NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

January 30, 2006

The 152nd meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Monday, January 30, 2006, in Conference Room E1/E2, Building 45, National Institutes of Health. Dr. Anthony S. Fauci, Director, National Institute of Allergy and Infectious Diseases (NIAID) presided as Chairman.

In accordance with the provisions of Public Law 92-463, the meeting was open to the public from 10:30 a.m. to 11:40 a.m. and from 1:00 p.m. to 5:00 p.m. The meeting was closed to the public from 8:30 a.m. to 10:30 a.m. and from 11:40 a.m. to 12:00 p.m. for review and consideration of individual grant applications. Notice of the meeting was published in the *Federal Register.*

Council Members Present:

Dr. Barbara Baird
Dr. Anthony D'Alessandro
Dr. Charles Davis
Dr. Kathryn Edwards
Dr. Richard Insel
Dr. J. Brooks Jackson
Ms. Anne Munoz-Furlong
Dr. Martin Myers
Rev. Raymond O'Brien
Dr. Shelley Payne
Dr. Martin Rosenberg
Dr. Ruth Ruprecht
Dr. Gary Schoolnik
Dr. Megan Sykes
Dr. Nathan Thielman
Dr. Gail Wertz

***Ex Officio* Members Present:**

Dr. Mitchell Cohen
Dr. Anthony Fauci
Major General Eric Schoomaker

Council Members Absent:

Dr. Stanley Chapman
Dr. Anjana Rao

***Ex Officio* Members Absent:**

Dr. Lawrence Deyton

***Ad Hoc* Members:**

Dr. James Gern
Dr. Christian Larsen

NIAID Senior Staff:

Dr. Hugh Auchincloss
Dr. John McGowan
Dr. Carol Heilman
Dr. Cliff Lane
Dr. Daniel Rotrosen
Dr. Ed Tramont
Dr. Kathryn Zoon

Others Present:

Dr. Harvey Fineberg

I. REVIEW OF GRANT APPLICATIONS

The National Advisory Allergy and Infectious Diseases Council convened in closed session to consider applications in the areas of allergy and immunology, microbiology and infectious diseases, and AIDS.

Funding Actions: The Council reviewed 2,102 research and training applications with primary assignment to NIAID for a requested amount of $735,725,761 in first-year direct costs and recommended approval of 468 applications for $323,465,457 in first-year direct costs. Seven Method to Extend Research in Time (MERIT) award were recommended for approval.

II. REMARKS OF THE DIRECTOR, NIAID - Anthony S. Fauci, M.D.

Dr. Fauci opened the Council session by welcoming visitors to the meeting. He announced the appointment of four new Council members: Dr. Barbara Baird, Cornell University; Dr. Kathryn Edwards, Vanderbilt University; Dr. Martin Rosenberg, Promega Corporation; and Dr. Megan Sykes, Harvard Medical School and Massachusetts General Hospital. He also noted that Drs. Chapman and Rao were unable to attend the meeting.

Dr. Fauci introduced two ad hoc Council members, Dr. Christian Larsen, Emory University, and Dr. James Gern, University of Wisconsin at Madison. He also noted that *ex officio* Council member, Brigadier General Eric Schoomaker, was promoted to Major General.

Consideration of Minutes of Previous Meeting
The minutes of the September 26, 2005, meeting were considered and approved as written.

Consideration of Operating Procedures
The 2006 Council operating procedures were considered and adopted as written.

Staff and Organizational Changes
Dr. Fauci announced several new appointments in NIAID. Dr. Hugh Auchincloss, Jr. has been appointed the new principal deputy director of the Institute. Dr. Auchincloss comes from Massachusetts General Hospital and as principal deputy director will have broad program and management responsibilities.

Two other deputy director positions in the Institute have been formalized. Dr. Cliff Lane, who has served as acting principal deputy director since December 2004, has been appointed the deputy directory for clinical research and special projects. He will continue as NIAID's clinical director and the director of the Office of Clinical Research, which will be elevated to the Division of Clinical Research. Dr. John McGowan has been appointed the deputy director for science management. He will direct all of the business and administrative responsibilities of the Institute and direct science planning, policy, and integration.

With Dr. McGowan assuming his new position, his former position as director of the Division of Extramural Activities is vacant, and Dr. Paula Strickland has agreed to serve as the acting director while a search for a permanent director is conducted.

Dr. Kathryn Zoon has been appointed director of the Division of Intramural Research.

In the Division of AIDS, Dr. Jorge Flores has been appointed deputy director of the Vaccine and Prevention Research Program, and Dr. Richard Hafner is the new director of the Office for Policy in Clinical Research Operations.

Dr. Fauci formally announced the establishment of the Immediate Office of the Director. Mr. Greg Folkers will lead the office and serve as Dr. Fauci's chief of staff.

Dr. Pamela McInnes, who was the deputy director of the Division of Microbiology and Infectious Diseases, left NIAID to become the director of the Center for Integrative Biology and Infectious Diseases at the National Institute of Dental and Craniofacial Research.

Budget Update

The NIAID budget for FY 2006 is $4.41 billion, an increase of $12 million or 0.3 percent from FY 2005. Dr. Fauci noted that NIAID continues to fare better than most of the other ICs. The total NIH FY 2006 budget decreased 0.1 percent or $33.9 million in comparison to the FY 2005 budget. The overall NIH budget reflects an across-the-board rescission of $287 million by Congress. The rescission was part of the Department of Defense Appropriation Act of 2006 and equals a one percent cut, which is applied to each discretionary account. For NIAID this means that each research area: AIDS, biodefense, and traditional non-AIDS and non-biodefense programs must absorb a one-percent reduction.

Based on the enacted FY 2006 budget, NIH established a policy for all noncompeting research project grants, which will be awarded at 97.65 percent of their committed level.

Legislative Update

Congressional interest in NIAID's research activities continues with most of the interest focused on pandemic influenza. On November 1, 2005, President Bush visited NIH to announce the national strategy for pandemic influenza. Since NIAID has the primary responsibility in the federal government for research associated with influenza, Dr. Fauci had ongoing briefings with the president, vice president, Secretary Leavitt, and other cabinet members with regard to NIAID's role in the strategy.

Following the president's announcement, Dr. Fauci accompanied Secretary Leavitt to numerous House and Senate committee briefings. Dr. Fauci also testified before House and Senate committees regarding the role of biomedical research in pandemic influenza preparedness.

Dr. Josiah Wedgwood briefed several representatives on autoimmune diseases, and Drs. Linda Lambert and Pamela McInnes briefed the Congressional Budget Office on pandemic flu.

Other Information Items

Dr. Fauci's main focus was on the many activities at NIAID with regard to pandemic influenza. The Institute's research is primarily concerned with vaccines and antivirals and is heavily based on basic research. Major goals are to build up vaccine production capacity and move from egg-based to cell-based or recombinant DNA technology.

As of January 28, 2006, the NIAID influenza genome project had completed the full genomic sequences of almost 800 human isolates. These sequences are available in a public database.

Dr. Fauci gave an overview of current and planned projects on influenza antivirals, particularly how best to use drugs like Oseltamivir and Tamiflu in young people. He also outlined the work being done on several influenza vaccine candidates.

The last point that Dr. Fauci emphasized was that everything that applies to pandemic influenza also applies to seasonal influenza. To address the crisis of pandemic flu, we need to do better with seasonal flu, including better drugs and how to use them.

III. PRESENTATION: "Lessons from the Swine Flu Affair" – Harvey V. Fineberg, M.D., Ph.D., President, Institute of Medicine, The National Academies

Dr. Harvey Fineberg began by giving background information about the 1918-1919 influenza pandemic and how in 1976 many people thought we were facing a similar outbreak. In 1976 in response to an outbreak of flu at Fort Dix, New Jersey, the U.S. began the most ambitious campaign against influenza ever undertaken.

Dr. Fineberg highlighted several critical features of the process that led to poor decision making: overconfidence and responding to meager evidence; pre-existing agendas; premature commitment; and how the media was used to communicate information to the public.

He summarized what had been learned through this process: the importance of a base for program review; public understanding and support is important for the initial decision all the way through to implementation; the implementation needs to be thought through completely; spokespersons should be informed and authoritative to maintain credibility; and new scientists and analysts should be brought in throughout the process to give the evidence a fresh look.

IV. REPORT OF THE DIVISION OF ALLERGY, IMMUNOLOGY AND TRANSPLANTATION COUNCIL SUBCOMMITTEE - Daniel Rotrosen, M.D., Director

Dr. Rotrosen presented the following new staff members, scientific and division activities:

STAFFING/ORGANIZATIONAL CHANGES

Michael Minnicozzi, Ph.D. Dr. Minnicozzi joined the Asthma, Allergy, and Inflammation Branch in October 2005 as a Program Officer. He received his doctoral degree in physiology from the University of Medicine and Dentistry of New Jersey. Prior to joining the Division, Dr. Minnicozzi was a Principal Research Scientist at the Schering Plough Research Institute. He also served on the Northeast Peer Review Consortium of the American Heart Association and was an Adjunct Professor at University of Medicine and Dentistry of New Jersey.

Julie Schwaninger, M.S. Ms. Schwaninger joined the Asthma, Allergy, and Inflammation Branch in September 2005 as a Health Specialist. She received her Master's degree in biotechnology from Johns Hopkins University, where she was a Research Technician working in the area of radiation oncology and prostate cancer research.

Terrolyn B. Thomas Ms. Thomas joined the Transplantation Immunobiology Branch in November 2005 as a Program Specialist. She received her Bachelor's degree in chemistry from Howard University, and is now pursing her master's in management/healthcare administration from University of Maryland. Prior to joining the Division, she was a Program Assistant with the American Society of Clinical Oncology.

SCIENTIFIC INITIATIVES

NIH

NIH Support for Conferences and Scientific Meetings (PA-06-041): The NIH recognizes the value of supporting high quality conferences/scientific meetings that are relevant to its scientific mission and to the public health. A conference/scientific meeting is defined as a gathering, symposium, seminar, scientific meeting, workshop or any other organized, formal meeting where persons assemble to coordinate, exchange, and disseminate information or to explore or clarify a defined subject, problem, or area of knowledge. Support of such meetings is contingent on the fiscal and programmatic interests and priorities of the individual Institutes and Centers, which are linked to the NIH Conference Grant Web site, http://grants.nih.gov/grants/funding/r13/index.htm. Therefore, a conference grant application is required to contain a letter from the appropriate NIH staff (see Contacts List) documenting advance permission. Investigators are urged to initiate contact well in advance of the application receipt date. Please note that agreement to accept an application does not guarantee funding.

Academic Research Enhancement Award (PA-06-042): The NIH is continuing to make a special effort to stimulate research in educational institutions that provide baccalaureate or advanced degrees for a significant number of the Nation's research scientists, but that have not been major recipients of NIH support. Since Fiscal Year (FY) 1985, Congressional appropriations for the NIH have included funds for this initiative, which NIH has implemented through the Academic Research Enhancement Award (AREA) program. Based on the expectation that funds will continue to be available each year, the NIH invites applications for AREA grants (R15) through a standing, ongoing Funding Opportunity Announcement (FOA).

Mentored Quantitative Research Development Award (K25) (PA-06-087): The goals of NIH-supported research training and career development programs are to help ensure that diverse pools of highly trained scientists are available in adequate numbers and in appropriate research areas to address the Nation’s biomedical, behavioral, and clinical research needs. NIH mentored career development awards provide mentored research experiences to gain additional expertise in a new research area or in an area that will significantly enhance an investigator’s research capabilities. It is expected that the mentored research and career development experience will lead to an independent and productive research career.

Pilot Study to Shorten the Review Cycle for New Investigator R01 Applications (NOT-OD-06-013): Shortening the review cycle is a high priority for the National Institutes of Health and the biomedical and behavioral research communities. There is also great interest in the career development of scientists and NIH is committed to supporting new investigators in their efforts to obtain R01 research grant funding. Since new investigators by definition do not have R01 support, any delay in the ability to submit an amended application could have a negative impact on their careers. Cognizant of the pressure on new investigators to obtain NIH R01 funding, the Center for Scientific Review convened a trans-NIH working group to develop a process to shorten the referral and review cycle in order to permit a new investigator to submit an amended application for the next submission date. Although the number of new investigators who will be able to take advantage of this rapid turnaround process will be relatively small, the impact on the careers of these new investigators could be significant. The working group recommended an initial pilot, followed by an evaluation phase before consideration of modification and/or expansion.

First Phase of the Interdisciplinary Research Consortium Program:
Transition to the SF424 (R&R) Form and Electronic Submission through Grants.gov (NOT-RM-06-009): The purpose of this notice is to inform applicants who plan to submit pre-applications for the

Interdisciplinary Research Consortium program (announced in http://grants.nih.gov/grants/guide/notice-files/NOT-RM-05-006.html) that they will be required to submit their applications online to the NIH through Grants.gov (http://www.grants.gov/) using the SF424 Research and Research Related form.

Small Business Innovation Research (SBIR) and Small Business Technology Transfer Research (STTR) announcements:

Small Business Innovation Research Program Parent Announcement (PA-06-006): The purpose of this announcement is to invite eligible United States small business concerns to submit SBIR Phase I, Phase II, and Fast-Track grant applications through Grants.gov.

Small Business Technology Transfer Program Parent Announcement (PA-06-007): The purpose of this announcement is to invite eligible United States small business concerns to submit STTR Phase I, Phase II, and Fast-Track grant applications through Grants.gov.

Small Business Innovation Research to Improve the Chemistry and Targeted Delivery of RNAi Molecules (PA-06-003) and **Small Business Technology Transfer to Improve the Chemistry and Targeted Delivery of RNAi Molecules** (PA-06-004): This funding opportunity uses the SBIR (R43/R44) and the STTR (R41/R42) grant mechanisms. Applications may be submitted for support as Phase I, Phase II or Fast-Track grants as described in the SF424 (R&R) SBIR/STTR Application Guide (MS Word or PDF). A parallel funding opportunity announcement of identical scientific scope (PA-06-004) utilizes the Small Business Technology Transfer (STTR) grant mechanism. Applicants may not submit simultaneously identical/essentially identical applications under both this funding opportunity and another HHS FOA, including the SBIR or STTR Parent announcements (PA-06-006 or PA-06-007).

Small Business Technology Transfer to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes (T1D) and its Complications (RFA-DK-05-015) and **Small Business Innovation Research to Develop New Therapeutics and Monitoring Technologies for Type 1 Diabetes (T1D) and its Complications** (RFA-DK-05-016): This funding opportunity uses the STTR (R41/R42) and SBIR (R43/R44) grant mechanisms. Applications may be submitted for support as Phase I, Phase II or Fast-Track grants as described in the SF424 (R&R) SBIR/STTR Application Guide (MS Word or PDF). A parallel funding opportunity announcement of identical scientific scope (RFA-DK-05-016) utilizes the Small Business Innovation Research (SBIR) grant mechanism. Applicants may not simultaneously submit identical/essentially identical applications under both this funding opportunity and RFA-DK-05-010 and another HHS FOA, including the SBIR or STTR Parent announcements (PA-06-006 or PA-06-007).

Bioengineering Nanotechnology Initiative (PA-06-008) and **Bioengineering Nanotechnology Initiative** (PA-06-009): An initiative of the trans-NIH Bioengineering Consortium (BECON), this announcement invites Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grant applications for projects for developing and applying nanotechnology to biomedicine. Nanotechnology is defined as the creation of functional materials, devices and systems through control of matter at the scale of 1 to 100 nanometers, and the exploitation of novel properties and phenomena at the same scale. Nanotechnology is emerging as a field critical for enabling essential breakthroughs that may have tremendous potential for affecting biomedicine. Moreover, nanotechnologies developed in the next several years may well form the foundation of significant commercial platforms that shift the paradigms of clinical applications.

Innovations in Biomedical Computational Science and Technology Initiative (PAR-06-088) and **Innovations in Biomedical Computational Science and Technology Initiative** (PAR-06-089): This announcement solicits Small Business Innovation Research (SBIR) Small Business Technology Transfer (STTR) grant applications from small business concerns that propose innovative research in biomedical computational science and technology to promote the progress of biomedical research. The NIH is interested in promoting research and development in biomedical computational science and technology that will support rapid progress in areas of scientific opportunity in biomedical research. Biomedical computing or biomedical information science and technology includes database design, graphical interfaces, querying approaches, data retrieval, data visualization and manipulation, data integration through the development of integrated analytical tools, and tools for electronic collaboration, as well as computational research, including the development of structural, functional, integrative, and analytical models and simulations.

DIVISION ACTIVITIES

Workshop on Immunological Basis for Antigen-Specific Asthma and Allergy Therapeutic Strategies: On November 14, 2005, the NIAID sponsored a workshop to explore the immunological basis for allergen immunotherapy. Topics presented included the contribution of the innate immune system in the treatment of asthma and allergies, potential roles for regulatory T cells in tolerance, allergen and immunotherapy standardization, comparisons of sublingual and subcutaneous immunotherapy for both prevention and treatment of asthma and other allergic diseases, and criteria for selection of natural and recombinant allergens for use in immunotherapy.

Biodefense Program on Population Genetics: The first annual meeting of the NIAID Population Genetics Analysis Program: Immunity to Vaccines/Infections was held on October 14 and 15, 2005, and included presentations on the progress of the program in the study of genetic polymorphisms in human immune response genes and how these variations associate with an individual's immune response to immunization against or infection by the NIAID category A-C and emerging and re-emerging pathogens.

Epitope Discovery and Immune Epitope Database Contractors Annual Meeting: The second annual meeting of the Immune Epitope Database/Analysis Resource (IEDB) and Large-Scale Immune Epitope Discovery programs was held on November 1-3, 2005. The IEDB staff provided an overview of the immune epitope database, which will be publicly available in February 2006. This resource will contain antibody and T cell epitope information on Category A-C priority pathogens, in addition to other emerging/re-emerging infectious diseases. This information is obtained from existing literature and from the 14 contracts supported under the Large-Scale Immune Epitope Discovery program. The Epitope Discovery investigators focus primarily on identification of CD4 and CD8 T cell epitopes to most of the Category A-C pathogens. Many of the investigators have identified novel T cell epitopes in pathogens such as *vaccinia, Bacillus anthracis, Mycobacterium tuberculosis, Yersinia pestis*, and influenza.

Immune Epitope Database Analysis Tools Workshop: On November 4, 2005, the NIAID sponsored a workshop to obtain critical feedback regarding the utility of epitope prediction tools and analysis tools being developed for the Immune Epitope Database (IEDB) Analysis Resource. The Analysis Resource, which will be publicly available via the internet, will include: tools to help researchers locate and analyze information contained in the Immune Epitope Database; and data mining algorithms, mathematical models, and other sophisticated analytical tools to help researchers identify novel antibody and T cell epitopes from genome or protein sequence information, predict the immunogenicity and/or antigenicity of epitopes, and predict host immune responses to particular epitopes. The workshop participants included T cell and antibody epitope prediction and analysis tool developers and users. These experts provided

feedback on current tools being developed by the IEDB team, recommended deletion or addition of currently available tools to the IEDB, and identified knowledge gaps for future research and development of improved epitope prediction and analysis tools (e.g., improved antibody epitope prediction tools).

Kickoff Meeting: Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations Program: On November 17-18, 2005, the NIAID sponsored a kick-off meeting for the Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations program. Investigators presented their research plans and initiated collaborations among the group. Research projects focused on two areas: the discovery of basic biological mechanisms that cause immune deficits in groups such as children/neonates, elderly, pregnant women, and patients with autoimmune diseases receiving immunosuppressive therapies; and testing of treatments that are designed to increase the safety and efficacy of vaccines and immunotherapies in these immunocompromised populations. It is expected that research resulting from this program will provide information that ultimately contributes to the development of new or improved vaccines and/or immunotherapeutic treatments against potential bioterrorism agents or emerging/re-emerging infectious diseases, with a focus on protecting/treating immunocompromised individuals. Awardees' institutions include Children's Hospital of Philadelphia, Emory University, Mount Sinai School of Medicine, Oklahoma Medical Research Foundation, Oregon Health and Science University, The Blood Center of Southeastern Wisconsin, The Wistar Institute, University of Rochester, University of Washington, and Yale University.

Kick-off Meeting: Modeling Immunity for Biodefense Centers: A kick-off meeting for four Immune Modeling Centers (Duke University, Mount Sinai School of Medicine, University of Pittsburgh, and University of Rochester) was held on December 5, 2005. The goals of this meeting were to provide an opportunity for the investigators to present their research plans to the group and to initiate discussions for resource sharing. These multi-disciplinary centers will develop mathematical modeling packages validated in experimental systems, and provide tools for modeling of host immune responses to infection and vaccines. Each Center has a strong bioinformatics and teaching component. Knowledge gained from these studies will advance our understanding of the complex events required to induce protective immunity; guide laboratory experiments of host immune responses; and lay the foundation for development of models that can extrapolate human immune responses to infection based on results from relevant in vitro and in vivo studies. In addition, results obtained from these programs will contribute to the advanced development of novel or improved vaccines, prophylactics, and immunotherapeutics against emerging and re-emerging infectious diseases.

Centers for Medical Countermeasures against Radiation: Eight universities or research institutes (University of Rochester Medical Center, Columbia University Medical Center, Duke University, Fred Hutchinson Cancer Research Center, Medical College of Wisconsin, University of California, Los Angeles, Dana-Farber Cancer Institute, and University of Pittsburgh) received NIAID grants to establish the Centers for Medical Countermeasures against Radiation program, with a focus on basic and applied research to develop new products for measuring radiation exposure, to protect against exposure, and to minimize and treat the effects of exposure to a wide range of radioactive compounds.

Accelerated Product Development Grants for Radiation Countermeasures: One-time, 18-month grants were awarded to four research organizations to support projects focused on protecting the immune system from radiation or restoring the immune system following radiation exposure. Products that provide pre-exposure protection could be used by first responders to prevent bone marrow damage, while post-exposure products would help restore immune system cells that are formed within bone marrow.

Immunobiology of Xenotransplantation (RFA AI-04-042): In FY 2005, the NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases made five cooperative agreement awards to conduct interdisciplinary research for the development of pre-clinical, porcine to non-human primate models of xenotransplantation to address immunological and physiological issues critical to the engraftment, survival, and function of xenografts. The long-term goal is to develop novel and efficacious strategies for broad application of xenotransplantation in the clinic.

HLA Genetics in Immune-Mediated Diseases (RFA AI-04-039): In September 2005, the NIAID and the National Institute of Neurological Diseases and Stroke made five cooperative agreement awards (University of California San Francisco, Cincinnati Children's Hospital Medical Center, Fred Hutchinson Cancer Research Center, Boston University, Roche Molecular Systems) to establish a research program to address the role of genetic polymorphisms in the MHC region of human chromosome 6 on immune-mediated diseases and transplant outcome. Among the diseases being studied are rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, and graft versus host disease and survival outcome in bone marrow transplantation.

Breeding and Maintenance of the NIAID Specific Pathogen Free (SPF) Cynomolgus and Indian Rhesus Macaque Colonies (RFP DAIT-05-15): In September 2005, the NIAID and NIDDK awarded a contract to Alpha Genesis, Inc. to continue the breeding colony care, maintenance, ongoing breeding program, and provision of macaques to the NHPCSG. In addition, Alpha Genesis will continue to establish, as appropriate, directed breeding harems based on MHC typing and detailed pedigree history and analysis. The colonies were formerly funded through a cooperative agreement with Alpha Genesis, Inc.

Expert Panel on Transplantation Research: On September 27-28, 2005, the NIH convened an expert panel to develop a trans-NIH Action Plan for Transplantation Research. The panel reviewed the ongoing and planned NIH programs in transplantation research and identified research priorities in four areas: inducing immune tolerance; improving clinical outcomes; developing alternatives to organ transplantation and improving the health of patients on the transplant waiting lists; and establishing research resources and infrastructure. The Action Plan for Transplantation Research will be forwarded to Congress in FY 2006.

Diversity and Disparity in Solid Organ Transplantation: On September 21-22, 2005, a workshop was held to address the biological, medical, and socioeconomic barriers to solid organ transplantation for ethnic minorities in the United States. Topics included: epidemiology of end-stage organ disease, differences in transplant outcomes among ethnic groups, and access to transplantation for minorities. The American Society for Transplantation organized the workshop, with co-sponsorship from NIAID.

Non-Human Primate (NHP) Transplantation Tolerance Models: Immune Assays and Analysis Workshop: On September 20-21, 2005, the NIAID sponsored an assay workshop at the Emory Conference Center in Atlanta, Georgia. This meeting was organized by the Non-Human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) Steering Committee to facilitate an open exchange of information and experiences surrounding transplantation using non-human primate models. The goal of the meeting was to share detailed assays and analysis protocols and included the following topics: Immune Assays and Flow Cytometry in NHP, Genomics and Typing in NHP, and Transplant Models and Animal Care Issues in NHP.

DIVISION ADVISORY COUNCIL PRESENTATION

NIAID Non-Human Primate Transplantation Tolerance Cooperative Study Group AND Update on the Inner City Asthma Consortium

The following program was presented by division staff and guest: Kristy Kramer, Ph.D., Chief, Transplantation Basic Sciences Section discussed **DAIT's Program in Non-Human Primate Transplantation Tolerance Cooperative Study Group;** Christian Larsen, M.D., Director, Emory Transplant Center, Emory University gave an update of **Non-Human Primate Transplantation Tolerance Cooperative Study Group**. Peter Gergen, M.D., Medical Officer, Asthma and Inflammation Section presented an **Update on the Inner City Asthma Consortium**; and James Gern, M.D., Professor of Pediatrics, University of Wisconsin discussed **Urban Environment Childhood Asthma (URECA) Progress Report**.

CONCEPT REVIEW

The following concepts were presented and approved.

Centers for Medical Countermeasures against Radiation (CMCR): This initiative will operate in a flexible, cooperative, and multidisciplinary manner to provide comprehensive research support to counter radiation damage. The program will support both basic and translational research. Funds will also be available for critical infrastructure needs, animal model development and utilization, pilot projects, and web-based informatics and database support. The CMCR program will support both laboratory training and formal coursework in radiobiology for medical and graduate students, postdoctoral fellows, and independent investigators to expand the number of radiobiologists for future countermeasure development and the treatment of casualties. Ongoing training programs may be expanded and new programs established. The following research areas will be supported:

- Practical biodosimetry devices and techniques, biomarker assays, and other automated diagnostic systems to rapidly assess levels of radiation exposure, and assess tissue damage early after the event and during the treatment and recovery phase;
- Radioprotectant drugs and therapeutic regimens with emphasis on broadly effective activity, ease of administration, and safety;
- Therapeutic antibiotic regimens using single or combinations of antimicrobial drugs to control post-exposure infection in the context of immunosuppression and trauma;
- Innate and adaptive immunological enhancement and reconstitution mediated by cytokines, growth factors, defensins, and hematopoietic stem cell transplantation;
- Mechanisms of radiation injury at the systemic, organ, cellular, and molecular levels with emphasis on hematopoietic, immunological, gastrointestinal, and pulmonary function;
- Mechanisms of host response to radiation injury in different tissues that either exacerbates or ameliorates damage and disease;
- Identification and characterization of injury and therapy in subpopulations that are at risk of radiation damage from even low doses that do not affect healthy adults; and
- Study of long term medical effects that compromise health in radiation survivors.

Novel Radiation Nuclide Decorporating Agents: This program will support cooperative agreement grants on basic, applied or translational research to understand the physiological consequences of internal exposure to radionuclides that constitute terrorist threats to civilian populations. Characteristic properties of each radionuclide will be examined, together with the various physical forms by which the radionuclide may enter the body, the normal routes and timing of elimination, and methods to speed

normal elimination or induce rapid elimination by other means. Both in vitro and animal studies will be employed.

Organ-Targeted Therapies for Radiation Damage: This program will support single- or multi-project cooperative agreement grants on basic, applied or translational research to develop novel medical countermeasures to prevent or treat damage mediated by radiation in the bone marrow, gastrointestinal tract, lungs, kidneys, skin, cardiovascular system and/or central nervous system. Research will focus on the underlying mechanisms of tissue damage, mechanisms that prevent or repair the damage, and development of novel drugs and therapies that are practical for use after a terrorist event. Relevant doses of radiation are those in the moderate and higher ranges, as might be delivered by terrorist devices.

Combined Injuries after Radiological or Nuclear Event: This program will support cooperative agreement grants on basic, applied or translational research to determine the effectiveness of therapies to treat injury due to internal or external radiation exposure in the context of accompanying injuries resulting from lacerations, burns or crushing. Research will focus on understanding the impact of concurrent injuries, will work to develop the most effective treatments, and will establish guidelines for emergency treatment and medical follow-up care that account for physiological responses that differ from those induced by each single threat separately.

Long-Term Consequences of Radiation Exposure: This program will support cooperative agreement grants on basic, applied or translational research to study the molecular mechanisms responsible for radiation-induced carcinogenesis and other long-term health effects such as fibrosis in the lung or kidney. Research will identify potential molecular targets for the development of drugs that can be administered after acute radiation exposure in the 1-10 Gray range, as might be encountered after detonation of a terrorist radiation dispersal device (RDD), improvised nuclear device (IND) or conventional nuclear bomb. Animal models will be developed to most efficiently study different stages of the biological changes that lead to late disease.

Strengthening National Laboratory Capabilities to Support Radiation/Nuclear Countermeasure Development: This initiative will focus on the significant radiobiological expertise that exists within the National and Federal Laboratory system will be mobilized in a coordinated effort to 1) develop new medical countermeasures to protect against, mitigate the effects of, and treat the short- and long-term consequences of radiation exposure; 2) develop rationally designed, nontoxic, effective chelating agents that can be administered via the oral or inhaled route; 3) characterize potential biomarkers for estimating radiation dose; and 4) develop faster, more accurate, and scalable methods, techniques, and devices for performing dose assessment and biodosimetry. The program will support both basic and translational research. Funds will also be available for critical infrastructure needs, animal model development and utilization, and web-based informatics and database support. Ongoing training programs may be expanded and new programs established. The following research areas will be supported:

- Practical biodosimetry devices and techniques, biomarker assays, and other automated diagnostic systems to rapidly assess levels of radiation exposure, and assess tissue damage early after the event and during the treatment and recovery phase;
- Radioprotectant drugs and therapeutic regimens with emphasis on broadly effective activity, ease of administration, and safety;
- Innate and adaptive immunological enhancement and reconstitution mediated by cytokines, growth factors, defensins, and hematopoietic stem cell transplantation;
- Mechanisms of radiation injury at the systemic, organ, cellular, and molecular levels with emphasis on hematopoietic, immunological, gastrointestinal, and pulmonary function;

• Mechanisms of host response to radiation injury in different tissues that either exacerbates or ameliorates damage and disease.

Radiation/Nuclear Countermeasure Product Development Support Services Contract: The initiative will provide funds to continue and expand product development of radiation countermeasures efforts of the current medical countermeasures against radiological threats: product development support services program. The program will provide a comprehensive and broad range of non-clinical and clinical support services. The program will support product development efforts for licensure of both candidate drugs and biodosimetry devices. The types of product development support services include: screening and efficacy evaluation of candidate drugs, GLP toxicology and safety pharmacology in animal models, cGMP manufacturing support, GLP pivotal animal efficacy studies, Phase I clinical safety and pharmacokinetic studies, and regulatory submission support for candidate drugs and biodosimetry devices.

Radiation/Animal Testing Facilities and Renovations: This initiative will establish or renovate research laboratories to provide radiation facilities, animal treatment and testing laboratories, and animal housing facilities to support the development of effective and safe medical countermeasures against radiation.

V. JOINT MEETING OF THE AIDS SUBCOMMITTEE, NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL AND AIDS RESEARCH ADVISORY COMMITTEE - Ed Tramont, M.D., Director, DAIDS

Dr. King Holmes, Chairperson of the ARAC, welcomed the ARAC members, NIAID staff, and invited guests.

Director's Report – *Edmund Tramont, M.D.*

Dr. Edmund Tramont, Director of DAIDS, NIAID, welcomed the participants to the 43rd ARAC public meeting. He announced two new members to the Committee, Dr. Kathryn Edwards and Col. Nelson Michael (ex-officio representative, DoD). Dr. Merle Sande, the new liaison to the Office of AIDS Research Advisory Council, was unable to attend the meeting.

Dr. Tramont announced new NIAID staff appointments – Dr. Jorge Flores, the new Deputy Director of the DAIDS Vaccine and Prevention Research Program, and Dr. Richard Hafner, the new Director of the DAIDS Office for Policy in Clinical Research Operations. Dr. Hugh Auchincloss, Jr., has been named the new Principal Deputy Director of NIAID, and Dr. Scott Hammer is the new Chair of the AIDS Vaccine Research Working Group (AVRWG), a subcommittee of the ARAC.

Dr. Tramont reviewed recent Federal budgetary decisions, including an across-the-board rescission of 1 percent for NIH discretionary accounts for FY 2006. As a result, the budgets of all institutes except NIAID are experiencing a decline. Although NIAID's FY 2006 proposed budget was reduced by $44 million, the final budget represents a $12.5 million increase over FY 2005. DAIDS is the recipient of much of that increase, with AIDS receiving a 2.1 percent increase over FY 2005. Non-competing research project grants (RPGs) will be funded at 97.65 percent of committed levels.

DAIDS activities for 2007 will include continuing the phase-out/phase-in of the restructured clinical trials networks, vaccine trials, and the microbicide trial. Ongoing DAIDS activities will include basic and translational research programs and integrated preclinical/clinical programs for vaccines, microbicides, and therapeutics. In addition, unsolicited research will account for about one-third of the portfolio.

Renewal activities include translational research programs, expansion of the N-VITAL program, and expansion of the PAVE. New activities include programs involving HIV-1 proteins with cellular binding partners (a collaboration with the NIGMS), and the revised Phased Innovation Awards Program for AIDS vaccine research and microbicides.

Developing an Evaluation System for DAIDS and Its Funded Research Programs
– Jonathan Kagan, Ph.D.

Dr. Jonathan Kagan, Deputy Director of DAIDS, described the ongoing development of a strategy to evaluate DAIDS and its funded HIV/AIDS clinical trials networks. A goal is to learn how best to position the research networks for the future in light of a changing epidemic and the evolution of scientific understanding. How should we combine prevention and therapeutics? How can the programs be made more efficient? An evaluation strategy is one element in the broader effort to maximize DAIDS' future work. This evaluation should be distinguished from the ongoing role of scientific review, which was discussed at the last ARAC meeting.

Mary Kane, of Concept Systems, Inc., and part of the evaluation project team, stated that a critical goal of the evaluation will be to support the success of DAIDS and its research networks. The planning team will deliver a preliminary framework and plan for an evaluation system of DAIDS and its clinical trials networks. Implementation of the evaluation would occur later. Ms. Kane described upcoming efforts to communicate with stakeholders to learn about issues, define what success would look like, and create a logic model and framework for an evaluation plan.

Dr. William Trochim, of Cornell University and also part of the evaluation project team, described in greater detail the development of a concept map of key issues and elements. This involves developing a focus, identifying participants, structuring ideas, computing maps, and interpreting/analyzing them. After elements are clustered and abstracted, ways to measure them must be found.

The effort will result in (1) a framework that illustrates what constitutes research progress against HIV/AIDS, (2) a list of evaluation tools and resources, (3) a plot of milestones where evaluation can be integrated, (4) measurement/marker approaches, (5) a pilot evaluation plan, and (6) a plan for system design and implementation.

Discussion

The ARAC members inquired about past results from this process. Ms. Kane responded that her firm has observed transformative events in organizations, and considers the use of the resulting plan a measure of success. Dr. Kagan noted that the program will result in a draft evaluation plan, which will then be piloted with the networks. Unlike a controlled trial, it will offer information, although it will not ascribe causality.

Dr. Kagan emphasized that the process will evaluate the whole DAIDS system and will not be restricted to network investigators. It will not evaluate sites, although site evaluations will be included as one component in the analysis. Dr. Davis encouraged the project team to consider not only standards but also ways to elicit new standards. The project team welcomed input from the ARAC members.

The ARAC members expressed concern about small groups whose opinions might bias the evaluation system. Ms. Kane and Dr. Trochim responded that the process will extend to the breadth of the DAIDS

system and will include a careful sampling strategy. The planners will look at the range of outcomes rather than frequencies.

Dr. Holmes asked whether the process will be a self-evaluation or an independent evaluation for DAIDS. It was noted, DAIDS will be self-evaluated. In addition, it was noted that the process will focus on the DAIDS clinical networks, yet eventually could apply to all large programs. Dr. Holmes suggested creating a working group of ARAC members to inform the process. Drs. Davis, Edwards, and Lennox volunteered to serve in such a group.

The SMART Study: Update – *Wafaa Al-Sadr, M.D.*

Dr. Wafaa Al-Sadr presented an overview of the results of the Strategies for Management of Anti-Retroviral Therapies (SMART) trial, which was recently closed to enrollment. See attached press release and Questions and Answers.

Scientific Framework

Basic Sciences

Dr. Carl Dieffenbach, Director of the DAIDS Basic Sciences Program, outlined the Division's work in basic sciences, which integrates epidemiology, basic science/pathogenesis, and therapeutics. DAIDS identifies trends affecting incidence and treatment of HIV infection, works to discover fundamental mechanisms that drive the disease, and devises proof-of-concept therapeutic approaches.

One example of a common thread being studied today is the central role of CD4+ T cell activation. Scientists are studying transmission by disease stage and recognize the paradox that immune activation favors HIV replication. Dr. Dieffenbach reviewed recent findings indicating that few virions successfully cross the mucosa, infection takes on a focal nature, and once the virus reaches gut-associated lymphoid tissue, CD4+ T-cells are wiped out. The current view of pathogenesis is that up to 70 or 80 percent of CD4+ T cells in the gut are lost very early. Another area of active interest is the development of vaccines to improve antigen delivery using dendritic cells.

Basic science is investigating aspects of the HIV lifecycle, creating better understanding of the envelope structure, of interactions with CD4 and co-receptors (e.g., conformational changes), and cell entry. Researchers are seeking entry inhibitors and agents that can prevent integration. These inhibitors are being considered as therapeutics and preventive agents.

Therapeutics Research

Dr. Sandra Lehrman, Director of the DAIDS Therapeutic Research Program, cited the strides that have been made in the past 2 decades, since the first randomization of patients to AZT treatment. Following Dr. Dieffenbach's thread, Dr. Lehrman listed a dozen new entry-inhibiting drugs currently being studied in trials. A future challenge will be integrating such drugs into therapeutic cocktails to maximize benefits.

The area of integrase inhibitors has moved forward more slowly, although two candidate drugs are now in Phase II trials. Another area of research—maturation inhibitors—also features a compound in a Phase II trial. That compound—known as PA-457—blocks normal maturation of viral particles, leading to abnormal virions. Dr. Lehrman stated that the complexity of clinical trial design will be a big challenge for the future. Such trials may involve combinations of agents and multiple targets.

In the area of co-infections, Dr. Lehrman noted current trials for interactions and timing of antiretrovirals and tuberculosis treatment and drug development targeting HIV with Hepatitis C, now the cause of death in nearly 20% of HIV-infected persons in the U.S. Much work in these areas needs to be done. Other general challenges include decreasing the length of TB treatment, better understanding of drug interactions, and the potentially earlier treatment of TB in HIV-infected subjects.

Vaccine Research

Dr. Peggy Johnston, Director of the DAIDS Vaccine and Prevention Research Program, reviewed progress in vaccine research, which included: determining the structure of the unliganded envelope, elucidating the destruction of memory CD4+ T-cells, and establishing a global vaccine research enterprise. Advancement in research on HIV neutralizing antibodies has been slow, and should be a priority for the near future. One new area of research involves antibody-dependent cell-mediated virus inhibition. Dr. Johnston cited other progress, such as the work using the DNA + rAd5 vaccine, which has reduced viremia in infected monkeys.

The Center for HIV Vaccine Immunology (CHAVI) was established by NIAID in 2005 to address key scientific roadblocks in HIV vaccine development. This large international consortium, led by Dr. Barton Haynes of Duke University, has begun to establish contracts and communication pathways and has already written five protocols.

The Phase III trial in Thailand—the largest HIV vaccine trial—became fully enrolled in November 2005. The Data and Safety Monitoring Board for the Thai trail, an independent body, has reviewed the data and recommended that the trial continue. They will continue to meet about every 8 months. The new Merck vaccine phase 2b trial of adenovirus vectors began enrolling in December 2004 and is expected to complete enrollment by December 2006. In addition, HVTN is considering another phase 2b trial that will involve the evaluation of a Clade B vaccine in a Clade C region.

Prevention Science

Dr. Mary Fanning, Director of the DAIDS Transition Office of International Research Integration, reviewed efforts in prevention, emphasizing that they work in partnership with areas such as therapeutics and vaccines. NIAID's prevention research involves biomedical modalities, such as microbicides, antiretrovirals for pre- and post-exposure prophylaxis, and drugs targeting co-factors such as STIs, and behavior (injection drug use) as well as those used to prevent mother to infant transmission perinatally and during breastfeeding.

Microbicides are a high priority in prevention research. NIAID's topical microbicide efforts features an array of approaches in areas of basic research, preclinical development, and clinical trials, including early product selection and development, a focus on combination products, and behavioral research (e.g., acceptability of products). In addition, NIAID recognizes the need to develop methods to increase selectivity in clinical efficacy trials for prevention. Future efforts may likely include the evaluation of combinations of all prevention approaches.

Discussion of the Scientific Framework

Dr. El-Sadr cited the difficulty of bringing together researchers in HIV and tuberculosis to seek remedies for co-occurring cases. Dr. Lehrman suggested that new drugs and a coordinated infrastructure may help to solve this problem. She also proposed leveraging the research of the military and working with regulators worldwide to seek innovative designs. Dr. Holmes suggested this could be an area for PEPFAR to pursue. Dr. Tramont stated that restructuring of the NIAID clinical trials networks may help address issues such as these that would benefit from increased collaboration. Dr. Davis raised the need to involve more African American patients in trials and this was noted as another important goal of the restructuring effort.

Dr. Margolis recognized the success we've achieved to date, and questioned the inability to move beyond the current levels of success, suggesting that researchers pursue completely new avenues and foci (other models and chemistries). Perhaps the NIAID could offer RFAs for research that considers new chemistries and new delivery systems across therapeutic areas. Dr. Tramont noted that trials are becoming larger and more expensive, which necessitates new ways to make use of them and develop new efficiencies.

VI. REPORT OF THE DIVISION OF MIRCROBIOLOGY AND INFECTIOUS DISEASES COUNCIL SUBCOMMITTEE - Carole Heilman, Ph.D., Director

Dr. Carole Heilman, Director of the Division of Microbiology and Infectious Diseases (DMID), chaired the January 30, 2006 NAAID Microbiology and Infectious Diseases Subcommittee meeting. Dr. Heilman then turned to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their own respective new hires.

Dr. Heilman introduced Dr. Maria Giovanni, DMID's Assistant Director for Microbial Genomics & Advanced Technology. Dr. Giovanni provided the Subcommittee Members with an overview on NIAID's latest genome sequencing activities, including a discussion of the numerous sequencing centers NIAID is currently supporting. She mentioned that the centers are currently conducting 40 ongoing genome sequencing projects in diverse areas such as bacteria, fungi, parasites, invertebrate vectors of diseases, viruses, and in plants. Dr. Giovanni also discussed the NIAID Influenza Sequencing Project, which, to date, had sequenced 769 (she mentioned this number is probably already outdated) completed influenza genome sequences. She described each sequencing center in detail and closed her presentation by reiterating the Institute's over-arching objective, which is to release all relevant sequencing information to the public domain in a timely manner through Genbank.

Following a question and answer period, the following concepts were presented for consideration:

Development of Therapeutic Agents for Selected Bacterial Diseases
This effort will support the development of promising therapeutic candidates against anthrax, plague and tularemia or therapeutic candidates that have broad spectrum activity that targets an antimicrobial resistant pathogen (NIAID Category C) and at least one of the Category A bacterial pathogens.
The Subcommittee unanimously approved this Initiative.

Development of Third Generation Anthrax Vaccines
Under this initiative, enhancements would be sought to improve upon the current presentation of existing anthrax vaccines with regard to stability, immune response rate, safety, and a delivery method or route suitable for mass immunization. The initiative is to include pilot-scale manufacture and product

characterization, safety and efficacy non-clinical studies, and Phase I/Optional Phase II clinical trial(s).
The Subcommittee unanimously approved this Initiative.

NIAID Structural Genomics Centers for Infectious Diseases

This initiative builds upon the goals of NIAID Genomics Initiatives and in particular, the proteomic centers, and addresses the Institute's need to further expand the knowledge of the proteome by determining the three dimensional atomic level structure of targeted proteins. These protein structures will aid scientists to better characterize the biological properties of proteins and provide needed information such as the protein's active sites and surface-exposed binding pockets and the protein folding and interactions with other molecules.
The Subcommittee unanimously approved this Initiative.

Therapeutics and Diagnostics for Biodefense Toxins

This initiative will support the development of high throughput screening assays; novel approaches to delivering drugs to specific cell types; discovery and evaluation of candidate inhibitors; selection, evaluation and characterization of lead inhibitors; approaches that link drug delivery to drug discovery; and diagnostic platforms amenable to rapid screening for exposure to biodefense toxins. The development of new or improved animal models, as well as alternatives to animal models, will also be supported. Translational research to support, or which might lead to, the development of therapeutics or diagnostics for biodefense toxins is encouraged.
The Subcommittee unanimously approved this Initiative.

Therapeutics and Diagnostics for Category B Bacteria and Viruses

In this initiative, collaborative projects using multidisciplinary approaches will design and develop therapeutics and diagnostics for the NIAID Category B bacterial and viral pathogens. This program will be available for some or all of the steps in the product development pipeline for therapeutics and diagnostics, up to but not including clinical trials. Collaborations between researchers from different disciplines and from industrial laboratories are strongly encouraged in order to bring all the necessary expertise and facilities to bear, thereby optimizing the likelihood of successful product development. Manufacturing of product for pre-clinical evaluation using established or new animal models is included.
The Subcommittee unanimously approved this Initiative.

VII. ADJOURNMENT

The meeting of the Council was adjourned at 5:40 p.m., on Monday, January 30, 2006.

We do hereby certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.

-s- **5/9/06**

Anthony S. Fauci, M.D. Date
Chairman, National Advisory Allergy
and Infectious Diseases Council
Director, National Institute of Allergy
and Infectious Diseases

-s- **5/2/06**

Paula Strickland, Ph.D. Date
Executive Secretary
National Advisory Allergy and Infectious
Diseases Council
Acting Director, Division of Extramural Activities
National Institute of Allergy and Infectious
Diseases

These minutes will be formally considered by the Council at its next meeting; any corrections or notations will be incorporated in the minutes at the meeting.