NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL

MEETING MINUTES

October 21, 2004

I. CALL TO ORDER AND OPENING REMARKS - Dr. Barbara Alving

Dr. Barbara Alving, Acting Director of the National Heart, Lung, and Blood Institute (NHLBI), welcomed members to the 216th meeting of the National Heart, Lung, and Blood Advisory Council (NHLBAC).

Staff Updates

Dr. Alving informed the Council that the process for the appointment of a new NHLBI director was in the final stages.

Member Updates

Retiring Members:

Dr. Melissa Austin
Ms. Sue Byrnes
Dr. Jeffrey Drazen
Dr. Ananda Prasad
Dr. Pearl Toy

New Members:

The Secretary has invited five distinguished individuals to serve on the Council for terms beginning November 1. Although all accepted the Secretary's invitation, they are not "official members" until their administrative paperwork has been cleared. One of the invited members (Dr. High) was present.

- Dr. Katherine High is the William H. Bennett Professor of Pediatrics and Professor of Medicine and Pathology at the University of Pennsylvania School of Medicine.
- Dr. Charles T. Esmon is the Lloyd Noble Chair in Cardiovascular Research and also a member and Head of the Cardiovascular Biology Research program at the Oklahoma Medical Research Foundation.
- Ms. J. Hoxi Jones is the Director of Public Information and Volunteer Services at the Texas Department of Human Services.
- Dr. Jeffrey McCullough is Professor of Laboratory Medicine and Pathology at the University of Minnesota.

- Dr. Patricia Wahl is Dean and Professor of Biostatistics at the School of Public Health and Community Medicine at the University of Washington.

Special Guests:

Each year the Institute invites a representative from each of its advisory committees to attend a council meeting to see what happens. The following people were present:

- Dr. Theodore Wun, Associate Professor, Division of Hematology-Oncology, Department of Internal Medicine Univsersity of California, Davis Cancer Center. He is the Chairperson of the Sickle Cell Disease Advisory Committee.
- Dr. Shelly Carter is a Senior Statistician and project manager at the Emmes Corporation. She is a member of the Clinical Trials Review Committee.
- Dr. Cheryl Hillery is an Associate Investigator at the Blood Research Institute at the Blood Center of Southeastern Wisconsin. She is a member of the Heart, Lung, and Blood Program Project Review Committee.
- Dr. Pamela Davis is Professor in the Department of Pediatrics at Case Western Reserve University School of Medicine School of Medicine. She is the Chair of the Board of Scientific Counselors.

Guest Speakers:

- Dr. Michael Martin, Director of the Division of Physiology in the Center for Scientific Review, NIH.
- Dr. Paul Sorlie, Division of Epidemiology and Clinical Applications, NHLBI, NIH.

Publications

In addition to the Council Briefing Book, the following publications were provided:

- Descriptive pamphlets for each extramural program division
- “Think Tank on Enhancing Obesity Research at the NHLBI”
- “NHLBI Black Bag Supplement”

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II. REVIEW OF CONFIDENTIALITY & CONFLICT OF INTEREST - Dr. Barbara Alving

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. Alving also reminded the Council members that they are Special Government Employees and are subject to Departmental conduct regulations.

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III. REPORT OF THE ACTING DIRECTOR - Dr. Barbara Alving

Dr. Alving introduced Ms. Sandra Gault, the NHLBI Budget Officer, who gave a presentation on the NIH budget for FY 2005. She reported that Institute had no appropriation and would therefore be operating under a continuing resolution until November 20, 2004. Ms. Gault showed the House allowance which was the same as the President’s budget and contained a three percent increase over the Fiscal Year 2004 budget. The Senate budget contained a 3.6 percent increase. The

number of FTEs for the NHLBI showed a decline as a result of the A-76 competition and centralization. The NHLBI planned to try to maintain an increase in the competitive RPG portfolio. The October payline was projected to be 16 th percentile and P01s would be funded to a 160 priority score for the overall score and 200 for the individual project score. Dr. Alving emphasized that NHLBI had cost measures in place to control spending.

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IV. CSR and the Review of Applications Assigned to NHLBI - Dr. Michael Martin

Dr. Michael Martin, the Director of the Division of Physiology and Pathology in the Center for Scientific Review (CSR), NIH, described the process by which the CSR study sections were evaluated and reconfigured to address current scientific needs. Working groups consisting of extramural researchers were brought together to assess the scientific boundaries, the scope and breadth of the science, the new scientific directions and emerging areas, the qualifications of the reviewers and the fairness of the review in the study sections. As a result of the working groups' recommendations, twenty-four Initial Review Groups (IRGs) were proposed that would be designed to focus on organ systems or diseases. New configurations for the NHLBI-related IRGS have been implemented and include the Hematology IRG, the Cardiovascular Studies (CVS) IRG, the Respiratory Sciences IRG, and the basic science IRGs. The overall system will be monitored and evaluated by the external IRG working groups, internal data analysis, and periodic surveys of customers on a yearly basis and reevaluated every 4-6 years.

Council noted that Peer Review at the NIH works very well and that this effort on the part of CSR is very positive and will yield improvements. Dr. Martin emphasized that principal investigators may request assignment to specific study sections in their cover letter and that 80 percent of such requests are honored. If they are not honored, it may be because of a conflict of interest. A question concerning the lower success rate for new investigators was discussed and Dr. Martin emphasized that all study sections are routinely oriented to treat new investigators with more lenience. In response to another question, Dr. Martin indicated that roughly 40% of incoming applications are revisions and this is partly due to the decrease in the NIH budget.

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V. Hispanic Populations in the U.S. Demographics and Health B Dr. Paul Sorlie

Dr. Paul Sorlie from the Division of Epidemiology and Clinical Applications gave a presentation that was also given to the recent joint meeting of the NHLBI and Pan American Health Organization. He showed the demographics, including size, age distribution, country of origin, social and economic status, and geographical distribution, of Hispanic populations in the United States. Dr. Sorlie also presented data on mortality and risk factors, including cardiovascular death rates, blood pressure, cholesterol, and obesity. In general the Hispanic population is young, diverse, and urban, and has lower education and income than other populations in the US. The cardiovascular disease mortality is lower in Hispanics and this is a paradox since lower socio-economic status usually contributes to higher cardiovascular disease mortality. However, control of blood pressure is low and the incidence of obesity is increasing. These data have significant implications for the future health risk of Hispanics in the United States.

Council considered these data to be important for addressing current and future health problems in the country. Dr. Sorlie noted that the proportion of the Hispanic population born in the US is unclear and that a relatively healthy immigrant population might explain the apparent reduced mortality from cardiovascular disease.

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VI. Board of Extramural Advisors -- Summary of Systems Biology Presentations and Discussion- Dr. Stephen Mockrin

Dr. Stephen Mockrin, Director of the Division of Heart and Vascular Diseases summarized the presentations at the last Board of Extramural Advisors Meeting on September 21, 2004. The theme was systems biology and the presenters were Dr. Leroy Hood, Dr. Peter Sorger, and Dr. Andrew McCulloch. In general, biology is so complex that emergent properties and interactions of proteins, genes etc. can not be predicted. Systems biology is an integrative approach to understand biological

function. It examines multiple elements in a biological system (DNA, genes, mRNA, proteins, metabolites, cells, tissues, organs, organisms), measures their dynamic relationships, in time and space, and uses computational models and data to predict the behavior of a system and its elements and responses to biological or environmental perturbations. In the 20 th century biologists took a reductionist approach to understand biology at the smallest level. However, in the 21 st century, biologists will use systems biology to understand how the various elements interact to produce observed biological function. Systems biology is quantitative, integrative, iterative dynamic, multi-scale, multi-disciplinary, hypothesis generating, and has predictive power. It is crucial to involve scientific disciplines that are not traditionally supported by NIH, such as chemistry, mathematics, computer science, and physics. Advances in technology, bioinformatics, computational methods, and imaging are responsible for the renewed interest and current advances in systems biology. Systems biology is expected to influence medicine by providing a new way to look at disease, changing the drug discovery process (identify targets, develop drugs, and screen for side effects in silico), and developing new diagnostic procedures. In terms of future directions for NHLBI systems biology programs, the Institute should focus on key problems and areas within NHLBI mission, catalyze team science, train investigators (linked directly to research goals), develop and transfer technologies and computational tools, encourage functional and structural integration, promote standards for model representation and sharing, provide open access to models (not just data), use RFAs that are not overly prescriptive and promote risk, and form links that take advantages of other ongoing activities, Examples of these activities include NHLBI Programs (Programs for Genomic Applications, Proteomics Initiative, Microarray Facilities, Programs of Excellence in Nanotechnology), NIH Raodmap programs (Building Blocks, Biological Pathways, and Networks; Molecular Libraries and Imaging ; Structural Biology ; Bioinformatics and Computational Biology; Nanomedicine), and other agency activities (DOE, DARPA, NSF/NIH/DOE/NASA: Interagency Opportunities for Multi-Scale Modeling in Biomedical, Biological, and Behavioral Systems).

Council was enthusiastic about the BEA meeting and questioned whether there would be special mechanisms developed to foster systems biology research. Dr. Mockrin indicated that most of this was being accomplished with the use of RFAs and special programs. Council also emphasized that the goal should be to utilize this information to impact the health of this country. In addition, the data and the models must be rigorously derived in order to be relevant and this requires significant discipline. In response to questions regarding whether to tackle systems in heart, lung, blood and sleep at the same time, Dr. Alving noted that NHLBI would convene a working group to discuss how the Institute should develop systems biology programs. Council members wereasked to suggest names and email them to Dr. Mockrin.

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VII. Discussion of BEA Initiatives- Dr. Stephen Mockrin

1. TITLE: A Phase II Randomized, Placebo-Controlled Clinical Trial of Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease

OBJECTIVES: The goal is to evaluate, in a randomized, double-blind, placebo-controlled Phase II trial, the safety and efficacy of 18 weeks of therapy with sildenafil (Viagra), a nitric oxide potentiator, on exercise capacity, symptoms, and hemodynamic parameters including pulmonary artery pressure in adult patients with sickle cell disease and pulmonary hypertension.

Council recommended this initiative.

2. TITLE: Critical Issues in Post-phlebitic Syndrome

OBJECTIVES: To support research on venous biology, venous post-thrombotic response, and valve function changes that will result in better management of post-phlebitic syndrome.

Council strongly supported this initiative.

3. TITLE: Design and Analysis for Genome-wide Association Studies

OBJECTIVES: To develop and test innovative, appropriate, and cost effective study designs and analytical strategies to successfully perform genome-wide association studies on heart, lung, and blood diseases.

Council expressed high enthusiasm for this initiative.

4. TITLE: Large-Scale Genotyping of NHLBI Cohorts

OBJECTIVE: This initiative will expand the utilization of NHLBI's well-phenotyped observational cohorts for genetic association studies, through the application of large-scale genotyping and widespread dissemination of these data for genotype-phenotype correlation. The goal is to provide extensive, high-quality genotyping and appropriate infrastructure for identifying genetic variants related to sophisticated, objective measures of heart, lung, blood, and sleep disorders and their risk factors, and to predict the clinical progression and outcome of these conditions.

Council was very enthusiastic about this initiative.

5. TITLE: Identification of Novel Therapeutic Targets in Asthma

OBJECTIVES: This program will promote innovative, exploratory research that will seek to identify new molecular targets, providing the basis for development of interventions that will prevent asthma development and/or exacerbation.

Council expressed concern about the duration and felt that the likelihood for identifying therapy was not high. Council recommended revising this initiative.

6. TITLE: Innovative Technologies for Engineering Small Blood Vessels

OBJECTIVES: This program will provide the foundation to develop functional blood vessels (< 5.0 mm Internal Diameter (ID) for clinical evaluation. It will stimulate multidisciplinary investigators to use biomolecules (angiogenic, growth, and differentiation factors) and novel biomaterials that provide physical and chemical cues to direct the organization, growth, and differentiation of cells to accelerate the process of forming functional blood vessel substitutes with improved longevity.

Council was excited about this initiative and recommended it.

7. TITLE: Off-Pump versus Conventional Coronary Artery Bypass Graft Surgery

OBJECTIVES: To conduct a prospective randomized multicenter trial to compare the short- and long-term outcomes of off-pump and conventional coronary artery bypass grafting.

Council recommended this initiative and was disappointed with the BEA ranking.

8. TITLE: Platelet Proteomics

OBJECTIVES: To initiate focused and targeted proteomic studies on blood platelets and validate the technology in disorders of platelet function.

Council indicated that this initiative had significant merit and was surprised at the low BEA ranking.

9. TITLE: Protein Interactions Governing Membrane Trafficking in Pulmonary Health and Disease

OBJECTIVES: Completion of the human genome project and technological advances now make it possible to probe the molecular pathology of pulmonary diseases associated with conformational disorders in membrane trafficking pathways. The purpose of this initiative is to delineate the global protein interactions governing membrane trafficking pathways operative in pulmonary disease and develop novel therapeutic interventions.

Council did not recommend this initiative with high enthusiasm.

10. TITLE: Risk of Cardiovascular and Lung Disease in Hispanic Populations

OBJECTIVES: To identify risk factors for cardiovascular and lung disease in Hispanic populations, to determine the role of acculturation in the prevalence and development of these diseases, and to identify risk factors playing a protective or harmful role in Hispanics. This initiative will be developed more fully in collaboration with other Institutes.

Council expressed enthusiasm for this initiative.

11. TITLE: Role of Cardiac Memory in Arrhythmia Initiation, Progression, and Termination

OBJECTIVES: This initiative will foster studies to elucidate the role of cardiac memory in arrhythmia initiation, progression, and termination following long- and short-term perturbations in cardiac rhythm and conduction. Multidisciplinary approaches relating to persistent changes in cardiac electrical characteristics attributed to development of cellular and molecular memory, using animal models or human tissue, are encouraged as are pre-clinical experiments to demonstrate the efficacy of new antiarrhythmic interventions affecting cardiac memory.

Council recommended this initiative.

12. TITLE: Short Courses on Application of Genomics and Proteomics to Complex Heart, Lung, Blood, and Sleep Disorders

OBJECTIVES: The goal of this initiative is to provide hands-on training to investigators interested in learning how to leverage genomic and proteomic technologies and resources to understand the mechanisms of heart, lung, blood, and sleep disorders and to disseminate available genomic and proteomic resources and technologies.

Council recommended this initiative with enthusiasm.

Initiatives for Program Announcements: These were presented briefly to Council but not discussed. Program Announcements do not involve a “set-aside” of funds from the Institute.

TITLE: Nutrition and Diet in the Causation and Treatment of Heart Failure

OBJECTIVES: This Program Announcement would encourage submission of investigator-initiated research applications on the role of nutrition and diet in the causation and treatment of cardiomyopathies and heart failure (HF). The overall goal is to develop a satisfactory science base for preventive approaches in with high-risk individuals, and rational nutritional management of patients in various stages of HF.

TITLE: Innovative Research Program to Apply Genomics and Proteomics to Heart, Lung, Blood, and Sleep Disorders

OBJECTIVES: This initiative will support hypothesis-driven studies designed to utilize genomic and proteomic technologies and resources, and apply them to relevant biological questions that will advance our knowledge of heart, lung, blood, and sleep health and disease.

TITLE: Initial (Acute) Respiratory Tract Responses from Inhaled Exposure to Highly Hazardous Aerosolized Toxic Chemicals

OBJECTIVES: To investigate acute mucosal irritation in the upper and lower respiratory tract occurring after aerosol exposure to toxic chemicals with the goals to: 1) minimize initial injury promptly, 2) retard and ameliorate progressive mucosal irritation or inflammation, and 3) offer prophylaxis against pulmonary edema if created by acute lung injury.

TITLE: Diagnostic Laboratories for Diseases of Red Cells and White Cells

OBJECTIVES: The objective of this initiative is to develop laboratories that can diagnose diseases in red cells and white cells using DNA chip analyses that would otherwise go unidentified.

Council recommended all the initiatives for Program Announcements.

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VIII. Recognition of Retiring Council Member - Dr. Barbara Alving

The retiring Council members were honored by Dr. Barbara Alving and received an NHLBI crystal in recognition of their outstanding service to the Institute.

CLOSED PORTION

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.

IX. REVIEW OF APPLICATIONS

The Council considered applications requesting $ in total direct costs. The Council recommended applications with total direct costs of. A summary of applications by activity code may be found in Attachment B.

ADJOURNMENT