NATIONAL HEART, LUNG, AND BLOOD ADVISORY COUNCIL

MEETING MINUTES
October 30-31, 2003

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

[Top of Page]

Dr. Barbara Alving, Acting Director of the National, Heart, Lung, and Blood Institute opened the meeting and welcomed the Council members to the 212th meeting of the National Heart, Lung, and Blood Advisory Council (NHLBAC).

Member Updates

Dr. Robert Jesse is the new ex officio member representing the Department of Veterans Affairs. He is the Chief of Cardiology at the Richmond VA Medical Center and Professor at the Medical College of Virginia, Virginia Commonwealth University.

The Secretary has invited four distinguished individuals to serve on the Council for terms beginning November 1, 2003. While they have all accepted the secretary=s invitation, they are not Aofficial members@ until their administrative paperwork has been cleared.

The new members are: Dr. Roberto Bolli, Chief of the Division of Cardiology at the University of Louisville, Dr. Richard C. Boucher, Director of the Cystic Fibrosis/Pulmonary Research and Treatment Center at the University of North Carolina-Chapel Hill, Ms. Mary H. Deer, founding member of the American Indian Community House in New York, and Dr. Robert F. Lemanske, Professor of Medicine and Pediatrics at the University of Wisconsin.

Drs. Eliasson, Henderson, Mason, and Newberger did not attend the meeting.

Guests and Speakers

Dr. Alving introduced the guests and the speakers:

Guests:

Dr. Theodore Wun, Associate Professor at the University of California, Davis Cancer Center, member of the Sickle Cell Advisory Committee.

Dr. Fernando Martinez, Professor of Pediatrics at the University of Arizona, member of the Board of Extramural Advisors.

Speakers:

Dr. Amy Patterson, Director of the Office of Biotechnology Activities for the Office of the Director of NIH.

Dr. Gordon Bernard, Director of the Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine

Dr. Bruce McManus, Scientific Director of the Canadian Institute of Health Research.

Dr. John Barrett, Section Chief of the Allergenic Stem Cell Transplant Program in the NHLBI Intramural Program

Dr. Neal Young, Chief of the Hematology Branch in the NHLBI Intramural Program

New Publications

- Pamphlets for Heart Attack Signs designed for low literacy
- Keep the Beat Heart Healthy Recipes
- Fact Sheets on Heart Truths for African Americans and Latinos
- Facts about the Dash eating plan
- Public Interest Newsletter from the NHLBI

[Top of Page]

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

[Top of Page]

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.

[Top of Page]

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

[Top of Page]

Dr. Alving reported on the status of the search for the new NHLBI Director. A search committee is in the process of being chosen and the committee will be co-chaired by Dr. Francis Collins, Director of the National Genome Institute and Dr. T.K. Li, Director of the National Institute of Alcohol Abuse and Addiction. The government is currently operating under a continuing resolution which expires October 31, 2003. The NIH is still considering the report of the Institute of Medicine and the recommendations for NIH. The NIH Roadmap is ongoing and many of the initiatives have been published in the NIH Guide for Grants and Contracts. Dr. Alving announced that Dr. John Watson, Program Director of Clinical and Molecular Medicine in the Division of Heart and Vascular Diseases, will be retiring after 27 years at the Institute.

[Top of Page]

IV. BARRIERS TO CLINICAL RESEARCH - Dr. Lawrence Friedman, Dr. Amy Patterson and Dr. Gordon Bernard

[Top of Page]

Dr. Lawrence Friedman, Acting Deputy Director of NHLBI, introduced Dr. Amy Patterson, Director of the Office of Biotechnology Activities for the Office of the Director of NIH. Dr. Patterson addressed the Council on the harmonization of clinical research which is a top priority of the Roadmap Initiative. The major theme is that there are many impediments to performing clinical research. There are redundancies in the various requirements for oversight of clinical studies with respect to adverse events and conflict of interest issues between agencies and within NIH. The solution is to promote responsible conduct of high quality research and have opportunities to convene other Federal agencies to harmonize their efforts. The goal is to catalyze Federal cooperation through harmonization, standardization, and streamlining the various regulatory processes. The priority issues include harmonizing adverse event reporting requirements across agencies, clarifying the roles and responsibilities of Data Safety Monitoring Board (DSMBs), Institutional Review Board (IRBs) and other review mechanisms, reconciling requirements for auditing and monitoring of clinical trials, and devising standards for electronic submission of safety and clinical research information. Other issues include examining the application of Health Insurance Portability and Accountability Act (HIPAA) to clinical research, clarification of the interpretation of human subject regulations, examining the characteristics of central versus local IRBs, the variable approaches to providing informed consent and sharing best practices, and guidance on investment financial disclosure and conflict of interest. These issues require sustained attention and will involve outside experts as well as education and outreach to the community.

Dr. Friedman introduced Dr. Gordon Bernard, Professor at Vanderbilt University and an NHLBI Council member, who addressed Council on the status of Institutional Review Boards. Currently Dr. Bernard is the Medical Director of the IRB at Vanderbilt University. The IRB goals are to protect human subjects as well as to adhere to regulations, communicate, and educate. The challenges which face an IRB include the increased scrutiny required by Federal regulations, expanded interpretations, increased media attention, increased legal liability, a decrease in credibility of institutions, a decrease in public trust, an increase in workload, and overlapping oversight. The growth in volume of new studies is 23% and as a result the IRB must meet for two hours each week. Consequently, members are now paid for their time and percent effort. IRBs now have new responsibilities for oversight of committees including human subject radiation and radioactive drug research committees. There are other areas including the HIPPA Privacy Board for Research and The Association for the Accreditation of Human Research Protection Programs (AAHRPP) Accreditation and Office of Human Research Protection (OHRP QI) Program. A big issue is also the complexity of review of multi-center trials which require reformatting consent/patient survey forms, input from multiple IRBs, and multiple re-reviews for each concern identified. The critical point is that all the extra effort expended does not seem to have provided any extra benefits in terms of human subject protection. The conclusion is that the processes should be streamlined to reduce effort and cost while maintaining current standards of protection.

Council commented that NIH should take a leading role in bringing this problem to the attention of the Department. HHS should establish a commission to deal with the conflicting and repetitive requirements between agencies and resolve conflicts between OHRP and NIH. The regulatory burdon has become so heavy that clinical research as well as public health-oriented research has been compromised. Council passed a resolution to present to Dr. Zerhouni which states:

“The National Heart, Lung, and Blood Advisory Council expresses concern that the complexity of the regulation of the participation of human subjects in research settings is limiting scientific progress without necessarily enhancing the protection of subjects from research risks. Because research of this type is regulated by the NIH, FDA, and OHRP and others, the NHLBI Advisory Council asks the Office of the Director of the NIH to petition Secretary Thompson to appoint a single commission with the charge to harmonize regulations among entities while providing the best possible protection for human subjects in research trials.”

[Top of Page]

V. INTRAMURAL SCIENTIFIC PRESENTATIONS: BONE MARROW TRANSPLANTATION PROGRAM

[Top of Page]

Dr. Elizabeth Nabel, Director of the Clinical Intramural Program at NHLBI, introduced two scientists from the Hematology Branch of the NHLBI Division of Intramural Research. The NHLBI hematology program has had a longstanding interest in stem cell biology including graft engineering in the leukemias and stem cell failure.

Dr. John Barrett , Chief of the Allogeneic Stem Cell Transplantation Section, described the progress which has been made in allogeneic stem cell transplantation utilized in treating leukemias and lymphomas which are not responsive to regular treatment. Dr. Barrett described a sequence of protocols which have been modified over the last 10 years to provide subjects with better outcomes. The results have shown that the graft versus leukemia response is a major contributor to success rate. The limitations include toxicity, graft-versus host disease, viral reactivation, and relapse. In 1993 a study was conducted using HLA-matched siblings between the ages of 10 and 55 where various options were attempted including increasing the dose of CD 34 cells, using Granulocyte Colony Stimulating Factor (GCSF) to increase T cells, selective enrichment of CD 34 cells, and the use of acyclovir to reduce the incidence of cytomegalovirus infection. As a result disease free survival rose from 37 % to 46%. The next decade of research will utilize selective depletion of T cells to reduce the need for immunosuppression and leukemia-specific T cell therapy. Dr. Neil Young, Chief of the Hematology Branch, described studies on the pathophysiology of aplastic anemia (AA) where a reduction in stem cells is evident. Studies have shown that immunosuppression improves the outcome for these patients. These patients have conditions which promote T cell attack of cellular targets. For example, AA patients have Paroxysmal Nocturnal Hemoglobinuria (PNH) where there is a gene defect in the synthesis of a membrane anchor protein. An aggressive T cell attack is mounted as a result of the gene defect and the immune response causes severe damage. Dr. Young noted that the NIH Clinical Center is the largest referral center for aplastic anemia.

[Top of Page]

VI. NHLBI T32 TRAINING PROGRAM - Dr. Lawrence Friedman

[Top of Page]

Dr. Friedman presented the recommendation for a T32 funding policy. The subcommittee of Council which studied T32 funding did not recommend a budget cap for T32s. The concern remained, however, that tightening the budget in future years will make it difficult for Type 1 T32s to obtain funding. After analysis of prior year data, it was recommended to have a set-aside of at least 15% of the awards for Type 1 grants. Also it was recommended that another application receipt date be added to deal effectively with the growing volume of T32 applications. The receipt dates would be January 10 and May 10. Applications would be funded twice a year after the October and February councils. The Council agreed with these recommendations and emphasized the importance of these training programs. Dr. Friedman presented the recommendation for a T32 funding policy. The subcommittee of Council which studied T32 funding did not recommend a budget cap for T32s. The concern remained, however, that tightening the budget in future years will make it difficult for Type 1 T32s to obtain funding. After analysis of prior year data, it was recommended to have a set-aside of at least 15% of the awards for Type 1 grants. Also it was recommended that another application receipt date be added to deal effectively with the growing volume of T32 applications. The receipt dates would be January 10 and May 10. Applications would be funded twice a year after the October and February councils. The Council agreed with these recommendations and emphasized the importance of these training programs.

[Top of Page]

VII. JOINT INITIATIVES WITH THE CANADIAN INSTITUTES OF HEALTH RESEARCH- Dr. Bruce McManus

[Top of Page]

Dr. McManus is the Scientific Director of the Institute of Circulatory and Respiratory Health (ICRH) of the Canadian Institutes of Health Research (CIHR). The mission of the CIHR is to do biomedical and clinical research, and to promote the health of the Canadian people. There are thirteen Institutes and the number of grants funded has increased significantly. ICRH and NHLBI are jointly sponsoring three initiatives including the Clinical Consortium to Improve Resuscitation Outcomes, Cellular and Molecular Imaging of Cardiovascular, Pulmonary and Hematopoietic Systems, and Inflammation and Thrombosis. These initiatives are currently posted in the NIH Guide for Grants and Contracts and will be funded in FY 2004. It is hoped that joint sponsorship will foster more interactions between Canada and the United States in basic and clinical research.

[Top of Page]

VIII. INITIATIVES FOR FISCAL YEARS 2004/2005 - Dr. Lawrence Friedman, Dr. James Kiley, Council Members

[Top of Page]

Seventeen initiatives as well as three Specialized Centers of Clinically Oriented Research were presented to Council. Each initiative is summarized below. Council comments are also noted.

1. **TITLE:** Asthma Exacerbations: Mechanisms of Resolution

OBJECTIVES: The objective is to promote clinical and basic research that will elucidate the biologic mechanisms of resolution following asthma exacerbations.

In response to questions from Council, staff emphasized that the study would focus on the resolution not the trigger of acute asthma exacerbation. Council was enthusiastic for this initiative.

2. **TITLE:** Community-Responsive Interventions to Reduce Cardiovascular Risk in American Indians and Alaska Natives

OBJECTIVES: The purpose of this initiative is to test the effectiveness of interventions for improvement in behavioral cardiovascular disease (CVD) risk factors such as obesity, diet, smoking, sleep restriction, stress, and sedentary lifestyle in American Indian/Alaska Native (AI/AN) populations. These lifestyle-related risk factors are important targets for primary prevention of CVD. The initiative concept was developed in consultation with AI/AN Tribes, recognizing the government-to-government relationship between AI/AN Tribes and the United States, and incorporates recommendations of a working group of AI/AN health experts. The long-term goal is to reduce health disparities in AI/AN. This initiative focuses on primary prevention, an important approach that can contribute to that goal.

Council considered this to be an important initiative and that the timing was good. They indicated that the emphasis should be on the interventions and to be aware of the limitations.

3. **TITLE:** Enhancing the Use of Longitudinal Data on Cardiovascular Disease and its Risk Factors in Older Adults: The Cardiovascular Health Study (CHS)

This proposal is different from the usual BEA initiative in that it requests approval of a concept rather than a specific research activity. Large longitudinal studies provide unique resources, allowing many questions to be addressed that are outside the scope of the original primary study aims. Cohorts for longitudinal studies are difficult to establish and expensive to maintain. During the study, it is important to take advantage of opportunities for ancillary studies as long as they do not compromise the primary investigations of the project. The end of the primary study often provides additional opportunities to get new information from the cohort, either by analysis of existing data or samples or by collecting additional information from cohort members.

At present, when the objectives of the primary study are met, only two options are available: 1) funding stops and, in most cases, the study infrastructure and access to the cohort collapses or 2) new research goals are added and the study is funded by NHLBI for another cycle. This proposal provides a third alternative, an option to preserve key study resources and potential access to the cohort using a mechanism to transfer responsibility for subsequent study design, management and support to interested investigators willing to seek funding for their individual research proposals. This proposal stresses the need to encourage participation by new investigators and will expand access to the original study data, sample repositories and the cohort for the general research community. The Cardiovascular Health Study (CHS), a study currently scheduled to end in 2005, will be used to illustrate a concrete example of this approach.

Council commented that there was tremendous value in the CHS study and the data sets generated and that this proposal would set a significant precedent. The study has considerable momentum and it should be continued.

4. **TITLE:** Genetic and Cellular Discovery in Myelodysplastic Syndromes (MDS) and Myeloproliferative Disorders (MPD).

OBJECTIVES: To stimulate research on the causes and progression of MDS and MPD to enable new therapeutic discovery.

Council agreed that this was an important initiative.

5. **TITLE:** Interstitial Lung Fibrosis Clinical Research Network

OBJECTIVES: To develop a network of clinical centers to conduct multiple treatment trials on patients with established idiopathic pulmonary fibrosis (IPF). For patients who require an open lung biopsy for diagnosis, living lung tissue (also blood and other biological products) can be studied for cellular genomic and immunopathogenic changes; excess tissue samples could be contributed to a lung tissue repository (NHLBI Lung Tissue Research Consortium).

Council recommended that there should be a mechanism for longer follow-up and was otherwise very enthusiastic about this study.

6. **TITLE:** Minority Investigator Summer Institute Program (MISIP)

OBJECTIVES: The MISIP is a faculty development program that will fund summer institutes to provide under-represented minorities (African Americans (AA), Hispanic Americans (HA), Native Americans (NA), and non-Asian Pacific Islanders (N-API)) with: 1) research skills and guidance for career development; 2) individual mentoring; and 3) opportunities for networking with established investigators in heart, lung, blood, and sleep (HLBS) disorders.

Council was very enthusiastic about this well-planned initiative which is very much needed. It is modelled after a very good program.

7. **TITLE:** National Registry of Patients with Marfan Syndrome

OBJECTIVES: This initiative will establish a registry to collect and analyze clinical data and samples (e.g. blood and tissue) of Marfan patients in order to improve understanding of cardiovascular complications and therapies for this disorder. Ultimately the registry will provide an essential resource to improve clinical care for patients afflicted with Marfan Syndrome.

Council highly recommended this initiative.

8. **TITLE:** NHLBI Centers for the Application of Nanotechnology to Heart, Lung, Blood, and Sleep Disorders

OBJECTIVES: The objective is to create multidisciplinary teams capable of applying nanotechnology and nanoscience to the diagnosis and treatment of cardiovascular, pulmonary, hematopoietic and sleep disorders.

This initiative was recommended.

9. **TITLE:** NHLBI Clinical Proteomics Programs

OBJECTIVES: This initiative will promote systematic, comprehensive, large-scale validation of existing and new candidate protein markers that are appropriate for routine use in the diagnosis and management of heart, lung, blood, or sleep disorders. Clinical Proteomics Programs, created specifically for this purpose, will facilitate validation of protein panels that may be used to predict disease susceptibility or to assist in differential diagnosis, disease staging, selection of individualized therapies, or monitoring of treatment responses. In addition, the Clinical Proteomics Programs will provide training to clinical and scientific investigators in the multidisciplinary approaches to clinical proteomics.

Council considered this initiative to be very important and was pleased to see a training component in the program.

10. **TITLE:** NHLBI Competitive Supplements for Vascular Repair

OBJECTIVES: The objective of this initiative is to provide supplemental funds to enhance existing regenerative medicine programs to create engineered small diameter (< 5.0 mm ID) blood vessels with functional characteristics similar to the internal mammary artery. This program provides the underpinning for developing functional blood vessels for clinical evaluation and trial.

Council was enthusiastic about this initiative.

11. **TITLE:** An NHLBI/NHF cooperative research program for improved hemophilia therapy

OBJECTIVES: The objective of the initiative is to support research for improved treatment of hemophilia and von Willebrand disease through a collaborative funding program with the National Hemophilia Foundation (NHF).

Council thought this was an important initiative and was interested in a collaboration with the

American Haemophilia Foundation.

12. **TITLE:** Pathogenesis of SARS lung disease: In vitro studies and animal models

OBJECTIVES: To rapidly advance understanding of the pathogenesis of severe acute respiratory syndrome (SARS) in the lung using *in vitro* techniques, existing animal models of related coronavirus infections, non-human primate models of severe acute respiratory syndrome (SARS), and new rodent models. The RFA invites R01 applications for both high risk hypothesis generating research and hypothesis driven projects (if sufficient preliminary data are available), relevant to the pathogenesis of human lung disease caused by the human SARS coronavirus (SARScoV).

Council endorsed this initiative which is an important public health problem and agreed with the pulmonary and virology community involvement.

13. **TITLE:** Randomized Trial of Heart Failure Management

OBJECTIVE: The objective of this initiative is to fund a multi-center randomized clinical trial to assess the effect of systematic approaches to the clinical management of heart failure (HF) on morbidity and mortality. Specifically, two systematic approaches to HF care, differing in level of intensity, will each be compared with a control (provider education regarding standard of care for HF), and with each other if appropriate. The primary outcome will be time to death or first readmission to the hospital for any cause following an index hospitalization for heart failure, among persons at high risk for readmission. Days alive outside of the hospital, other morbidity outcomes, mortality, healthcare costs, quality of life, cost-effectiveness, physician compliance with HF guidelines, and patient adherence to prescribed treatments will also be assessed. The larger goal is to identify and disseminate clinically useful and effective tools for translation of proven therapies for HF into clinical practice, in order to reduce morbidity and mortality from HF.

Council was very enthusiastic about this initiative and emphasized that the study will be very important and that it should also examine cost-effectiveness. Of importance is the emphasis on the behavior of physicians and the patients, the patient environment and the family.

14. **TITLE:** Recovery of Heart Function with Circulatory Assist

Council was very supportive of this initiative noting that the Ventricular Assist Device (vad) is a precedent for remodelling and would also answer the question of whether remodelling is sustained.

15. **TITLE:** A Scientific Database for New Cell-based Therapies for Heart, Lung, Blood, and Sleep Disorders

OBJECTIVES: The purpose of this initiative is to quickly enable data accrual and analysis of clinical activities in new cell-based therapies for repair and regeneration of damaged and/or dysfunctional tissue and/or dysfunction of the heart, vascular, lung, and blood systems. There is a critical need to obtain methods and expertise in performing these functions. This initiative will provide funding for a pilot developmental and demonstration project to fulfill the aim of the initiative.

Council noted the need for warehousing clinical ideas and enhancing communication and collaboration with these therapies.

16. **TITLE:** Transfusion-Related Acute Lung Injury (TRALI)

OBJECTIVES: To support research on the mechanisms responsible for acute lung injury after blood transfusion, and stimulate the development of strategies to prevent and treat the disorder.

Council noted the concern with this syndrome among the transfusion community and the importance of clearly defining the problem.

17. **TITLE:** The Jackson Heart Study (JHS)

OBJECTIVES: The objectives of the JHS are both scientific and operational. The primary scientific objective is to investigate genetic and environmental causes of the disproportionate burden of cardiovascular disease (CVD) in African-Americans and to learn how best to prevent these diseases. The operational objectives are to build research capabilities in minority institutions, address the critical shortage of minority investigators in epidemiology and prevention, and reduce barriers to dissemination and utilization of health information in a minority population.

Council noted the importance of continuing the commitment to this study and the importance of maintaining data collection and the commitment to training.

18. Specialized Centers of Clinically-Oriented Research (SCCOR) Initiatives

a. Title: SCCOR in Transfusion Biology and Medicine

Objectives: to support the development and application of new knowledge essential for improved safety, efficacy, and availability of blood, blood components, and plasma derivatives, and to transfer these research findings into clinical evaluation and application.

b. Title: SCCOR in Hemostatic and Thrombotic Diseases,

Objectives: to foster multidisciplinary research on clinically relevant questions enabling basic science findings to be more rapidly applied to clinical problems in hemostasis and thrombosis.

c. Title: SCCOR in Cell-Based Therapy.

Objectives: to support clinical and basic investigations related to cell-based therapies and regenerative medicine for heart, lung, blood, and sleep disorders.

Council was very enthusiastic about these three SCCOR programs and emphasized that language should be added to clearly differentiate the three so that investigators will apply to the appropriate program.

[Top of Page]

CLOSED PORTION

[Top of Page]

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with 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).

There was 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 832 applications requesting $982,672,699 in total direct costs. The Council recommended 831 applications with total direct costs of $966,039,894. A summary of applications by activity code may be found in Attachment B.

ADJOURNMENT

The meeting was adjourned at 9:00 a.m. on October 31, 2003.

CERTIFICATION

I hereby certify that the foregoing minutes are accurate and complete.

Barbara Alving, M.D.

Acting Director

National Heart, Lung, and Blood Advisory Council

on December 30, 2003