NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

January 29, 2007

The 155th meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) was convened at 10:30 a.m. on Monday, January 29, 2007, 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 chair.

In accordance with the provisions of Public Law 92-463, the meeting was open to the public from 10:15 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 10:00 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. Barbara Baird
Dr. Robert Brooks
Dr. Stanley Chapman
Dr. Satya Dandekar
Dr. Kathryn Edwards
Dr. Richard Insel
Dr. J. Brooks Jackson
Dr. Sharon Kiely
Dr. Martin Myers
Dr. Shelley Payne
Dr. Marc Rothenberg
Dr. Ruth Ruprecht
Dr. Gary Schoolnik
Dr. Megan Sykes
Dr. Nathan Thielman
Dr. Gail Wertz
Dr. David Wilkes

***Ex Officio* Members Present:**

Dr. Mitchell Cohen
Dr. Anthony Fauci
Dr. Ronald Valdiserri

Council Members Absent:

Dr. Martin Rosenberg

***Ex Officio* Members Absent:**

Major General Eric Schoomaker

***Ad Hoc* Members:**

Dr. John Richert
Dr. Roland Tisch

NIAID Senior Staff:

Dr. Hugh Auchincloss
Dr. Carl Dieffenbach
Dr. John McGowan
Dr. Charles Hackett
Dr. Carole Heilman
Dr. Marvin Kalt
Dr. Cliff Lane
Dr. Paula Strickland

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 2,009 research and training applications with primary assignment to NIAID for a requested amount of $496,547,430 in first-year direct costs and recommended approval of 266 applications for $74,528,804 in first-year direct costs. One Method to Extend Research in Time (MERIT) award was 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 five new Council members: Dr. Robert Brooks, Florida State University; Dr. Satya Dandekar, University of California, Davis; Dr. Sharon Kiely, Allegheny General Hospital in Western Pennsylvania; Dr. Marc Rothenberg, Cincinnati Children's Hospital Medical Center; and Dr. David Wilkes, Indiana University School of Medicine. He noted that Dr. Ronald Valdiserri was replacing Dr. Lawrence Deyton as the *ex officio* member from the U.S. Department of Veterans' Affairs. He also noted that Dr. Martin Rosenberg and Major General Eric Schoomaker were unable to attend the meeting.

Dr. Fauci introduced two *ad hoc* Council members, Dr. John Richert, National Multiple Sclerosis Society, and Dr. Roland Tisch, University of North Carolina at Chapel Hill.

Consideration of Minutes of Previous Meeting
The minutes of the September 18, 2006, meeting were considered and approved as written.

Consideration of Operating Procedures
The 2007 Council operating procedures were considered and adopted as written.

Staff and Organizational Changes
Dr. Fauci announced that Dr. Richard Krause, NIAID director from 1975 to 1984, retired from NIH as of December 31, 2006. Dr. Krause served NIH in many capacities, most recently as senior scientific advisor at the Fogarty International Center.

Dr. Marvin R. Kalt was appointed director of the Division of Extramural Activities (DEA), NIAID. He comes to NIAID from the Global Health Program of the Bill & Melinda Gates Foundation. Dr. Fauci thanked Dr. Paula Strickland for serving as the acting director of DEA while the Institute conducted the search for a new DEA director.

Dr. Ed Tramont has moved from his position as director of the Division of AIDS to become the associate director for special projects in the NIAID Division of Clinical Research. Dr. Carl Dieffenbach has agreed to serve as the acting director of DAIDS. Also in the Division of AIDS, Dr. Susan Plaeger has been appointed the acting director of the Basic Sciences Program, and Carole Andres is the new chief of the Clinical Research Resources Branch in the Office for Policy and Clinical Research Operations.

Several changes have occurred in key administrative positions in the Institute. John Mathis was named director of NIAID's Office of Administrative Services within the Office of Management and Operations. Juli Brown has been appointed director of the NIAID Office of Workforce Effectiveness and Resources. Laurie Doepel has been selected chief of the News and Public Information Branch in NIAID's Office of

Communications and Government Relations. Ralph Tate is now the chief of NIAID's new Mission Planning and Integration Branch. Katie Kuri left her position as branch chief for the NIAID Intramural Administrative Management Branch. Gwen Shinko will serve as the acting branch chief.

Dr. Fauci recognized several NIAID scientists for special achievements. In October, Dr. Mark Dybul, former special assistant for medical affairs in the Office of the Director, was sworn in as the U.S. Global AIDS Coordinator, a position that has the rank of Ambassador. In December, Dr. Ed Berger received the NIH World AIDS Day Award. Dr. Cliff Lane was elected to the Institute of Medicine of the National Academy of Sciences.

Budget Update

NIAID is still operating under a continuing resolution that expires on February 15, 2007. Dr. Fauci revisited the President's Budget request for FY 2007. The NIH allocation in the FY 2007 budget request is $28.6 billion, the same as FY 2006. NIAID's allocation for FY 2007 is $4.4 billion, an increase of $12 million, or 0.3 percent over FY 2006. The proposed FY 2007 budget increase of $12 million would support pandemic influenza, HIV/AIDS vaccine research, and NIAID's contribution to the NIH Genes and Environment Initiative.

Following guidance provided by NIH, NIAID developed a provisional financial plan to provide support to grantees while we operate under the continuing resolution. When we receive a full-year budget, we anticipate adjusting awards and increasing the paylines for unsolicited awards and career and fellowship training awards.

Legislative Update

The 109th Congress passed two bills of interest to NIH and NIAID, the National Institutes of Health Reform Act of 2006, also referred to as the reauthorization bill, and the Pandemic and All Hazards Preparedness Act of 2006.

The Reform Act of 2006 creates a Common Fund in the NIH Office of the Director to be used to support trans-NIH research. Other provisions in the Act include a new special projects program to encourage high-risk, high reward research; a new scientific management review board to review NIH programs and organizational structure; replacing existing reports with a biennial NIH-wide report and several annual reports from the NIH director; and limiting the number of NIH institutes and centers to the current number of 27.

The Pandemic and All Hazards Preparedness Act of 2006 established authority in DHHS to accelerate advanced research and development of medical countermeasures that are related to biodefense and emerging infectious diseases.

Dr. Fauci reviewed changes in congressional committee leadership for committees of interest to NIAID.

Since the last Council, Representative Chris Van Hollen and Senator Edward Kennedy have visited the NIH campus. In December, Dr. Fauci met with congressional staff to discuss research related to topical microbicides. At the end of January, Dr. Fauci testified at a hearing on pandemic influenza.

Other Information Items

During the President's State of the Union Address, he mentioned two programs of great relevance to NIH and NIAID, the PEPFAR program and the President's Malaria Initiative. Both programs have been very successful.

Dr. Fauci discussed two studies sponsored by NIAID, one in Kenya and one in Uganda, in which adult male circumcision significantly reduced the risk of acquiring HIV. The findings are very impressive. PEPFAR, WHO, and other organizations are examining the results to determine whether or not they can appropriately implement this in various regions of the world.

Dr. Fauci also summarized the Institute's progress in the areas of malaria, tuberculosis, and influenza.

III. GUEST SPEAKER – Toni Scarpa, M.D., Director, Center for Scientific Review

Dr. Toni Scarpa presented some of the challenges facing the peer review process and the changes that the Center for Scientific Review (CSR) is implementing to improve the process.

One problem is that the process is too slow. To address this issue, CSR is using artificial intelligence to assign applications to review groups and shorten the review cycle. Other concerns are that there are not enough senior, experienced reviewers and the process favors predictable research instead of significant, high-impact research.

To get input from the community, CSR is holding six open houses. Chairs of study sections and leaders of professional societies and organizations are invited to attend and give suggestions to improve the review process.

To recruit reviewers, CSR is changing the way review meetings are held. CSR is beginning to hold virtual face-to-face meetings. Another change being considered is shortening the length of the grant application.

The DAIDS subcommittee discussed potential problems with the January 2 submission date for AIDS and AIDS-related grant applications. Since academic institutions tend to slowdown significantly during the month of December, research departments could have a problem getting electronic applications submitted. The full Council put forth a motion to CSR to consider moving the January 2 deadline to January 15.

IV. REPORT OF THE DIVISION OF ALLERGY, IMMUNOLOGY AND TRANSPLANTATION COUNCIL SUBCOMMITTEE – Charles Hackett, Ph.D., Deputy Director

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

STAFFING/ORGANIZATIONAL CHANGES

Alkis Togias, MD Dr. Togias joined the Asthma, Allergy, and Inflammation Branch as the chief of the Asthma and Inflammation Section. He earned his medical degree from the National and Kapodistrian University Medical School in Athens, Greece, and was a fellow at the Johns Hopkins University School of Medicine in the Division of Allergy and Clinical Immunology. Dr. Togias has held several faculty appointments at the John Hopkins University School of Medicine, most recently as Associate Professor of

Medicine in the Division of Allergy and Clinical Immunology and in the Division of Pulmonary and Critical Care Medicine.

SCIENTIFIC INITIATIVES

Immune Mechanisms of Viral Control (R21) (RFA-AI-07-008): To support the first phase of a two-stage program to investigate the underlying mechanisms of immunity to viral infection and vaccination. The first phase, to be awarded in 2007, will use R21 exploratory/developmental grants to address key questions related to viral immunity. The second phase, planned for 2009, will support a substantially larger effort involving collaborative teams funded through U01 and U19 single and multiple project cooperative agreement grants.

Competitive Supplements for B Cell Immunology and Methods to Induce Broadly Reactive Anti-HIV Neutralizing Antibodies (NOT-AI-07-010): DAIT and the NIAID Division of AIDS plan to issue a Request for Applications for competitive supplements to currently funded NIAID grants to expand collaborative research among HIV and immunology investigators focused on B cell immunology on the mechanism by which broadly protective neutralizing anti-HIV-1 antibodies can be induced and maintained.

DIVISION ACTIVITIES

Animal Models for Acute Radiation Syndrome (ARS) with a Focus on Models of Gastrointestinal Toxicity: On September 21, 2006, NIAID sponsored a one-day meeting in Bethesda, MD to discuss the use of both small (rodent, minipig) and large (non-human primate) animals as models to study radiation-induced gastrointestinal and hematopoietic injury. Research studies presented included regulation of radiation-induced damage by innate immune responses to commensal bacteria and the use of somatostatin analogues or selenium as countermeasures against intestinal radiation toxicity. Attendees included researchers from the Korean Institute of Radiological and Medical Sciences, project leaders from the Centers for Medical Countermeasures against Radiation, and representatives from the NIH, Department of Defense, and Food and Drug Administration.

Annual U.S.-Japan Immunology Board Joint Meeting: On September 4-7, 2006, the twenty-fourth annual joint meeting of the U.S. and Japanese Immunology Boards of the U.S.-Japan Cooperative Medical Sciences Program convened on Awaji Island, Hyogo, Japan. This meeting was held in conjunction with the Sixth Awaji International Forum on Infection and Immunity. Current research results were presented by members of the U.S. and Japanese Boards.

Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations Annual Meeting: On September 27-28, 2006, the NIAID convened the second annual meeting for the "Immune Function and Biodefense in Children, Elderly, and Immunocompromised Populations." The main purpose of this meeting was to provide the investigators in this program a chance to describe their progress in the past year and to encourage discussion among members of the different research groups, NIAID Bioinformatics Integration Support Contract (BISC) staff and NIAID program and contracts staff. As part of its biodefense research mission, DAIT launched this program in 2005 to support research aimed at understanding the mechanisms of immune deficiency in certain populations, such as the very young, pregnant women, the elderly, people receiving chemotherapy for cancer, transplant recipients, and patients with autoimmune disease receiving immunosuppressive drugs. Ultimately this information could lead to new methods that trigger both innate and acquired immunity to provide better vaccines and

immune-based therapies to protect against infection and minimize harmful side effects for these populations.

NIH Tetramer Facility Workshop: On November 6, 2006, NIAID program and NIH Tetramer Core Facility staff organized a MHC class II tetramer workshop that included leading experts in MHC class II protein expression, function, and tetramer production. The main goals of this workshop were to: 1) review technologies for MHC class II tetramer production being used by the NIH Tetramer Facility; 2) provide recommendations for improving class II tetramer production – protein expression, purification, peptide exchange; 3) identify HLA class II molecules/ CD4 T cell epitopes associated with immune-mediated diseases and host responses to infection; and 4) prioritize HLA and mouse MHC class II alleles for the next round of custom class II tetramer production. The workshop participants proposed a series of recommendations focused on improving MHC class II protein expression, purification, and peptide exchange. The NIH Tetramer Facility is working with NIAID program staff and the workshop participants to enact these recommendations.

Annual Immune Epitope Database and Discovery Workshop: On November 7-8, 2006, the NIAID held the Third Annual Immune Epitope Database and Discovery Workshop to provide an opportunity for the investigators of the Immune Epitope Database and Analysis Resource (IEDB) and the Large Scale Antibody and T Cell Epitope Discovery programs to present their research and discuss future plans and collaborative efforts. Significant progress had been achieved by many of the contractors, and the IEDB became publicly available in February 2006 (www.immuneepitope.org). Currently, the relevant epitope references for NIAID Category A-C priority pathogens and emerging/re-emerging infectious diseases have been curated. In terms of epitope discovery, novel human T cell epitopes have been identified for Mycobacterium tuberculosis, Influenza A, and vaccinia virus; and improvements to MHC class I epitope prediction algorithms were reported. The discovery groups will continue their collaborations to share reagents and expertise, and to submit their data to the public IEBD website in the coming year.

Population Genetics Analysis Program: Immunity to Vaccines/Infections Annual Meeting: The second annual meeting for the "Population Genetics Analysis Program: Immunity to Vaccines/Infections" was held on November 14-15, 2006 in Gaithersburg, MD. The main goal of the meeting was to provide the investigators the opportunity to present their latest progress and discuss the possibilities of further collaboration and data sharing in the coming year. Data submission to "ImmPort," the NIAID BISC centralized database, was among the topics discussed. Overall, all projects progressed significantly in the last year. It is anticipated that the groups will continue productive collaborations, sharing data, reagents, and expertise, and submitting their data to ImmPort in the coming year.

NIAID Workshop on Regulatory T Cells: On November 20-21, 2006, the NIAID convened a workshop for the purpose of identifying the research still needed before regulatory T cells can be utilized to prevent and treat human disease. Invited outside experts on the basic immunology of regulatory T cells joined with prominent specialists in the regulation of immune-mediated and infectious diseases by suppressor T cells to outline research gaps and recommend future research activities.

Considerations in Allogeneic Hematopoietic Cell Transplantation for Nonmalignant Disorders, Including Autoimmune Diseases: On October 20-21, 2006, representatives of CIB, DAIT, NIAID, Experimental Transplantation and Immunology Branch, NCI, and Clinical Research Division, Fred Hutchinson Cancer Research Center, co-chaired an international workshop in Bethesda, sponsored by NIAID, NCI, and the Office of Rare Diseases, NIH. Transplantation regimens were discussed with regard to particular challenges and the risk benefit ratio for patients with nonmalignant diseases, including autoimmune disease. The content and recommendations of this workshop will be published.

DIVISION ADVISORY COUNCIL PRESENTATION

NIAID Overview of the Autoimmunity Prevention Centers

The following program was presented by division staff and guest: Thomas Esch, Ph.D., Program Officer, Autoimmunity Section, Clinical Immunology Branch discussed an **Update on the Autoimmunity Prevention Centers**; David Hafler, M.D., Breakstone Professor of Neurology, Brigham and Women's Hospital presented the **Whole Genome Scan for Multiple Sclerosis Susceptibility Gene**; and C. Garrison Fathman, M.D., Professor and Chief, Division of Immunology and Rheumatology, Stanford University Medical Center presented **Roadmap to Inflammation in the NOD Mouse**.

CONCEPT REVIEW

All concepts were presented and approved.

Inner-City Asthma Consortium: This initiative will continue an established consortium of basic scientists and clinical investigators who have conducted a series of studies which evaluated the safety, efficacy, and mechanisms of innovative immune-based therapies among inner-city children with asthma. The goals of this initiative are to assess promising asthma therapies, evaluate innovative methods for disease monitoring and to identify and understand the factors involved in the development of the immune system and asthma among inner-city children. Focused studies aimed at the underlying mechanisms of promising therapeutic approaches will be an integral part of all trial.

B Cell Immunology for Protective HIV Vaccines: The objective of this initiative is to support investigator-initiated projects that address fundamental questions in B cell immunology that will facilitate the rational development of vaccines capable of inducing broadly-reactive antibody-mediated protection to HIV-1 infection.

Center for International Blood and Marrow Transplantation Research: This initiative will continue the effort of supporting a data resource for analysis of blood and marrow transplants. The availability of the Center for International Blood and Marrow Transplantation Research (CIBMTR) to investigators and health policy makers will help define the usefulness of transplants in various clinical situations, identify prognostic factors, compare transplant regimens, compare transplant and non-transplant therapies, assess inter-transplant center variability in diagnosis, practice and outcome, evaluate transplant costs and cost-effectiveness, plan new clinical trials or treatment protocols and develop approaches to evaluating transplant outcomes.

V. JOINT MEETING OF THE AIDS SUBCOMMITTEE, NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL AND AIDS RESEARCH ADVISORY COMMITTEE – Carl Dieffenbach, M.D., Acting Director, DAIDS

Dr. El-Sadr welcomed the ARAC members, NIAID staff, and invited guests to the meeting. She introduced Dr. Dieffenbach, the new Acting Director of DAIDS, and asked the participants to introduce themselves. The ARAC members approved the minutes of the previous meeting.

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

Dr. Dieffenbach welcomed the participants and acknowledged Dr. El-Sadr as the new ARAC Chairperson. He introduced the five new ARAC members, Drs. Brooks, Dandekar, Hazuda, Kovacs, and Valdiserri. He announced that former DAIDS Director Dr. Edmund Tramont has become Associate Director for Special Projects in the Division of Clinical Research, and noted that Dr. Susan Plaeger has become Acting Director of the Basic Sciences Program and Dr. Carol Andres was appointed Chief, Clinical Research Resources Branch in the Office for Policy in Clinical Research Operations.

In his budget update, Dr. Dieffenbach noted that the Division continues to operate under a continuing resolution. The President's budget request features a 0.3 percent increase for the NIAID, which includes a $12 million increase to support pandemic influenza, HIV/AIDS vaccine research, and the Division's contribution to the Genes and Environment Initiative. Under the continuing resolution, the Institute has been awarding grants at 80 percent of budgeted amounts and has employed a provisional 10-percent percentile for awarding grants. When a new budget passes, the payline will rise to the 12th percentile, and likely the 14th percentile for first-time investigators. To sustain the payline, the Division has realigned contract funding, realigned intramural funding, and cut funding to centers' programs. The Division is considering additional financial options for an extended continuing resolution. Dr. Dieffenbach stated that he would provide a full report on success rates and new investigator support at the May ARAC meeting.

The Division presented Network Leadership Awards in July 2006 and is in the process of making awards for the Clinical Trials Units (CTU); approximately 18 awards have been made to date. The final FY06 dollar amount for Network Leadership Awards (first year) was $150.73 million. Once the majority of the CTU awards are made, NIAID will make a public announcement and all the units and their affiliated clinical research sites will be posted on the NIAID Web site.

Recent scientific highlights included the publication of results from the SMART trial, which showed reductions in risk for major cardiovascular/kidney/liver diseases, opportunistic disease, and death in cohorts given continuous ART when compared to a drug-conservation group that had episodic therapy based on CD4 levels. In discussion, Dr. El-Sadr noted that SMART study results did not vary by age. Dr. Dieffenbach noted that the results point to the need for future research to address the extent of complications associated with HIV disease, and to determine when therapy should be started.

A second scientific highlight was the publication of results of the circumcision trials, which showed that medically performed circumcision significantly reduces a man's risk of acquiring HIV through heterosexual intercourse. DAIDS has been working with the WHO to create an implementation strategy and policy in light of these results, and continues to build a multi-component strategy for HIV/AIDS prevention. In discussion, Dr. Dieffenbach noted that the circumcision research results and WHO discussions address adult males, although the circumcision of newborns likely will be considered eventually.

Working Group Update (AVRWG)—Susan Buchbinder, M.D.

Dr. Buchbinder reported on recent meetings of the AIDS Vaccine Research Working Group (AVRWG), which took place on May 25–26, 2006, and August 29, 2006. The May meeting was a workshop focusing on mucosal immunity. Topics included measurement challenges, the difficulty of getting vaccines to induce mucosal immunity, and how to incorporate the issue of central CD4 memory into vaccine trials.

The August meeting, which took place in Amsterdam, featured sessions on criteria for vaccine candidates for large-scale trials, an updated on the VRC vaccines, and how to obtain comparative data from vaccine trials (standardizing reagents, assays, etc.). The AVRWG discussed the question of whether nonhuman primate challenge data is important for making go/no-go decisions for vaccine clinical trials and there was consensus on the need for nonhuman primate challenge data to be better validated. Another question was whether decisions to move a vaccine forward should be generated only by using validated immunogenicity assays. The field suffers from not having a clear immune correlate of protection. There was consensus that validated assays are needed for looking for what was termed a "take-rate" or the primary immunogenicity measurement needs to be with a validated assay. Another question raised at the meeting was whether DAIDS should require the use of standard HIV gene inserts. The AVRWG is averse to that idea but supports the use of standardized reagents and assays.

Dr. Buchbinder reported that an upcoming AVRWG workshop (January 30–31) would focus on adenoviral vectors, which are well along in development. Of special note, the PAVE 100 trial (a large collaboration) will be observing the effect of an adenoviral vector, with boosting, on HIV infection and viral load. A second 2007 AVRWG meeting will take place in August.

In discussion, Dr. Buchbinder noted that the STEP study and PAVE trial are using different vaccine products. She noted that the AVRWG has had many discussions about milestones that should be required in leading up to an efficacy trial. The hope is to broaden the magnitude and breadth of the immune response in future vaccine trials.

Working Group Update (SWG)—Carl Dieffenbach, Ph.D.

Dr. Dieffenbach reported on the HIV Clinical Trials Network's Strategic Working Group (SWG), which held its first meeting on January 17–18. The SWG will provide expert advice on scientific priorities for high-resource, high-impact studies of the networks and will bring forward crosscutting scientific issues that will require more than one network to address. The SWG can help in network planning and will provide guidance to the leadership of the NIAID and the DAIDS about the scientific priorities. The SWG's process is transparent, soliciting input from stakeholders and with a goal of understanding the many vectors that inform scientific priorities. At the January meeting, the SWG discussed issues that cut across institutes of the NIH and become important in network efforts.

The SWG comprises leaders of the six networks, community representation, and a group of external advisors. The January meeting featured a presentation on PEPFAR, and on three protocols dealing with the issue of "when to start." One study was presented by International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), one by the AIDS Clinical Trials Group (ACTG), and the third by the ACTG in collaboration with the HIV Prevention Trials Network (HPTN). The SWG members discussed strengths and weaknesses of the three protocols.

The SWG intends to meet two or three times each year. Ms. Lein suggested that the group consider the issue of resources required for a protocol to proceed.

Concept Clearance
HIV Vaccine Design and Development Teams —Michael Pensiero, Ph.D.

Michael Pensiero, Ph.D., of the Preclinical Research Development Branch, DAIDS, reviewed and presented for consideration by the ARAC members an initiative for HIV Vaccine Design and Development Teams (HVDDT). The goal of the initiative is to advance the development and evaluation

of novel, innovative, safe, and immunogenic preventive HIV/AIDS vaccine candidates in Phase I clinical trials. The concept presented proposed use of a contract mechanism (N01) and a Broad Agency Announcement (BAA). The concept represents a renewal of a previous initiative, with a total first year cost of $8 million, reduced from the originally proposed budget of $16 million. It is anticipated that one or two awards would be made with duration of 5–7 years.

The concept for this initiative addresses the need to advance the development of promising, novel candidate preventive vaccines into human testing and includes the private sector as part of the consortium of scientists. It is the sixth competition, with 12 awards having been made in the past. The new initiative will include revisions to the program, such as closer interactions with DAIDS program staff, a mandatory GMP compliance audit prior to vaccine manufacturing, new deliverables (sample aliquots), and the possible extension to 7 years. During the preliminary review, ARAC reviewers expressed strong support.

In discussion, Dr. Birx commented on the success of the program, emphasizing that it would not have been possible without the strong involvement of the DAIDS staff in the teams. Dr. Birx also noted that the revisions made to the concept for this initiative would help ensure the success of the new program. Dr. Buchbinder stressed the importance of non-human primate testing of products, investigating immunogenicity before moving forward. Dr. Pensiero stated that non-human primate studies likely will be supported by DAIDS. He noted that the use of the BAA mechanism expedites the review process and provides flexibility in negotiating the statement of work.

The ARAC members voted, giving their approval for the concept.

Synthesis of Therapeutic Agents—Steve Turk, Ph.D.

Steve Turk, Ph.D., of the Drug Development and Clinical Sciences Branch of the Therapeutics Research Program, DAIDS, presented for consideration by the ARAC members a program for the synthesis of therapeutic agents for treatment of infectious diseases. The initiative will provide resources for the synthesis of promising microbicides and compounds for the treatment of HIV, opportunistic infections, tuberculosis, and other infectious diseases of relevance to the research agenda of NIAID. The proposed mechanism is N01. It is a renewal for $1 million and will award one contract for 7-years duration.

The contract includes synthesis of metabolites and reference standards for metabolism studies, analytical characterization of synthesized compounds, synthesis in compliance with current good manufacturing practice (cGMP) regulations when needed, and a focus on re-synthesis of known molecules rather than new analogs. In the program, requests for synthesis are made by NIAID program staff, academic investigators, and small biotech companies then evaluated by the DAIDS Preclinical Therapeutics Development Committee or Topical Microbicide Team. In the past 6 years, 130 compounds were synthesized, 20 on a large scale. They have been used mainly for in vitro and animal efficacy studies and animal PK and toxicity studies. One compound was synthesized under cGMP regulations for use in clinical trials.

In response to the reviewers' comments on the new concept, Dr. Turk's group noted that the program focuses on smaller molecules and not large biologics. The average cost for a compound is about $30,000. ARAC members discussed the cost associated with this program, and the substantial yearly increase of $400,000 over the current contract. Dr. Lehrman cited a flexibility afforded by the increased funding. Many investigators in academia have good ideas but insufficient funds to perform such synthesis tasks. Dr. Dieffenbach cited a committee chaired by Dr. Marty Rosenberg that looked at the Institute's preclinical drug development programs at all of the extramural divisions. One of the major gaps found

was the amount of money committed to chemical synthesis and resynthesis was insufficient to buy the resources we needed in microbicides, in biodefense, in TB, and in HIV. The level of funding proposed for this program addresses that.

Dr. El-Sadr cited a need to increase momentum in developing microbicides and drugs that can address the challenge of resistant TB. Dr. Turk stated that the program responds to requests as they arrive, although it can set priorities among those requests. Consumers of the program's products are mainly extramural investigators.

The ARAC members voted, giving their approval for the concept.

Integrated Preclinical/Clinical Program: Novel Therapeutics—Sandra Bridges, Ph.D.

Sandra Bridges, Ph.D., of the Basic Sciences Program, DAIDS, reviewed and presented for consideration by the ARAC members a program for novel therapies in an integrated preclinical/clinical program. The goal of the program is to rapidly move innovative treatment concepts to the clinic for initial evaluation. The initiative would be a cooperative agreement (U19), and there would be 2 to 4 projects awarded each year, each with a 5-year duration. The concept represents the renewal of a previous initiative, with a first year cost of $4 million to $6 million. Applicants to the program must have a defined strategy for a new therapeutic concept. The work can be preclinical research, such as small molecule inhibitors of HIV, or bench-to-bedside research involving pilot-scale clinical studies in humans. Each applicant must propose a minimum of three interrelated research projects with a consortium of investigators from academia and the private sector. Dr. Bridges reviewed current projects within the program noting that the current pilot-scale projects have up to 30 research subjects. The program excludes some topics that are handled elsewhere, such as microbicides and prophylactic vaccines.

Dr. Bridges presented preliminary reviewer comments, which were supportive of the concept. She noted that the program, which has been operating since 1997, supports about equal numbers of preclinical and clinical projects.

The ARAC members voted, giving their approval for the concept.

Programmatic Highlights and Scientific Direction

The final session of the meeting was devoted to reports from the three scientific programs of DAIDS—basic sciences, therapeutics, including prevention, and vaccine research.

Basic Science—Carl Dieffenbach, Ph.D.

Dr. Dieffenbach reviewed operations in the DAIDS basic sciences program, which integrates basic findings in basic sciences and pathogenesis, with population-based studies in epidemiology that help drive both therapeutics and prevention-type research and devise/test proof-of-concept prevention and therapeutic approaches.

Basic research addresses the common pathway of HIV infection, beginning with replication, which requires immune activation. All methods of prevention – Pre-exposure prophylaxis, microbicides, circumcision, and vaccines – reduce HIV and target cell interactions. Vaccines, if we had an antibody, would work by preventing virus from entering the tissue, CTLs work via clearing infected cells and

interrupting the chain of transmission, and circumcision by removing the number of target cells. One key is to determine a breakpoint, below which transmission will not occur.

Recent published results have emphasized that tissue is important, in particular, gastrointestinal-associated lymphoid tissue (GALT). We need to understand why the GALT does not rebuild itself after infection. Should we develop therapies that rebuild not only CD4 cells but also the GALT?

Researchers recently have shown that exhausted T-cells express the PD-1 marker as they become non-functional. Can these T-cells be awakened—perhaps by blocking PD-1? Other work has found that chronic AIDS patients have an increase in the level of lipopolysaccharides (LPS) in the circulation, suggesting that damage in the gut is allowing leakage of materials and additional states of activation. This skews the processes by which cells drive immunity.

DAIDS needs to maintain its payline and a robust portfolio to address such basic research issues and emerging questions. DAIDS-supported researchers must find additional AIDS restriction genes; in addition, to the work being done by the Center for HIV/AIDS Vaccine Immunology (CHAVI) in this area, other research is needed as it will define the targets for the next generation of therapeutics. DAIDS also supports limited targeted programs in areas that are hard to fund, such as structural biology and multidisciplinary drug development. In the end, the hope is to link all studies and findings to epidemiological studies and clinical trials.

Therapeutics— Sandra Lehrman, M.D.

Dr. Lehrman discussed new opportunities in the area of acute infection include identifying infections early via prevention trials, treating early with new drug combinations that potentially preserve T-cells and block creation of reservoirs, and lowering the transmission and modifying the course of disease by early attenuation of viral load.

Recent research in the area of new drugs and regimens has included class-sparing combination regimens and regimens employing new classes, such as integrase inhibitors and CCR5 blockers. Two-class, class-sparing regimens have shown promise in strengthening CD4 counts. One integrase inhibitor of the Merck Company (MK-0518) has been shown to produce strong decreases in HIV viral loads, and other inhibitors are making progress.

In addition to the finding of superior HIV-related outcomes with continuous versus CD4 cell count guided intermittent antiretroviral therapy, the SMART study found higher rates of serious non-AIDS co-morbid events in persons who had episodic therapy compared to persons who maintained had continuous therapy. It also found no difference in organ-specific toxicities in comparing interrupted therapy and viral suppression, raising the idea of benefits of earlier treatment in preventing end-organ failure.

Regarding co-infections, a recent report of a cluster of HIV-TB in South Africa revealed resistant forms (MDR-TB and XDR-TB). How do we respond to such resistant forms and outbreaks? Dr. Lehrman listed tuberculosis drugs currently in development (Phase I, II, and III studies). Current studies focus on drug interactions and timing of antiretroviral therapy and TB treatment.

Prevention approaches being applied include education and behavior modification, treatment and prevention of alcohol abuse, clean syringes, condoms and other barrier methods, circumcision, interrupting transmission from mother to child, topical microbicides, prophylactic antiretroviral therapy, treatment of other sexually transmitted diseases, and vaccination. The boundaries between prevention

and treatment are blurring—for example, mothers are treated to prevent disease in their children – as various studies have shown the benefit of reduced HIV viral load in reducing transmission. In order to adequately cover the breadth of prevention research, DAIDS partners with several NIH institutes.

Current research on microbicides includes integrated approaches to prevention and treatment. Dr. Lehrman described the ongoing HPTN 035 and MTN 003 studies of safety and efficacy of microbicide methods to prevent sexual transmission. She described the research pipeline for microbicides and lamented the lack of products ready for advanced-stage drug development (i.e., clinical research).

In discussion, the ARAC members considered the need to move microbicide research forward. Dr. Lehrman noted a study being planned by the Microbicide Trials Network on the effectiveness of oral Tenofovir compared to PMPA gel, examining safety for both uninfected and infected women, efficacy and acceptability of various ways to approach prevention of infection.

Vaccine Research—Peggy Johnston, Ph.D.

Dr. Johnston, Director of the Vaccine Research Program (VRP), reviewed areas of research and progress, dividing VRP's activities into (1) efforts to discover and understand and (2) the application of knowledge and technologies that benefit public health.

One avenue of research involves inducing broadly neutralizing antibodies with vaccines. Most sera from infected individuals do not target the conserved neutralizing epitopes. Some broadly neutralizing sera target a site near to but not overlapping the CD4 binding site. Investigator attempts to induce antibodies have progressed incrementally.

The CHAVI is a key driver in the investigation of early infection. Its advances include the single genome sequencing to characterize the transmitted virus, and completion of analysis of envelope sequences from acute infections and controls from chronic infections. CHAVI also is performing whole-genome SNP analysis for viral set-point. It has developed and/or developing 11 clinical protocols with partners in 7 countries.

Investigators are studying the impact of apoptosis, the behaviors of the envelope, and other features that may lead to the better design of neutralizing antibodies. A large part of the VRP focuses on such early stages of the vaccine discovery pipeline. The program recently began to offer a supplement mechanism for investigators with grants that focus on a link between B-cell immunology and inducing broadly neutralizing antibodies.

Another area of research involves the targeting by cytotoxic T lymphocytes (CTLs). Lower viral load is associated with recognition of Gag epitopes. Higher viral load is associated with greater targeting of Env by CTLs. Vaccine products currently being evaluated in DAIDS-supported clinical trials include envelope subunit proteins, DNAs, adenovirus type 5, pox virus, cytokine plasmid adjuvants, and alphavirus replicon.

The STEP trial is evaluating the Merck Ad5 vector and has enrolled 2,000 volunteers so far. It will observe safety and the reduction in HIV-1 infection rate and/or viral load at 3 months post diagnosis. A new Phase IIb trial, Phambili, will begin soon in South Africa, with 3,000 volunteers; it will include an immunogenicity assessment of the first 600. The VRP is planning another large collaborative international trial—to be called the Partnership for AIDS Evaluation (PAVE 100)—evaluating a DNA-

Ad5 candidate HIV vaccine efficacy. A Phase III trial in Thailand completed immunizations in July 2006, now in follow up phase and will produce efficacy data and analysis in the summer of 2007.

Dr. Johnston cited options for future activities if the current vaccines fail, including alternative combinations and boosting. She listed additional products in develop and closed by stating that the program's missions are (1) to understand fundamental concepts and apply them to discover improved candidates and (2) to advance and evaluate vaccines in Phase I trials, and noted that the two must be linked.

In discussion, Dr. Birx suggested that the program consider how to share their knowledge, perhaps through a published paper, that describes the ways in which it has managed to support both efficacy and discovery research. In response to another member's comments, Dr. Johnston noted that work on mucosal vaccines has been slowed by difficulties in developing assays to measure mucosal immune responses.

At the end of the meeting, Dr. El-Sadr asked the ARAC members to suggest topics for future meetings. They proposed the following topics:

- How to develop drugs in today's environment
- Stimulating immune activation in mucosal tissues
- Multi-faceted approaches to prevention
- Leveraging resources from other groups
- Tuberculosis, possibly with the inclusion of representatives from the Division of Microbiology and Infectious Diseases
- Microbicides

Dr. Dieffenbach proposed a conference call to discuss how to handle possible agenda topics.

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

Dr. Heilman referred to the DMID branch chiefs to introduce new staff members who have joined the different DMID offices and branches since the last Subcommittee meeting.

Dr. Heilman provided a brief overview of DMID training efforts, acknowledging the Subcommittee's interest in learning more about division-specific training. She presented information about NIAID-wide training, referring to several slides summarizing Institute-wide activities related to training grants, fellowships and career development awards, which were prepared by Dr. Milton Hernandez, Director of NIAID's Office of Special Populations and Research Training. She then described DMID-specific training activities launched in recent years to address critical public health needs. For example, DMID has established career development projects through the Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases, which have helped to bring new investigators into the field of biodefense. DMID also supports a wide variety of international clinical research training activities, spanning all aspects of clinical research, including regulatory issues, good clinical practices (GCP) training, science writing and bioethics in an effort to train new investigators abroad. Finally, she noted that DMID sponsors a variety of workshops each year and that these activities also serve to educate the research community.

At the close of her remarks, Dr. Heilman informed the Subcommittee that DMID staff would present several concepts for their consideration, noting that the concepts fell into two broad categories: genomics and biodefense.

The concepts presented included:

- **Non-Biodefense Emerging Infectious Diseases Research Opportunities** – This initiative is designed to spur greater understanding of the natural history of microbial agents of human infectious diseases and events leading to the acquisition of pathogenic potential by non-biodefense pathogens. The Subcommittee believed the concept addressed an important area as there is little known about host-pathogen interactions, and they liked the idea of studying genomic changes and their relationship to disease. A concern about the breadth of the concept was successfully addressed during discussion. The Subcommittee unanimously approved the initiative.
- **Systems Biology Approach to Infectious Diseases Research** – The objective of this initiative is to apply a systems biology approach to better understand infectious disease pathogens and their interactions with the host. Subcommittee members enthusiastically supported this initiative by emphasizing the importance of studying biological systems and interaction networks among the molecular components of microbial organisms, as well as by pointing out the need to embrace new scientific approaches, even when their role still has yet to be completely established. Several members noted that the initiative proposes a massive research undertaking, but that it is the right time to try to overcome the substantive hurdles in this particular research field. The Subcommittee unanimously approved the initiative.
- **Clinical Proteomics Centers for Infectious Diseases and Biodefense** -- The Centers to be established under this initiative are intended to discover and validate pathogen and host biomarkers for infectious diseases. The Subcommittee felt the initiative will provide a valuable clinical proteomics and related technology resource to the community and it is an important step forward in this area of research. The Subcommittee unanimously approved the initiative.
- **Production of Monoclonal Antibody-Based Therapeutics for Botulism** – This initiative will develop monoclonal antibody-based therapeutics against the botulinum neurotoxin serotypes A, B and E for evaluation in preclinical and early phase clinical studies. The Subcommittee supported this objective as a logical step toward the eventual development of treatments that address all seven botulinum neurotoxin serotypes. They also acknowledged the importance of the long half-life of human monoclonal antibody products, as compared to the shorter half-life of the currently available equine-derived antitoxin. The Subcommittee unanimously approved the initiative.
- **Advanced Development of Multivalent Filovirus (Ebola and Marburg) Hemorrhagic Fever Vaccines** – This initiative will support advanced product development activities for multivalent vaccines for Filovirus hemorrhagic fever virus. The subcommittee felt that this was a very important undertaking and noted that this initiative is consistent with and will complement efforts being undertaken by other government agencies and private companies. The Subcommittee also expressed the sentiment that the high level of past inter- and intra-government coordination and collaboration has helped move Filovirus vaccines to their current state of development, and continued coordination will be important to ensure success of future activities. The Subcommittee unanimously approved the initiative.
- **Biodefense Vaccine Enhancement** -- This initiative will support advanced product development to integrate novel product stabilization and antigen delivery technologies with biodefense vaccines to significantly improve both product stability and vaccination effectiveness. Subcommittee members noted that thermal stability of vaccines is a critically important issue to

both the military and public health community and that it should be supported. Subcommittee members also expressed an interest in focusing the concept on stability and asked for clarification regarding novel adjuvants and devices that might be used to deliver vaccines. The Subcommittee was assured that the initiative would include the development of new technologies that would lead to the elimination of a cold chain for vaccines. The subcommittee unanimously approved the initiative.

VII. ADJOURNMENT

The meeting of the Council was adjourned at 5:30 p.m., on Monday, January 29, 2007.

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

_____-s-_____ **_3/20/2007_____**

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

Date

_____-s-_____ **_3/16/2007__ ___**

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.