) health care surveillance data than existing studies
- Promote research on clinical practice, quality of care, and uncommon phenotypes, and ensure access of CCRN to non-network extramural researchers

- Enable the assessment of new diagnostic and therapeutic technologies and clinical guidelines on CVD incidence, prevalence, care, and outcomes over time.

Council recommended this initiative.

***Evaluation of Novel Oxygen Therapeutics: Mechanisms of Toxicity and Efficacy of Candidate Blood Substitutes,* RFA**

Purpose: to support basic research studies to facilitate development of clinically useful oxygen-carrying red blood cell substitutes. The focus of this initiative is on the study of fundamental mechanisms of efficacy and toxicity of oxygen carriers.

Council acknowledged that basic research on blood substitutes is needed but that there have been no obvious innovative approaches. Industry has not concentrated on the basic science which is crucial. The suggestion was made to try to partner with the Department of Defense to obtain whatever data is currently available.

***Framingham Heart Study - Renewal* , RFP**

Purpose: to continue the Framingham Study in order to significantly expand knowledge about the complex influences of genes and environment on development and progression of heart, lung, blood and sleep (HLBS) diseases and disorders, by utilizing the extensive array of new and existing information on genetics, behaviors, biomarkers, imaging techniques, and environmental factors.

Council enthusiastically supported the renewal of this initiative.

***Mitral Valve Repair in Dilated Cardiomyopathy (MVR-DCM)* , RFP**

Purpose: to conduct a randomized clinical trial to determine whether mitral valve (MV) repair reduces a composite endpoint of cardiovascular death, heart failure hospitalization, heart transplantation, or insertion of an implantable circulatory assist device in patients with dilated cardiomyopathy and hemodynamically significant mitral regurgitation (MR) compared to standard medical therapy.

Council supported this initiative and commented that the design of the trial would be critical.

***Molecular Mechanisms of Aortic Valve Sclerosis* , RFA**

Purpose: to support research on the biology of aortic valve sclerosis (AVS), with a special emphasis on its initiation and progression. This program also encourages the development of relevant animal models to help understand the sclerotic process.

Council recommended this initiative.

***NHLBI GENELINK – Renewal* , RFP**

Purpose: to provide the infrastructure to facilitate gene finding by: 1) promoting sharing of results of genetic analyses, 2) providing a open resource consisting of linked, searchable linkage and association analysis results placed on a common physical map and 3) providing bioinformatics tools to assist researchers in prioritizing and following up findings from linkage and genome wide association studies.

Council recommended renewing this initiative and suggested that emphasis be placed on collating existing data

with standardized data entry.

New Strategies for Growing 3D Heart Tissues **, RFA**

Purpose: to bridge the knowledge gap between cardiovascular biology and the design and repair of heart tissue.

Council recommended this initiative.

Nuclear Receptor Signaling Consortium, **RFA**

Purpose: to develop a comprehensive understanding of the structure, function, and role of nuclear receptors (NRs) in disease and health.

Council recommended this initiative.

Randomized Trial of Genotype-Guided Dosing of Warfarin Therapy **, RFA**

Purpose: to conduct a randomized clinical trial to determine whether use of a genotype-enhanced dosing algorithm (using clinical information and information on genetic variants known to influence warfarin metabolism) to initiate warfarin treatment will improve anticoagulation status when compared to a dosing algorithm using only clinical information.

Council noted that this would be a difficult trial to conduct and that it would be very expensive. Council also commented that better anticoagulants are needed i.e. agents other than warfarin. Dr. Nabel stated that FDA had proposed such a study and that Kaiser Permanente may also be interested in participating.

Role of Epigenetics in Heart, Lung, Blood and Sleep Diseases and Disorders, **RFA**

Purpose: to identify the epigenetic mechanisms underlying the origin and progression of heart, lung, blood, and sleep (HLBS) diseases.

Council recommended this initiative.

Subpopulations and Intermediate Outcome Measures in COPD, **RFP**

Purpose: to define pathogenetically homogeneous subgroups of COPD subjects on the basis of biomarkers, genotypes, and CT images and to identify intermediate outcome measures for use in future clinical trials.

Council recommended this initiative.

The Circadian Biological Clock and Cellular Function in Heart, Lung, and Blood Tissues, **RFA**

Purpose: to elucidate the specific molecular pathways through which the genetic program of the circadian biological clock influences peripheral tissue function, and how mutations in the molecular clock components contribute to developmental pathogenesis and pathophysiology affecting heart, lung, and blood tissues.

Council recommended this initiative.

The Influence of Early Programming in the Development of Cardiovascular, Lung, Blood and Sleep Disorders, **RFA**

Purpose: to investigate how alterations in the intrauterine environment affect molecular and cellular mechanisms that are responsible for the development of heart, lung, and blood disorders later in life.

Council recommended this initiative.

[Top of Page]

VIII. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2).

The session included a discussion of procedures and policies regarding voting and confidentiality of application materials, committee discussions and recommendations. Members absented themselves from the meeting during discussion of and voting on applications from their own institutions, or other applications in which there was a potential conflict of interest, real or apparent. Members were asked to sign a statement to this effect.

The Council considered 1,015 applications requesting $1,684,300,350 in total direct costs. The Council recommended 1,014 applications with total direct costs of $1,663,889,010. A summary of applications by activity code may be found in Attachment B.

ADJOURNMENT

The meeting was adjourned at 3 :00 p.m. on June 13, 2006.

[Top of Page]