NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

January 26, 2009

The 161st meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Monday, January 26, 2009, in Conference Rooms E1/E2, Building 45, National Institutes of Health. Dr. Anthony S. Fauci, director, National Institute of Allergy and Infectious Diseases (NIAID) presided as chair.

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 4:30 p.m. The meeting was closed to the public from 8:30 a.m. to 10:00 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. Ann Arvin
Dr. Barbara Baird
Dr. Robert Brooks
Dr. Carol Carter
Dr. Satya Dandekar
Dr. Kathryn Edwards
Dr. Sharon Kiely
Mr. William McLin
Dr. Louis Picker
Dr. Regina Rabinovich
Dr. Marc Rothenberg
Dr. Samuel Stanley
Dr. Megan Sykes
Dr. Christopher Walker
Dr. Richard Whitley
Dr. David Wilkes

***Ex Officio* Members Present:**

Dr. Anthony Fauci
Dr. Bruce Gellin
Dr. Ronald Valdiserri

Council Members Absent:

Dr. Martin Rosenberg
Dr. Christel Uittenbogaart

***Ex Officio* Members Absent:**

Dr. Mitchell Cohen
Major General George Weightman

***Ad Hoc* Members Present:**

Dr. Beth Bell
Dr. Virginia Pascual
Dr. Shelley Payne
Dr. Ilya Schmulevich

NIAID Senior Staff Present:

Dr. Hugh Auchincloss
Dr. Carl Dieffenbach
Dr. Carole Heilman
Dr. Marvin Kalt
Dr. Cliff Lane
Dr. John McGowan
Dr. Daniel Rotrosen

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 2,290 research and training applications with primary assignment to NIAID for a requested amount of $1,104,071,270 in first-year direct costs and recommended approval of 504 applications for $433,332,396 in first-year direct costs. Six Method to Extend Research in Time (MERIT) awards 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: Mr. William McLin, Asthma and Allergy Foundation of America; Dr. Samuel Stanley, Washington University in St. Louis; Dr. Christopher Walker, Nationwide Children's Hospital in Columbus, Ohio; and Dr. Richard Whitley, University of Alabama in Birmingham. Two Council members, Dr. Uittenbogaart and Dr. Rosenberg, were unable to attend the meeting. Also, *ex officio* members, Dr. Mitchell Cohen and Major General George Weightman, were unable to attend the meeting. Major General George Weightman will retire from the Army at the end of March.

Dr. Fauci introduced four *ad hoc* Council members, Dr. Beth Bell, Centers for Disease Control and Prevention; Dr. Virginia Pascual, Baylor Institute for Immunology Research; Dr. Ilya Shumlevich, University of Washington; and Dr. Shelley Payne, University of Texas in Austin. Dr. Bruce Gellin, director, DHHS National Vaccine Program Office, is the new DHHS *ex officio* member.

Consideration of Minutes of Previous Meeting

Council considered the minutes of the September 15, 2008, meeting and approved them as written.

Consideration of Operating Procedures

Council reviewed the 2009 Council operating procedures and adopted them as written.

Staff and Organizational Changes

Dr. Fauci began by announcing several new appointments in the Division of AIDS. Dr. Susan Plaeger is now the director of the Basic Sciences Program. In the Office of the Director, the Office of Program Operations and Scientific Information was reorganized into two independent branches. The new branch chiefs are Ms. Mary Owens, chief of the new Science Planning and Operations Branch and Mr. Robert Gulakowski, chief of the new Scientific Communications and Information Branch.

Changes in other key administrative positions include Ms. Julie Cummings was named chief of the NIAID Human Resources Branch, and Ms. Olga Acosta-Polston was appointed deputy director of the Office of Acquisitions, Division of Extramural Activities.

Tributes and Awards

Dr. Fauci announced that former Council member, Martin Delaney, died of liver cancer. Marty founded Project Inform and served as a member of Council from March 1995 to October 1998. He made extraordinary contributions to framing the HIV research agenda in regard to antiretroviral drugs and access to therapy.

Two NIAID intramural scientists recently won awards. Dr. William Paul received the 2008 Max Delbrück Medal, and Dr. Warren Strober accepted the Scientific Achievement Award for Basic Science by the Crohn's and Colitis Foundation of America.

Dr. Fauci paid tribute to Dr. Elias Zerhouni who left NIH at the end of October after serving as NIH director for six years. In 2003, Dr. Zerhouni launched the NIH Roadmap for Medical Research, one of his main accomplishments.

Budget Update

NIAID is still operating under a continuing resolution that expires on March 6, 2009. For FY 2009 NIAID set interim paylines at the 10 percentile for research project grants and the 16 percentile for new and early-stage investigators.

Dr. Fauci revisited the President's Budget request for FY 2009. The NIH allocation in the FY 2009 budget request is $29.2 billion, a zero percent increase over FY 2008. NIAID's allocation for FY 2009 is $4.6 billion, an increase of $8 million, or 0.2 percent over FY 2008, $5 million of which goes to the Global Fund. After accounting for the Global Fund, NIAID's actual increase is $3 million or 0.1 percent, an amount comparable to that of most other NIH institutes and centers.

Dr. Fauci gave an overview of the economic stimulus package proposed by Congress and the President. The goal of the stimulus package is to infuse funds into the economy quickly, providing a quick stimulus to various sectors of the economy while generating long-term benefits. The proposal may be different by the time Congress passes the bill.

Dr. Fauci explained the difference between a new investigator and an early-stage investigator (ESI). Applications from new investigators will be given special consideration. Reviewer expectations for new investigators are set lower: they look for fewer preliminary data, resources, and publications than they do from more established R01 applicants.

NIH launched a new computerized budget reporting process called Research, Condition, and Disease Categorization, or RCDC, which categorizes the funding for biomedical research.

Legislative Update

Since Council last met, the 111th Congress convened. Dr. Fauci presented the changes in the leadership of Congressional committees relevant to NIAID.

On September 16, 2008, Dr. Fauci testified before the House Committee on Oversight and Government Reform for a hearing on HIV prevention. On October 31, 2008, Dr. Fauci, Dr. Carl Dieffenbach, and Dr. Carole Heilman met with Senator Byron Dorgan and constituents from North Dakota to discuss new technologies in vaccine development.

Drs. Hugh Auchincloss and Nancy Bridges attended a congressional meeting on December 11, 2008, to discuss the clinical trials of islet transplantation for treating type I diabetes.

Other Information Items

NIAID released its updated strategic plan which includes four major research themes: infectious diseases (non-AIDS); HIV/AIDS; allergy, immunology, and immune-mediated diseases; and essential foundations for the future. To read the entire plan, go to NIAID: Planning for the 21st Century 2008 Update.

NIAID launched a new Web portal offering easy access to information about our programs for improving minority health. For more information, go to the Minority Health portal.

Dr. Fauci discussed the importance of global health research and the Institute of Medicine's recommendations for the U.S. commitment to global health research. He reported on the global health burdens of tuberculosis, malaria, AIDS, and influenza and the research agendas that NIAID is helping develop for each of these areas.

Dr. Fauci closed by informing the Council that the Galveston National Laboratory, a BSL-4 facility in Galveston, opened in November 2008.

III. GUEST SPEAKER – Dr. Jeremy Berg, Director, National Institute of General Medical Sciences – Implementation of Changes to Strengthen Peer Review

Dr. Jeremy Berg reported on where NIH is in the process of implementing changes to strengthen peer review. The first phase of the process was an extensive diagnostic evaluation that began June 2007. It identified the status of peer review and issues that NIH needed to address. In March 2008, NIH initiated phase two, which required designing an implementation plan. We are now beginning phase three, a phased implementation of changes to peer review.

NIH is focusing on the following four priority areas: engaging the best reviewers, improving the quality and transparency of review, insuring balanced and fair reviews across fields and career stages and reducing administrative burdens, and providing adequate measurement to continuously review the peer review system.

For more information and to get the latest updates, go to the Enhancing Peer Review at NIH Web site.

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

DAIT STAFFING/ORGANIZATIONAL CHANGES: Dr. Rotrosen welcomed the National Advisory Allergy and Infectious Diseases Council members. Dr. Rotrosen informed the subcommittee members of new staff members to the division: Dr. Nate Hafer who joined the Radiation/Nuclear Program as an American Association for the Advancement of Science (AAAS) - Science Technology Policy Fellow and Dr. Margarita Gomez who joined the Asthma, Allergy and Inflammation Branch as a Medical Monitor.

Dr. Rotrosen stated that two ad hoc Council members would be presenting talks to the Council members and staff. He noted these talks would be complementing each other, one from the clinician's view and the other from the bioinformatics perspective.

Dr. Rotrosen concluded his remarks by letting the subcommittee members know that members of the division's branches and offices had participated in a number of workshops, symposiums and meetings. In addition, the division had released several scientific initiatives.

Following Dr. Rotrosen's remarks he presented Dr. Virginia Pascual, M.D from Baylor Institute for Immunology who gave an overall perspective on the "Use of Genomics to Identify Disease Activity Biomarkers and Therapeutic Targets in Rheumatic Diseases." This was followed by Dr. Ilya Shmulevich from the Institute for Systems Biology who spoke on "Computational Systems Biology Approaches in Immunology."

Dr. Rotrosen noted that several concepts will be presented for the Subcommittee's consideration. Dr. Rotrosen mentioned these concepts form the foundation for a number of the basic and clinical science programs within the division.

The following concepts were presented for the Subcommittee's consideration:

Bioinformatics Integration Support Contract (BISC): This contract will provide bioinformatics support to the DAIT-funded research community to advance the discovery and testing of new therapies for immune-mediated diseases and to further our understanding of innate and adaptive immunity by providing: advanced computer support for managing scientific data, analytical and statistical support, disseminating best practices in scientific data management and analysis, and building a platform for integrated research and data sharing. The Subcommittee felt that this contract provides a valuable resource and an important infrastructure to stimulate and advance research. The Subcommittee unanimously approved the initiative.

Inner-City Asthma Consortium Statistical Coordinating Center: The ICAC - Statistical and Clinical Coordinating Center will be responsible for various functions in support of ICAC clinical trials. These include: assisting in the development of protocols (design and statistical approaches), developing Manuals of Operation and Standard Operating Procedures, developing clinical trial case report forms, clinical site training and certification, monitoring good clinical practice, providing regulatory support for Investigational New Drug Applications and FDA reports, centralized data collection, data cleaning, quality assurance and analysis and the participation in publication of study findings. The Subcommittee also felt that this contract provides a valuable resource and an important infrastructure to stimulate and advance research. The Subcommittee unanimously approved the initiative.

HLA Region Genetics in Immune-Mediated Diseases: The goal of the HLA-Region Genetics in Immune-Mediated Diseases program is to associate and catalog sequence variations in the HLA and natural killer (NK) cell immunoglobulin-like receptor (KIR) genetic regions that determine susceptibility to immune-mediated diseases, including autoimmune diseases, primary immunodeficiencies, graft-versus-host disease, and graft rejection in organ and cell transplantation. The Subcommittee unanimously approved the initiative.

Immunobiology of Xenotransplantation Cooperative Research Program: The goals of this program are to: (1) delineate the cellular and molecular mechanisms of xenograft rejection and the induction of tolerance and accommodation; (2) develop effective strategies to improve xenograft survival and function; (3) characterize the physiological compatibility/limitations of xenografts; and (4) evaluate the risk and pathogenic consequences of cross-species infections in porcine to non-human primate (NHP) models of xenotransplantation. The long-term goal of this program is to develop novel and efficacious

strategies for safe clinical application of xenotransplantation. The Subcommittee felt that this initiative addresses a critical need and unanimously approved the initiative.

Non-Human Primate Heart/Lung Transplantation Tolerance: The goals of the NIAID and NIDDK Non-human Primate Transplantation Tolerance Cooperative Study Group (NHPCSG) program are to: (1) develop donor-specific immune tolerance induction regimens; (2) evaluate the preclinical safety and efficacy of candidate regimens; and (3) elucidate the mechanisms of the induction, maintenance, and/or loss of tolerance in non-human primate (NHP) models of islet, kidney, heart, and lung transplantation. The Subcommittee also felt that this initiative addresses a critical need and unanimously approved the initiative.

Centers for Medical Countermeasures Against Radiation: This program is to maintain a network of national research centers to develop effective and comprehensive medical responses applicable to all subsets of the civilian population in the event of radiological or nuclear emergencies. Multidisciplinary basic and translational research will produce new techniques and devices to measure radiation exposure in the human body and follow biomarkers of tissue damage and recovery; and will develop novel therapies to minimize tissue damage, hasten tissue recovery, restore normal physiological function, and improve survival. The Subcommittee unanimously approved the initiative.

Radiation/Nuclear Countermeasure Product Development Support Services Contract: This contract will provide additional funds to continue and expand nonclinical and clinical efforts for product development of radiation/nuclear medical countermeasure candidate drugs and biodosimetry devices for inclusion in the Strategic National Stockpile for use during a radiation emergency. The contractor will provide a comprehensive and broad range of nonclinical and clinical support services. The program will support product development efforts for licensure of both candidate drugs and biodosimetry devices. The Subcommittee unanimously approved the initiative.

V. REPORT OF THE DIVISION OF MICROBIOLOGY 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 26, 2009 NAAIDC Microbiology and Infectious Diseases Subcommittee meeting. Dr. Heilman acknowledged Dr. Shelley Payne, who completed her NAAIDC term last September (she returned today to serve as an *ad hoc* member of the Subcommittee), and presented her with a small token to express appreciation for her service. She then deferred to the DMID branch chiefs to report on recent staff changes in their respective branches.

Following the introductory remarks, Dr. Linda Lambert, Chief of DMID's Respiratory Diseases Branch, presented a brief overview of DMID's influenza vaccine research activities, providing a snapshot of the scope of the work that the Division has been supporting over the past several years related to both seasonal vaccine development as well as strategies for pandemic influenza preparedness, noting the different types of vaccines and delivery systems supported by DMID.

There were several concepts presented for the Subcommittee's consideration:

Respiratory Pathogens Research Network – these multidisciplinary research units will support translational and clinical research projects focused on respiratory pathogens and the diseases they cause. In this renewal, research on the emergence of drug-resistant pathogens such as *S. pneumoniae, Haemophilus influenzae* and influenza, and the impact of co-infections on disease progression and

severity will be key areas of focus. The Subcommittee noted the significant global health burden of respiratory infections and recommended that the initiative support research areas likely to have substantial impact. To ensure that the objectives of the program are met, the Subcommittee also recommended that the initiative clearly articulate what is meant by "translational" research. The Subcommittee discussed the potential value of developing an independent consultant group to provide periodic input on prioritization of proposed projects. The Subcommittee unanimously approved this initiative.

Enterics Research Investigational Network (ERIN) Cooperative Research Centers – this multi-center research program seeks to maintain a coordinated enterics research program that will bring together expertise in microbial ecology and pathogenesis; host response; and clinical research. The concept received enthusiastic support from several Subcommittee members, who emphasized the importance of enteric disease research efforts. Moreover, Subcommittee members were pleased with the incorporation of suggestions from the recent evaluation of the current program (the Food and Waterborne Diseases Integrated Research Network). The Subcommittee encouraged staff to consider the following issues in moving forward with an initiative: a focus on the human host, the inclusion of international collaborations (to improve access to clinical samples and vulnerable populations), and the pursuit of integrative, collaborative research through development of over-arching themes. The Subcommittee unanimously approved this concept.

Development of Technologies to Facilitate the Use of, and Response to, Biodefense Vaccines – this concept is designed to advance promising vaccine candidate(s) and technologies for select high priority biothreat pathogens. The product development efforts to be supported under this concept include: cGMP process development and manufacturing; product formulation and fill; product characterization and development of release assays; conduct of non-clinical safety and efficacy testing; product stability testing; Phase 1 and potentially early Phase 2 trials; and other appropriate activities. The Subcommittee expressed support for this concept because members thought it would help facilitate the transition of DMID-supported discovery efforts into products. Dr. Heilman noted that DMID staff maintain frequent and open communications with DoD, BARDA and DARPA to ensure that our efforts are integrated or complimentary, and do not overlap with the activities supported by these other agencies. The Subcommittee asked how the technology would be "validated;" staff indicated that a well-characterized vaccine product that has been evaluated in a Phase I trial could be used to help facilitate this step. Related to this issue, a question was asked concerning the timing of integration of new technology with the vaccine. DMID acknowledged the complexity of these issues and that they will be considered as this initiative is developed. The Subcommittee unanimously approved this initiative.

International Collaborations in Infectious Diseases Research (ICIDR) – this program will support collaborative research on infectious diseases that are endemic in resource-constrained international settings. The research will increase relevant research experience for both US and foreign investigators as well as enhance infrastructure development. Research must focus on a health issue that is of importance to the developing country. The Subcommittee noted the success of the ICIDR program in the past and how helpful the ongoing collaborations have been when US investigators are seeking new partnerships with scientists in developing countries. The Subcommittee unanimously approved this concept.

International Centers of Excellence for Malaria Research (ICEMR) – the goal of this initiative is to develop a multidisciplinary approach involving field-, clinical-, and laboratory-based research. The overall objective of this initiative is to expand our knowledge base and guide future research activities so as to ensure their relevance to having an impact on reduction of morbidity and mortality attributable to malaria. Clinical research and field site capabilities in malaria-endemic areas are essential components, and collaborative arrangements with US-based laboratories would be encouraged. In addition, pilot

projects that address emerging, high priority needs in malaria research and the development of a collaborative training program for the exchange of young investigators among participating institutions will be solicited. Data, information, and reagents generated under this initiative will be put into the public domain through NIAID-supported databases and resource centers (such as the Malaria Research and Reference Reagent Resource Center). The Subcommittee noted the significant global health burden of malaria, the impressive gains that are being made in malaria control and elimination, and the need to strive for the possibility of malaria eradication. Noting the changes in malaria epidemiology that are already occurring as a result of control and elimination programs, the Subcommittee enthusiastically endorsed this concept as a timely and innovative initiative that will provide necessary research support for public health efforts in malaria control, elimination and possible eradication. The Subcommittee unanimously approved the concept.

VI. JOINT MEETING OF THE AIDS SUBCOMMITTEE, NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL AND AIDS RESEARCH ADVISORY COMMITTEE (ARAC) – Carl Dieffenbach, Ph.D., Director, DAIDS

Dr. El-Sadr called the meeting to order and presented the minutes of the previous meeting, which the committee approved by unanimous voice vote.

Director's Report
Carl Dieffenbach, Ph.D., Director, DAIDS

Dr. Dieffenbach welcomed the participants and introduced three new members of ARAC: Judy Leiberman, M.D., Ph.D., Senior Investigator at the Immune Disease Institute, Harvard Medical School; Maureen Goodenow, Ph.D., Director of the Florida Center for AIDS Research, University of Florida; and Karen Goldenthal, M.D., who retired in 2006 as Director of the Division of Vaccines and Related Products Applications in the U.S. Food and Drug Administration and currently works as a consultant. Dr. Dieffenbach noted the recent passing of Martin Delaney, who served on ARAC from 1991 to 1995 and acknowledged his many contributions to the fight against AIDS. He also announced several organizational changes, including the appointment of Dr. Susan Plaeger as the Director of the Basic Sciences Program, Ms. Mary Owens as the Chief of the Science Planning and Operations Branch, and Mr. Robert Gulakowski as the Chief of the Scientific Communications and Information Branch.

Dr. Dieffenbach presented his scientific vision for DAIDS, emphasizing research that unravels the fundamental processes governing host-virus interactions and, based on these findings, to identify and test new ways to prevent, treat and cure HIV disease. This means shifting the focus of vaccine research from development to discovery, continued support for prevention trials, and the development of treatment regimens that have fewer side effects. He noted that the schedule for the recompetition of the HIV/AIDS clinical trials networks calls for the release of an RFA projected for November 2011, with applications due in May 2012 and awards in May 2013. DAIDS will issue a request for information seeking input on the recompetition, such as whether NIAID should take a more integrated approach to infectious diseases such as tuberculosis, hepatitis and malaria, as well as HIV/AIDS.

NIH remains under a continuing resolution through March 6, and the President's budget for FY 2009 contains no overall increase for NIH. NIAID's budget for FY 2009 is nearly $4.6 billion, an increase of only $3 million after deducting the institute's contribution to the Global Fund. NIAID has instituted a new policy to support Early Stage Investigators, who will receive special consideration during peer review. At present, the overall payline for NIAID grants is 12 percent, which the payline set for new investigators is 16 percent. The new Administration will submit its budget for FY 2010 in April rather

than February, and the proposed Stimulus Package contains up to $4 billion in additional funding for NIH, including $1.5 billion for research, half of it available immediately and half after October 2009. Dr. Dieffenbach then reviewed performance over the past year in terms of the payline, as well as the number and type of grants that were funded.

Finally, Dr. Dieffenbach reported that at their last meeting, the HIV/AIDS Strategic Working Group (SWG) Kevin De Cock was invited to address the group regarding the strategy of universal HIV testing and immediate treatment with antiretroviral therapies, the focus of the paper by Rueben Granich, et. al. published in Lancet a few months earlier. Dr. De Cook indicated that the "Test and Treat Program" warrants serious consideration. The HPTN was asked to focus on this issue and bring a proposal to the next SWG meeting. Because of the cost of the trials, there was discussion about two AIDS Clinical Trials Group (ACTG) trials – ACTG 5257 and ACTG 5260. In addition, the ACTG provided a strategic update and was asked to expand upon it at the February 9 meeting of the Conference on Retroviruses and Opportunistic Infections. Finally, Manizhe Payton (Director Office of Clinical Site Oversight, DAIDS) provided an overview of her office and the role it plays at DAIDS.

AIDS Vaccine Research Subcommittee – Update
Jim Bradac, Executive Secretary, AIDS Vaccine Research Subcommittee (AVRS)

Dr. Bradac reported that the AVRS has met twice since its last report to ARAC; in lieu of specific AVRS reports back to the ARAC, those updates have been incorporated into discussions about the STEP trial, PAVE 100 and PAVE 100A. Specifically, in May 2008, the AVRS had focused discussions on the STEP and Phambili trials and the proposal for the amended PAVE 100A trial. As noted previously at ARAC, taking into consideration the recommendations and comments from members of the AVRS and the Strategic Working Group, the Institute decided against going ahead with PAVE 100A and instead chose to test the Vaccine Research Center's vaccine in a smaller focused study. In September, the AVRS heard updates on new vaccine research activities that address the shifting emphasis on discovery and did considerable planning for the Workshop on Nonhuman Primates (NHP) for AIDS Vaccine Research. That workshop, held on November 12-13, recommended that the AIDS research community stress the value of NHP models in order to ensure that adequate numbers of animals are available for research; that mechanisms be put in place to coordinate and synergize NHP research in order to make the best use of animals; and that there be increased dialogue between the NHP and human clinical research communities, in order to reveal new opportunities.

At the next AVRS meeting that will follow the ARAC on January 27-28, there will be presentations and discussion on the preliminary analysis from the STEP trial, an analysis of Ad5-specific responses in vaccines, a report on the HVTN 505 protocol, and a series of presentations on the application of systems biology to the study of vaccine efficacy. Future meetings of the AVRS will be on May 19-20 and September 15-16, in Bethesda. Dr. Bradac closed by urging interested ARAC members to submit ideas for additional topics that AVRS should address.

Vaccine Research Program (VRP) – Review of Post-Summit Activities
Margaret (Peggy) Johnston, Director, Vaccine Research Program (VRP)

Dr. Johnston provided an update on VRP's activities, focusing on its stronger emphasis on basic discovery. The Basic HIV Vaccine Discovery RFA, approved by ARAC in May 2008, was published in August 2008, with applications due on January 22, 2009. The scientific and technical reviews should be completed by May and, following Council approval on May 18, the first grants will be awarded on in early July. In addition, the B-Cell Immunology Partnership RFA, approved by the ARAC in September

2008, should begin in FY 2010 with first-year funding between $4 million to $5 million. The goal is to foster cross-fertilization between B-cell immunologists and vaccinologists to help inform vaccine discovery, specifically around the problem of how to elicit broadly neutralizing antibodies. NIAID also held an HIV B Cell vaccine workshop on November 8-9, during which there were presentations on several new approaches to characterize the B cell repertoire and modify it to generate broadly neutralizing antibodies against HIV.

In addition, NIAID published an RFA on August 1 for the Highly Innovative Technologies to Interrupt Transmission of HIV (HIT-IT), which was approved by ARAC in January 2008. Applications for HIT-IT were received on November 3, and (following Council approval on May 18) the first awards will be made on in early July 2009. This is a cross-program concept within the Division , calling on input from the Basic Sciences Program, as well as the Prevention Sciences Program, to stimulate "out of the box," novel, unconventional approaches that might provide long-term, safe protection from HIV acquisition.

Dr. Johnston then highlighted two interesting presentations from the AIDS Vaccine 2008 meeting. One was on T cell responses to APOBEC that were found in a fair proportion of HIV-infected individuals, but not in the controls. The majority of these T cell responses were observed in long-term non-progressors. The other talk she highlighted was on LINE transposable elements. (LINE stands for long interspersed nuclear elements.) These, when intact, encode two proteins, and the group also observed LINE-specific CD8 T cell responses in a subset of infected individuals. Both presentations included data that suggested that there may be "host antigens" that could serve as targets for novel vaccine or immunotherapeutic approaches, although Dr. Johnston countered that safety testing of such approaches would need to be very rigorous.

Turning to the use of the NHP model, Dr. Johnston noted that the November workshop attracted 175 participants despite the lack of scientific presentations, and a second workshop in December on systems biology and NHP models of AIDS attracted over 100 participants. The goal of the workshop in November was to obtain additional advice on priority questions to be addressed in non-human primates, as well as the approaches and the resources needed to address those questions. The goal of the second workshop was to inform investigators about current capabilities and the potential of systems biology in the field, and to encourage partnerships between systems biology experts and non-human primate experts, building some new collaborations.

During the November workshop a number of areas were identified in which further research was recommended: early SIV infection in NHP, the basis for nonpathogenicity of SIV infections in natural host species, improved challenge models, pathogenesis in HIV infection, and new immunological reagents and assays. To support future NHP research, VRP has announced a joint effort with HVTN and CHAVI to provide Early Career Investigator (ECI) Scholar Awards for ECIs interested in improving NHP models and fostering collaboration between NHP and clinical scientists. A CHAVI-HVTN RFP was published in October, with applications due on February 23 and initial awards expected in April 2009.

In clinical research, analysis continues on additional cases of new infection from STEP, with results anticipated in spring 2009. This includes analysis of the impact of HSV-2 serostatus, HLA type, immune responses to specific genes, and Ad5 sero-status. Preliminary results from the Phambili trial of the Merck vaccine in South Africa seem to parallel those in the Step study. While the numbers of HIV infections are too small to draw any definitive conclusions, relatively more infections were found among those who were vaccinated, uncircumcised and with Ad5 titer $\geq$18.

In response to questions, Dr. Johnston explained that HVTN 505 would mostly likely begin accruing in the fall 2009 and will recruit participants only in the United States. Only men who have sex with men, are circumcised, and have no detectable neutralizing antibodies to Ad5 will be eligible to enroll. While the size of the trial size is small, only 1,350 participants in total, it is powered to detect one-log or more a difference in viral load between the vaccine and placebo recipients. There was some discussion about how few women became infected in the Step study even though the risk-taking behaviors that they reported were high. They were clearly engaging in high risk behaviors, but their partners probably weren't infected. The HVTN, which has the challenge of enrolling high risk women whose partners are actually infected, is doing additional clinical research about how to identify and enroll those women. Other discussion focused on the supply and demand for NHPs in AIDS research, which the ARAC may wish to address at a future meeting.

Basic Sciences Program (BSP) – Scientific Highlights and Future Plans
Susan Plaeger, Director, BSP

Dr. Plaeger noted that her program has the largest research portfolio in DAIDS, with over 450 active grants research covering a varied area of science: molecular and cellular biology of both the host and the virus, HIV immunology, epidemiology and modeling of HIV infection, host genetics, gene therapy, and identification of novel targets for interventions, both drug and microbicide. BSP also encompasses 7 contracts, 20 Centers for AIDS Research, and 3 consortia in HIV epidemiology, as well as 4 current RFAs and program announcements.

The overarching issues in BSP are the early events in HIV transmission particularly the earliest events, how the virus first crosses the mucosa, all the first cells that get infected, how it's spread, the innate immune response and what that triggers in terms of the adaptive response. These are critical for identifying new paradigms for prevention. Host factors in HIV replication are also important and there have been exciting new advances since the discovery of APOBEC3G, TRIM5 (alpha) in the last couple of years. Interventions are beginning to be designed around these host factors. The immune response is also critical as is the inflammatory response to HIV and BSP supports population-based studies to address some of these issues. These observational cohort studies are addressing the pressing issues in the era of global HAART relate to when to start or switch treatment, as well as toxicities and morbidities from both living longer with HIV and with HAART, and with a population of individuals living longer with HIV, aging.

Dr. Plaeger highlighted some recent findings, including the role of semen fibrils in HIV transmission, the role of tetherin in release of HIV from infected cells, the mechanisms of several new strategies for interfering in HIV binding to CCR5 on cells, and the events that lead to T-cell exhaustion. She noted that future plans include filling the gaps in understanding in the 4 areas previously outlined. In addition, the 2010 initiative in systems biology – Dissecting the Immune Response – will address both transmission and early immune responses. BSP will also support of a 2009 Keystone Workshop to look at host protein factors and their validation -- how to best go forward with those and how to validate them in different systems. Also, a new initiative to better understand and develop strategies to eradicate HIV reservoirs is planned for FY 2011, as is the renewal and/or expansion of the IeDEA program.

In response to questions, Dr. Plaeger said that BSP is beginning to get expressions of interest regarding the possible use of transplanted stem cells with the delta 32 mutation in the CCR5 co-receptor for HIV to "cure" AIDS, but that the concept is not well developed. She said that it might be fruitful for BSP to encourage broader collaboration with researchers working on other infectious diseases. Other questions dealt with the use of data from genome-wide screens; HIV-related SNP data are being moved to a new

repository, but the wealth of data on structural and host factors could be of use in the study of viruses other than HIV. The interaction between other opportunistic infections or other diseases and with HIV and the importance of cross-disciplinary efforts was also emphasized. One suggestion was for cross-disciplinary workshops that could synergize work in different areas.

Prevention Sciences Program (PSP) – Scientific Highlights and Future Plans
Sheryl Zwerski, Director, PSP

Ms. Zwerski presented PSP's priorities – to discover and develop new compounds and strategies that can be advanced into the microbicide and biomedical prevention pipelines, and to evaluate and optimize existing interventions. To accomplish this, PSP supports programs in early discovery, preclinical product development and clinical evaluation.

For microbicide-specific development support, there are the Integrated Preclinical/Clinical Program for HIV Topical Microbicides, the Microbicide Innovation Program (MIP) and the HIV Microbicide Design and Development Teams (MDDT), which are overseen by the DAIDS' Microbicide Research Branch; and the Sexually Transmitted Infections (STI) and Topical Microbicide Cooperative Research Centers and the Partnerships for Microbicide Development, funded through DMID. The highly successful MIP recruits new investigators and provides them with support in areas such as formulation, animal models and preclinical evaluation. Five publications have come out of the MIP R21s thus far, and many of the IPCP-HTM investigators were recognized with oral presentations at the Microbicides 2008 Conference in Delhi.

The Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM) has 12 current awards to promote the development of new microbicides and additional resources to expedite the advancement of candidates to clinical trials. They involve collaboration with industry partners, which is very important for the development pipeline. There are also two IPCP-HTM awards which currently involve partnerships with the International Partnership for Microbicides and/or CONRAD. The MDDT program is represented by only a single award that supports all the IND-enabling activities to advance a microbicide product into clinical trial and also supports safety testing of a defined microbicide candidate. Ms. Zwerski also described the Comprehensive Resources for Topical Microbicides and Biomedical Prevention, which was approved at an earlier ARAC meeting. The contract will provide gap-filling resources, "go/no-go" development plans for microbicide and biomedical prevention strategies progressing to clinical evaluation, and support "Best Practices" working groups.

She noted the two clinical trials networks – the Microbicide Trials Network (MTN) and the HIV Prevention Trials Network (HPTN) – which advance new microbicides and other prevention strategies into clinical trials.

Several clinical trials are underway or recently completed. HPTN-035, a Phase 2/2b trial of the safety and effectiveness of two vaginal microbicides, 0.5% PRO2000 and BufferGel, in preventing vaginal transmission, enrolled 3,100 women in the United States and southern Africa; data analysis continues, with results to be presented at CROI in February. MTN-002 is a Phase 1 trial to determine the pharmacokinetics and safety of a vaginal microbicide in women who are about to have a caesarian section; pending results demonstrating safety, future trials will move the test further back in pregnancy and eventually into early pregnancy. MTN-003 is a Phase 2B trial of topical Tenofovir, oral Tenofovir, and oral Truvada vs. placebos. Two other trials, MTN-006 and MTN-007, will test the safety and acceptability of the use of the vaginally formulated 1% tenofovir gel as a potential rectal microbicide. These trials will include novel safety and efficacy biomarker testing and a pharmacokinetic component.

In addition, MTN-015 and MTN-016, will be observational trials that follow women exposed to study agents in MTN as well as other prevention trials. The purpose of MTN-015 is to understand the nature of HIV progression and treatment response in HIV-positive women who had been using a topical microbicide or oral antiretrovirals as pre-exposure prophylaxis when they were infected. MTN-016 is designed to evaluate the prevalence of spontaneous pregnancy loss and the prevalence of major malformations in infants of mothers exposed to investigational agents during pregnancy.

In the prevention area, PSP's areas of emphasis are the application of new interventions, the use of treatment as prevention ("Test and Treat"), the use of combination prevention packages, and a renewed focus on the domestic epidemic. The ultimate goal of all these programs is to develop a comprehensive toolbox for preventing the transmission and acquisition of HIV. In describing the iPREX PrEP study, it was noted that it will evaluate safety and efficacy of Truvada and will also look to increase our understanding of attitudinal and behavioral correlates of failure or success, the type and quantity of sexual exposure and the patterns of adherence as well as the impact of Truvada on bone mineral density or body fat distribution in HIV uninfected individuals. In addition, the effect of cessation of chemoprophylaxis in non-infected individuals will be examined and for those who become infected while on PrEP, the impact on drug resistance, viral load, and immune responses will also be examined. Other interventions under investigation include substitution therapy among opiate-dependent injectors (HPTN 058), and "positive prevention" strategies for acutely infected individuals (HPTN 062) and in HIV infected individuals in international settings (HPTN 063). The two domestic studies – one in women at high risk and one in black MSMs – were also discussed.

In response to questions, Dr. Zwerski explained that the clinical trials done through the Integrated Preclinical/Clinical Program are small, early-stage safety studies. Once the safety of a new compound can be determined, they can move into larger efficacy trials. There was some discussion about the recently completed vaginally formulated UC781 rectal microbicide trial conducted within one of the IPCP-HTMs. A novel observation for this trial of ex vivo inhibition of HIV replication of in vivo exposed rectal tissues has identified a potential surrogate biomarker for microbicide efficacy; these observations will need to be confirmed and generalized. It is expected that RMP-02/MTN-006, which is in development, will provide additional information about this novel observation.
In looking at the domestic epidemic, PSP is gathering data on poverty, education and drug-seeking behavior, as well as HIV incidence, in "hot spots" such as New York City, Newark, DC, and Atlanta through HPTN 061 (a study in men who have sex with men) and HTPTN 064 (at-risk women). The study in women will also help inform vaccine efficacy trials and has been harmonized with the HVTN study looking at recruitment of women at high risk with the highest incidence of infection.

Future Meetings

Dr. El-Sadr announced that the next ARAC meeting will be on May 18th. Dr. Dieffenbach identified several topics that might be addressed, including NHP supply and demand, results from HPTN-035, AIDS therapeutics, which was not addressed at this meeting, and budget matters (Stimulus, FY 2010, draft FY 2011).

VII. ADJOURNMENT

The meeting of the Council was adjourned at 4:30 p.m., on Monday, January 26, 2009.

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

-s-	**3/17/2009**
Anthony S. Fauci, M.D. Chairman, National Advisory Allergy and Infectious Diseases Council Director, National Institute of Allergy and Infectious Diseases	Date

-s-	**3/12/2009**
Marvin R. Kalt, Ph.D. Executive Secretary National Advisory Allergy and Infectious Diseases Council Director, Division of Extramural Activities National Institute of Allergy and Infectious Diseases	Date

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.