NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

MINUTES OF MEETING

May 18, 2009

The 162nd meeting of the National Advisory Allergy and Infectious Diseases Council (NAAIDC) convened at 10:30 a.m. on Monday, May 18, 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. The meeting was also closed from 12:15 p.m. to 1:15 p.m. for discussion of the new peer review system and the effect on the electronic council book. 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. Kathryn Edwards
Dr. Sharon Kiely
Mr. William McLin
Dr. Louis Picker
Dr. Regina Rabinovich
Dr. Martin Rosenberg
Dr. Marc Rothenberg
Dr. Samuel Stanley
Dr. Megan Sykes
Dr. Christel Uittenbogaart
Dr. Christopher Walker
Dr. Richard Whitley

***Ex Officio* Members Present:**

Dr. Anthony Fauci

Council Members Absent:

Dr. Satya Dandekar
Dr. David Wilkes

***Ex Officio* Members Absent:**

Dr. Mitchell Cohen
Dr. Bruce Gellin
Dr. Ronald Valdiserri

***Ad Hoc* Members Present:**

Dr. Chris Goodnow
Dr. Elizabeth Bell

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 2,447 research and training applications with primary assignment to NIAID for a requested amount of $671,716,479 in first-year direct costs and recommended approval of 2447 applications for $671,716,479 in first-year direct costs. Three 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. E*x officio* member Dr. Mitchell Cohen was unable to attend the meeting. Dr. Elizabeth Bell from the Centers for Disease Control and Prevention attended in his place.

Dr. Fauci introduced one *ad hoc* Council member, Dr. Chris Goodnow from the John Curtin School of Medical Research, Canberra, Australia.

Consideration of Minutes of Previous Meeting

Council considered the minutes of the January 26, 2009, meeting and approved them as written.

Nominations and Appointments by the Obama Administration

Dr. Fauci announced several key nominations and appointments made by the Obama administration. Former governor of Kansas, Kathleen Sebelius is the new secretary of Health and Human Services. The Senate unanimously confirmed William Corr as the deputy secretary of Health and Human Services. Dr. Thomas Frieden was selected as director of the Centers for Disease Control and Prevention. President Obama nominated Dr. Margaret Hamburg to serve as the next commissioner of the FDA.

In March, the Senate confirmed Dr. John Holdren as the new director of the White House Office of Science and Technology Policy (OSPT).

In April, President Obama announced the appointment of members of the President's Council of Advisors on Science and Technology (PCAST). OSPT Director John Holdren will co-chair PCAST along with Dr. Eric Lander and former NIH Director Dr. Harold Varmus.

Budget Update

On March 11, 2009, President Obama signed into law the 2009 omnibus appropriation bill which provides NIH and NIAID funding support for FY 2009. The overall NIH allocation for 2009 is $30.4 billion, a 3.7 percent increase over FY 2008. NIAID received $4.7 billion, an increase of 3.1 percent over FY 2008. NIAID continues to support a payline to the 12 percentile for unsolicited research project grants and is supporting new and early-stage investigators to the 25 percentile.

The President signed the American Recovery and Reinvestment Act (ARRA) of 2009 into law on February 17, 2009. The bill provides NIH with $10.4 billion dollars to spend over a two year period. Each of the 27 Institutes and Centers and the Office of the Director received a portion of the money. NIH is

using the stimulus money to implement several new NIH-wide programs including RC1 Challenge Grants, RC2 Grand Opportunities (GO) grants, new faculty recruitment, summer jobs, and AREA grants.

NIAID's allocation of ARRA funds is $1.1 billion. NIAID plans to use the ARRA funds to support outstanding but unfunded research project grants and several signature projects, which include: stopping the HIV pandemic, protection of human health by immunology and vaccines, developing partnerships to translate research into new products in biodefense and emerging infectious diseases, and expanding research capacity in biodefense and emerging infectious diseases through the Regional Centers of Excellence Program.

Legislative Update

In March, Dr. Fauci accompanied Dr. Raynard Kington, acting director of NIH, to testify about NIH efforts and priorities for implementing the Recovery Act.

Recent congressional interest caused by the H1N1 (swine) flu outbreak, prompted several hearings. On April 28, Dr. Fauci joined witnesses from CDC, the U.S. Department of Agriculture, and the Association of State and Territorial Health Officials and participated in a hearing on "The Public Health Response to Swine Flu." On April 29, Dr. Fauci testified at a hearing on the public health and medical response to the 2009 H1N1 influenza virus. On May 6, he took part in a hearing entitled "Global Health Emergencies Hit Home: The Swine Flu Outbreak."

In addition to research on influenza, Congress remains interested in many other diseases within the Institute's purview. On May 13, Dr. Fauci gave the plenary address, "HIV/AIDS: Much Accomplished, Much to Do," at the amfAR and Research!America Capitol Hill Conference on "Future Directions in the Fight Against HIV/AIDS."

Dr. Fauci thanked NIAID staff for their assistance with congressional briefings. On February 22, Drs. Michael Kurilla and Dennis Dixon briefed Congressional staff on NIAID's antimicrobial resistance research and produce development. On April 30, Drs. Carole Heilman, Joe Green, and Adriana Marques met with congressional representatives and representatives from the Lyme Disease Association to discuss NIAID Lyme disease research.

Tributes and Awards

In November, the American Association for the Advancement of Science (AAAS) named Dr. Gary Nabel and Dr. Kuan-Teh Jeang as fellows. In February during the annual meeting, the AAAS recognized both for their contributions to medical sciences.

Dr. David Morens was elected to be the next president of the American Epidemiological Society.

Other Information Items

On March 9, 2009, President Barack Obama issued an Executive Order that changes the way NIH will fund and conduct research involving the use of human embryonic and adult stem cells. The HHS secretary, acting through the NIH director, will review existing NIH guidelines and other widely recognized guidelines and issue new NIH guidelines within 120 days of the Executive Order.

Recently, NIAID published two new booklets that explain NIAID research in two key areas. One publication focuses on our global research efforts, NIAID Global Research – Improving Health in a

Changing World, and the other highlights research opportunities in the Division of Intramural Research, Opportunities – Research and Training Programs for 2009-2010 NIAID Division of Intramural Research. A third publication entitled NIAID Influenza Research 2009 Progress Report is available on the NIAID Web site.

Dr. Fauci gave an update on the swine flu pandemic. He presented current statistics of confirmed and probable cases; the pandemic phases according to the WHO and what they mean; what NIAID and NIH are doing; and our collaborative efforts with CDC, WHO, pharmaceutical companies, and our Vaccine Treatment and Evaluation Units.

Dr. Fauci briefly discussed the importance of global health efforts, AIDS, tuberculosis, malaria, and food allergies.

III. GUEST SPEAKER – Dr. Gary Nabel, Director, NIAID Vaccine Research Center

The Vaccine Research Center (VRC) is working to develop vaccines for HIV, influenza, chikungunya virus, adenovirus serotype 14, and biodefense agents, such as Ebola and Marburg. The VRC is constantly revising their portfolio and adding and removing candidate vaccines.

Dr. Nabel gave a brief update on VRC's research on chikungunya, Ebola, and Marburg viruses. For Ebola and Marburg, they are in the process of selecting new vectors, and they have highly effective vaccines that work in non-human primates.

HIV remains the Center's highest priority. NIAID made a decision to proceed with a smaller version of the PAVE 100 trial. The trial is a Phase II randomized, placebo-controlled trial to evaluate the effect on post-HIV acquisition viremia safety and immunogenecity of our multiclade, DNA-prime, Ad-boost vaccine. Dr. Nabel presented the trial design and said they hope to have results in about three years. He also outlined what the VRC is doing to develop the next generation of HIV vaccines and the progress they are making.

Dr. Nabel summarized the Center's research on H1N1 (swine) flu. The VRC is taking a global look at flu and trying to determine whether or not it will be possible to generate broadly neutralizing antibodies that would allow development of a universal vaccine.

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

Dr. Rotrosen welcomed the members of the National Advisory Allergy and Infectious Diseases Council members. Dr. Rotrosen then took the opportunity to first inform the subcommittee there'll be an update from Dr. Linda Chiodetti, Chief Innate Immunity section on systems approach to immunity and inflammation. He noted that Dr. Chris Goodnow, B.V.Sc., Ph.D., F.A.A. (Ad hoc Council member) would be presenting "Translating DNA Sequencing into Immunological Systems."

He next informed the subcommittee members of two new staff members to the division: Mr. Steven Sigelman who joined the Asthma, Allergy and Inflammation Branch as a Project Manager and Dr. Cheryl Lapham who joined the Division as a Program Officer in the Basic Immunology Branch.

Following these introductory remarks, Dr. Rotrosen presented an overview of the division's expenditures for fiscal year 2008. In brief, the presentation outlined support in the scientific disciplines of the division.

Dr. Rotrosen noted that there were no concepts for review and approval.

Guest Speaker - Dr. Chris Goodnow, B.V.Sc., Ph.D., F.A.A. - "Translating DNA Sequencing into Immunological Systems."

Dr. Goodnow presented his work as part of a contract mentioned earlier by Dr. Chiodetti, "Systems approach to Immunity and Inflammation." He noted, that historically the focus of this work was the innate immune system, mostly TLR signaling and pathways, and a very limited number of infectious agents. However, this has been expanded to include innate and adaptive immune responses and a much broader range of pathogens will be studied, both in vivo and in vitro. He stated the overall purpose of his work is to look in a quantitative way to identify and measure dynamic networks in immune responses, both in normal and in pathological settings. One example Dr. Goodnow mentioned, in particular, was the NF kappa B pathway. He noted, "we're most interested in it from the perspective of normal immunity and autoimmunity, but it also, of course, plays a key role in malignancy." He mentioned that this pathway was complex and would require a systems approach to evaluate it in a quantitative way. In conclusion, Dr. Goodnow spoke to systems biology as really bringing together much expertise in the fields of cell biology, molecular biology, immunology, genomics, etc. where these data are sent to a central computational core; where there are analysis tools and a way of presenting the data. In particular, he expressed that one of the big translation gaps we face is the resequencing of all of the exons, or eventually the whole genome of people with immunological or infectious diseases where their immune system's not controlling it.

V. REPORT OF THE DIVISION OF MICRIBIOLOGY AND INFECTIOUS DISEASES – Carole Heilman, Ph.D., Director

Dr. Heilman recognized the recent accomplishments of two Subcommittee members: 1) she noted that the University of Alabama System Board of Trustees appointed Dr. Rich Whitley as Distinguished Professor of Pediatrics in February in recognition of his notable contributions to the field of antiviral research; and 2) she announced that Dr. Samuel Stanley will assume the Presidency of New York's Stony Brook University on July 1.

Dr. Heilman provided a brief report on DMID's 2009 H1N1 influenza research activities and informed the Subcommittee of recent updates made to the NIAID influenza website. In particular, she noted the creation of a flu funding opportunities page to help researchers find relevant initiatives/funding mechanisms. She also reported that NIAID had recently recompeted the Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) program, renewing funding support to the 10 previously funded sites and awarding funds to an additional site at Oregon Health & Science University to establish a new RCE in the Pacific Northwest.

Dr.Heilman then referred to the Branch Chiefs/Acting Branch Chiefs in attendance to introduce their respective new hires. Following Dr. Heilman's remarks, one concept was presented for the Subcommittee's consideration:

National Biocontainment Laboratories Operational Support

Objective: To provide operational support for the National Biocontainment Laboratories currently located at the University of Texas Medical Branch (UTMB) and Boston University (BU), enabling them

to develop and maintain resources and facilities necessary to meet national, regional, and local biodefense and emerging infectious diseases research needs.

Description: Operations at the NBLs will be supported through cores in five areas, including:

Facility Maintenance and Operation – Provides high containment operational management monitoring and oversight; routine facilities maintenance and upkeep of the physical plant that supports the high containment space including a preventative maintenance plan for all BSL4 equipment and systems; non-routine emergency repairs of BSL4 equipment and systems; and specialized training for facilities personnel working in and around BSL4 space and associated building systems.

BioSecurity -- Ensures compliance with all evolving legislation and regulations related to control of select agents; devises and directs relevant staff training activities; develops and implements prospective BSL4 staff screenings and background checks; assists in planning for required biosecurity drills; manages inventory and access to select agent inventories. Components of a laboratory biosecurity program include physical security, personnel security, material control & accountability, transport security, and information security.

Environmental Health and Safety Regulations and Requirements -- Provides critical health, safety, and training services; maintains consistency in biosafety and biocontainment practices; provides biosafety theory education and hands-on training; leads registration, record keeping and administrative activities of the Select Agent program. Continuously maintains and monitors the integrity of the BSL4 containment areas; provides expertise in areas of primary containment operations, maintenance and certification; leads decontamination, retesting, and certification of BSL4 containment facilities; maintains the capability to respond to potential emergency events and establishes a plan for the orderly shutdown and decontamination of containment due to weather or other events.

Regulatory Compliance -- Provides oversight and coordination of all research functions that require compliance with regulatory statutes and guidelines for the purpose of supporting product licensure, promoting accuracy and integrity of any data generated in such studies; conducts relevant GLP compliance training for core directors and key staff; develops policies and procedures pertaining to GLP research; provides advice and oversight for equipment procurement and facility commissioning activities.

Integrated Research Support Service -- Specialized services essential to support BSL4 research activities such as veterinary, imaging, insectary, and aerobiology services. These services are not expected to fully support research projects thus requiring the NBLs to develop and implement cost reimbursement business models to fully fund BSL4 level research projects involving these services.

Council Comments: The Subcommittee was enthusiastic about continued operational support for the National Biocontainment Laboratories (NBLs), which is shared with the awardee institutions (UTMB and Boston). In response to a question regarding accessibility, Ms. Boyd stated that the NBLs may be accessed by outside or visiting investigators, and that those interested in utilizing the facilities should contact the institutions directly.

The Subcommittee unanimously approved the initiative.

Human Microbiome Project, Dr. Maria Giovanni

Following Ms. Boyd's presentation, Dr. Maria Giovanni, Assistant Director for Microbial Genomics and Advanced Technology, provided an update on the NIH Human Microbiome Project (HMP), a five-year NIH Roadmap project that aims to characterize the microbes that inhabit the human body. Dr. Giovanni described the purpose of the program, and discussed ongoing collaborative efforts among participating Institutes and Centers and the research community. Dr. Giovanni described some of the studies that NIAID plans to support through the program, notably HMP sequencing efforts.

Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program Update, Dr. Diane Post

Dr. Diane Post, a Program Officer in DMID's Respiratory Diseases Branch provided an update on the Centers of Excellence for Influenza Research and Surveillance (CEIRS) program, a domestic and international animal influenza surveillance program established in 2007. Dr. Post described the overarching goals and history of the program, and described current activities and recent accomplishments, including efforts focused on 2009 H1N1 influenza. She also reported on ongoing efforts to create a publicly-accessible influenza research database that includes sequencing data generated by the CEIRS sites.

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

DIRECTOR'S REPORT AND STRATEGIC WORKING GROUP UPDATE
Carl W. Dieffenbach, Ph.D., Director, DAIDS

Dr. Dieffenbach welcomed everyone to the meeting and recognized HIV Vaccine Awareness Day (this very day), which honors the thousands of volunteers who participate in HIV vaccine trials. The day also celebrates the contributions of the many research partners around the world. Dr. Dieffenbach recognized the NIAID HIV Vaccine Research Education Initiative (NHVREI), which fosters partnerships with community-based organizations and the many activities being sponsored by funded sites globally and US-based NHVREI partner to thank volunteers and increase HIV vaccine awareness in honor of the day. He thanked the many volunteers, the staffs at DAIDS, the Vaccine Research Center (VRC), and the HIV Vaccine Trials Network (HVTN), and all collaborative partners for their effort and dedication to HIV vaccine research.

Budget Update

Dr. Dieffenbach reported that President Obama signed the FY 2009 Omnibus Appropriations Bill on March 11, providing the NIH with $30.4 billion, a 3.7-percent increase over the previous year. The bill provides NIAID with $4.7 billion—an increase of 3.1 percent. NIAID plans to fund noncompeting research program grants (RPGs) at fully committed levels, to support a payline at the 12th percentile and equivalent for unsolicited RPGs, to support new principal investigators and early stage investigators through the 25th percentile, to support a cap for Type 2 awards at 20 percent over the 2008 amount, and to provide selective pay and bridge awards pools with $9 million and $18 million respectively.

In addition to the appropriations budget, NIAID is receiving funds from the American Recovery and Reinvestment Act of 2009 (ARRA). The NIH will receive $10.4 billion, to be distributed among the 27 institutes and centers (ICs) and the Office of the Director (for a 2-year period). About $7.4 billion will be

directed toward the ICs to support research. About $800 million will go to the NIH Office of the Director, including $200 million for Challenge Grants. A significant amount will go to the National Center for Research Resources to support research infrastructure, such as instrumentation.

NIAID plans to use ARRA funds to support unfunded meritorious RPGs and other awards during the 2-year period stipulated by the program. The Institute will focus on stopping the HIV pandemic, advancing immunology and vaccines, and developing partnerships and capacity for biodefense and emerging infectious diseases research. ARRA funds will support the new Challenge Grants, recruitment of new faculty, and summer laboratory jobs for high school and college students. The NIAID ARRA funds will support research on accelerated aging in AIDS, early events in HIV infection, comparative effectiveness of HAART, reservoirs of latent HIV infection, new antiviral agents for prophylaxis, and bioethics. Dr. Dieffenbach reviewed the conditions for receiving administrative supplements, for which grantees can apply until July 15. He noted that the NIH has received more than 20,000 applications for Challenge Grants.

Scientific Update

Dr. Dieffenbach reported on four trials. The HPTN 035 trial tested two candidate microbicide gels for safety and the ability to prevent HIV infection in women. It was conducted at multiple sites in Africa and one site in the United States. Both PRO 2000, which inhibits the entry of HIV into cells, and BufferGel, which boosts the natural acidity of the vagina were found to be safe. PRO 2000 was found to be 30-percent effective in preventing HIV, although this result was not statistically significant. BufferGel did not alter the risk of HIV infection. This was the first human study to suggest that a microbicide (PRO 2000) may prevent male-to-female transmission of HIV. A second PRO 2000 trial in the United Kingdom conducted by the Medical Research Programme will complete follow-up in August 2009. In future studies, Dr. Dieffenbach noted that a trial of Tenofovir gel is being conducted, and there are plans for testing new delivery methods, developing rectal microbicides, developing products with outstanding safety and resistance profiles, and evaluating novel clinical trial methodologies.

The second study was ESPRIT which evaluated subcutaneous Proleukin (IL2) in addition to HAART compared to HAART in a randomized international trial, and SILCAAT evaluated the use of subcutaneous recombinant human interleukin-2 in HIV-infected patients with low CD4+ counts. Dr. Dieffenbach explained the design of each trial and emphasized that in both trials IL2 created a sustained increased level of CD4+ in the patients treated with IL-2. However, the primary endpoints of opportunistic disease and death were found to be the same for the interventions and the controls. In other words, there was no clinical benefit in adding interleukin-2 treatment to HAART.

The third study was the P1060 trial, a phase II randomized study of treatment for infants, conducted at 10 international sites. The results featured a 40-percent failure rate in the nevirapine (NVP) arm within 24 weeks (only 22 percent in the lopinavir/ritonavir [LPV/r] arm). Because prior exposure to NVP appeared to lead to the development of NVP-resistant virus, the Data and Safety Monitoring Board called for a halt to enrollment in the NVP cohort. The findings supported the WHO recommendation that HIV-infected infants who receive NVP at birth be started on an LPV/r-based regimen. NIAID concurred with that recommendation.

Strategic Working Group

Dr. Dieffenbach reported on a February 2009 meeting of the Strategic Working Group (SWG), which featured a presentation by the AIDS Clinical Trials Group (ACTG) of its research priorities and budget. Following the presentation, the SWG recommended that the ACTG promote current co-infection studies,

recognize the limited value of additional studies on optimizing ART regimens, establish a far-reaching research agenda, and establish a system for receiving ideas from outside the network. The February meeting also featured a discussion of the Test and Treat concept, including the recent *Lancet* article that reported on a model for reducing new HIV cases based on universal voluntary annual HIV testing followed by immediate antiretroviral therapy. The SWG expressed support for a pilot study of the Test and Treat concept. It emphasized the importance of treatment rather than referring to care, encouraged strategies to treat all infected people, suggested that the network consider new populations and modes of transmission, and recommended that the group build relationships with other networks and the Centers for Disease Control and Prevention (CDC) as they move forward.

In discussion, Dr. Dieffenbach noted that there is good evidence that a reduction in viral load leads to a reduction in infectiousness. The study of the Test and Treat concept will feature comparisons of different strategies in linking people to treatment.

AIDS VACCINE RESEARCH SUBCOMMITTEE UPDATE
Louis J. Picker, M.D., Vaccine and Gene Therapy Institute, Oregon Health Sciences University

Dr. Louis Picker reported on the last meeting of the AIDS Vaccine Research Subcommittee (AVRS), which focused its discussion on five topics.

STEP trial analysis. The major scientific questions emerging from the STEP trial are: (1) what are the reasons for the lack of vaccine efficacy? (2) what biological mechanisms might explain the increased HIV-1 acquisition in the vaccine group? These questions are being addressed both by HVTN investigators and investigators outside the HVTN who have been granted access to trial samples. To make trial sample acquisition more efficient, all trial specimens have been shipped to a repository in Seattle. In addition, a review process has been set up for outside investigators to gain access to trial samples. Data reported thus far indicate a high T-cell immune response rate in vaccinees, however only a small percentage of vaccinees (31%) generated both CD4+ and CD8+ responses. The level of CD8-specific responses was also much lower (median 43% lower) than that seen in long-term non-progressors.

Analysis of Ad-5-specific responses in STEP trial vaccines. The presenters specifically addressed the question of whether vaccine-stimulated memory responses to the Ad5 vector result in activated target cells that could possibly account for the increased HIV-1 acquisition observed. Data was presented that suggest this is likely not the case. Ad-specific CD4+T cells are found in Ad5 seropositives and seronegatives at similar frequencies. Ad-specific memory T cell responses following vaccination are attenuated in Ad5-seropositivies, and no sustained changes in target cell activation was observed following vaccination.

Correlates of immunologic control in elite controllers and STEP trial participants. The speakers presented data on analysis of elite controllers and extended that analysis to individuals who had received the Merck AIDS vaccine in an attempt to explain the lack of efficacy. It was observed that elite controller viruses exhibit reduced replication capacity (e.g., the CD8 T-cell response seemed to induce a less-fit virus); the epitopes targeted by elite controllers seem to have a better ability to predict viral load than does the HLA; and some CD8 T-cell responses have a superior anti-viral effect. One investigator studied vaccinees and determined that control of viral load was associated with targeting of specific good epitopes rather than the total number of epitopes. The design of a successful vaccine immunogen might hinge on the inclusion of good epitopes and the exclusion of others that distract the immune system from targeting appropriate regions. Another investigator presented data showing that HIV-1-specific CD8+ T cells from elite controllers had enhanced proliferative capacity and cytolytic function; the latter

characterized by superior lytic granule loading. The HIV-1-specific CD8+ T cells from individuals receiving the Merck vaccine showed no such enhancement.

Applying systems biology approaches to the study of vaccine efficacy. Recently published data on the application of systems biology approaches to delineate the correlate of protection in individuals receiving the yellow fever vaccine was presented. This was followed by presentations of systems biology approaches currently being used to study HIV/SIV vaccines in nonhuman primates and HIV vaccines in humans. Subcommittee members discussed how such approaches could and which approaches should be incorporated into the design and analysis of current and future AIDS vaccine trials.

HVTN 505 protocol update. The HVTN 505 protocol to evaluate the VRC's DNA + Ad5 vaccine for safety and the vaccine's ability to reduce viremia was discussed. The placebo controlled double-blinded study will involve 1,350 HIV-uninfected men who have sex with men in the U.S. To be eligible these men must be circumcised and Ad5-seronegative. The study will have a 90-percent power to detect a 1-log mean viral load difference. The investigators will monitor participants until 45 infections have occurred (about 36 months).

The next subcommittee meeting will take place May 19 and will feature STEP trial updates, discussion of the Enterprise, and a B-cell research workshop.

CONCEPT REVIEWS: PREVENTION SCIENCES PROGRAM

Integrated Preclinical/Clinical Program for Topical Microbicides

Jim Turpin, Ph.D., Preclinical Team Leader, Prevention Research Branch

The Integrated Preclinical/Clinical Program for Topical Microbicides has the objective of stimulating a diverse base of preclinical discovery and development of new topical microbicides and combination strategies for vaginal and rectal use. It supports translation from preclinical studies to pre-phase I clinical studies. The concept, a U19 cooperative agreement mechanism, is a renewal with expansion and has a first-year cost of $10 million. It is a flagship DAIDS microbicide program with 14 current awards. Each project requires an industrial partner. The expansion request is to meet the growing complexity of preclinical and early clinical testing and to provide research modules in animal efficacy studies, behavioral studies, critical path studies, and pre-phase I clinical studies. The ARAC reviewers expressed support for the concept, citing the program's strong accomplishments. They welcomed the proposed modules and suggested that the critical path studies be a defined project. Behavioral studies should be at the discretion of the applicants and encouraged. In discussion, it was noted that the program has had some success in encouraging basic scientists to incorporate behavioral research and one ARAC member suggested that collaboration with social scientists be encouraged as well. The ARAC members voted and approved the concept.

Next Generation PrEP

Fulvia Veronese, Ph.D., Health Scientist Administrator, Prevention Research Branch

This concept has the objective of creating a basic and preclinical framework for the development of second and subsequent generations of pre-exposure prophylaxis (PrEP) agents and regimens. It is a new concept using the R01 mechanism and, will have a duration of 5-years and a first year cost of $3 million (3–5 awards). Current basic and preclinical studies in the area of PrEP for HIV are very limited. Seven randomized clinical PrEP trials are testing either tenofovir alone or tenofovir and emtricitabine (Truvada), and efficacy results are going to be available as soon as 2010. Because of the possibility of decreasing adherence and increasing risk compensation and resistance over time, it is important to develop and test

new PrEP agents with optimized properties. Goals of the concept include expanding the pool of dedicated investigators, creating a rational pipeline for discovery and development, and developing a basic and preclinical algorithm to select PrEP candidates for advancement to clinical studies. The ARAC reviewers supported the concept enthusiastically, finding it timely and necessary. The ARAC members voted and approved the concept.

CONCEPT REVIEWS: BASIC SCIENCES PROGRAM

Understanding HIV Persistence

Presented by Carl Dieffenbach for Sandra Bridges, Ph.D. Chief, Targeted Interventions Branch

This concept has the objective of targeting HIV persistence, using collaborations between academia, the private sector, and the government. It is a new concept, using the U01 mechanism; it has a 5-year duration and first year cost of $8 million. Currently available HIV drugs have reached their potential. A better understanding of the basic biology of HIV reservoirs in the body is needed, and this information will be used to design and develop safe strategies for reducing and reversing latency. This concept will cover the spectrum, from basic research through preclinical development up to and including proof-of-concept. The concept features a collaboratory of research nodes (animal modeling, assays/modeling, drug development, basic research, etc.), all linked to a leadership group. Applicants will be required to include basic research, translational activities, and a private sector partner. The ARAC reviewers had a series of questions about the concept. In addressing their questions, it was noted that the concept does not allow immune-based strategies. The discovery and characterization of new and previously undefined cellular reservoirs of HIV in tissues will be encouraged. The concept goes beyond current efforts in persistence research to the development of agents and strategies that will be evaluated in pilot clinical studies. The project directors will be encouraged to include new investigators. In discussion, the ARAC members debated the size of the project, which envisions supporting two large projects. One ARAC member proposed having smaller and more projects. Others argued for the larger-sized projects so that all needed research program levels and resources could be brought to bear. Dr. Dieffenbach noted that DAIDS will be asking for new ideas but also will be requiring preliminary data for applications. A larger-sized program with flexibility will be able to determine its own focus as it proceeds (time and experience may require that the focus undergo change). The ARAC members voted and approved the concept, featuring the larger-sized projects.

International Epidemiologic Databases to Evaluate AIDS (IeDEA)

Carolyn Williams, Ph.D., Epidemiology Branch

This concept has the objective of addressing high-priority questions in an era of treated HIV that cannot be answered by individual studies because of the need for large samples and/or diversity of data. It is a renewal with expansion, using the U01 cooperative agreement mechanism. The duration of the project is 5 years, with a first year cost of $10 million (featuring contributions from other institutes). The concept features a focus on statistical techniques to study observational data and involves maintenance of large international databases for investigators to access. Among the novel methods to be applied are marginal structural mixed effects models, competing risk methods, and loss-to-follow-up models. The program currently collects data within 12 international regions. It has cleared major administrative hurdles, led to high-impact research publications, and features important collaborations (e.g., PEPFAR). The renewal concept will serve to expand analysis, data collection, and linkages to between HIV and other care settings. The ARAC reviewers expressed enthusiasm for the concept but questioned the plan to include other diseases (e.g., malaria). After a preliminary discussion with reviewers, program staff agreed that expansion to other disease would be done in a gradual way with an emphasis on the overlap between HIV and these other infectious diseases. ARAC members highlighted the differences between these

observational data and clinical trial data and expressed the need for both study designs. DAIDS staff acknowledged the distinct characteristics of the two study designs and agreed that any discussion of a study's results required a discussion of the limitations and benefits of its design. The ARAC members voted and approved the concept.

CONCEPT REVIEWS: VACCINE RESEARCH PROGRAM

Reagent Resource Support Program for AIDS Vaccine Development

Jon Warren, Ph.D., Microbiologist, Vaccine Research and Development Branch

This concept has the objective of enabling the production and purchase of high-quality reagents and assays to support preclinical AIDS vaccine research conducted by NIAID-supported investigators and partners. It is a renewal, using the N01 contract mechanism. The duration is 7 years with a first year cost of $2 million (up to $3 million if the full expiring base is approved), and only one award will be made. This concept addresses the need for reagents and assays and is vital for NIAID-funded research. The program has performed for more than 20 years. In the past 5 years it has distributed hundreds of quality-controlled reagents to more than 300 investigators. It supports consistency and standardization and saves money and time. The program has ongoing and planned activities such as the acquisition and characterization of primary isolate SIV challenge stocks and the acquisition of new clade B and C SHIVS. The ARAC reviewers acknowledged the continuing value of the program and strongly supported renewal. They expressed slight concern for the ability of the program to ensure access to the technologies (assays, etc.) by all NIAID-funded vaccine researchers, but staff agreed to work to ensure broad and unrestricted access for those investigators. The ARAC members voted and approved the concept.

Mechanisms and Prevention of Sexual Transmission of HIV/SIV

Geetha Bansal, Ph.D., Biologist, Vaccine Discovery Branch

This concept has the objective of fostering an understanding of the basic biology of the sexual transmission of HIV/SIV that could lead to the discovery of novel mechanisms and approaches to prevent transmission. It is a new concept, using the R01 funding mechanism; the duration is 3–5 years, with a first year cost of $5.1 million (supporting multiple grants at $500,000 per year maximum). HIV/SIV is primarily acquired through a mucosal route, yet we have no clear understanding of the influence of local cellular and mucosal factors in the genital and rectal tracts related to the acquisition. An understanding of interactions between HIV/SIV and the mucosa is essential for developing an effective preventive vaccine and other biomedical prevention strategies. The list of gaps in our knowledge of mucosal mechanisms is long. For example, for vaccines, what are the optimal mechanisms of induction of mucosal antibody and effector T-cells and the homing of memory cells to mucosal sites? For non-vaccine strategies, what are the mucosal and other factors affecting barrier function in genital and rectal epithelia? The ARAC reviewers supported the concept enthusiastically, calling it crucial and timely. They encouraged flexibility in the distribution of funds during the grant period—to allow additional funds within a given year as long as the average over the grant period does not exceed $500,000 per year. One member stressed that this work represents a core effort for all vaccine and microbicide research. Another encouraged that consideration be given to endogenous and exogenous hormones. The ARAC members voted and approved the concept.

Dr. El-Sadr thanked the all the DAIDS staff who presented the concepts. She noted that the next ARAC meeting will take place September 14, 2009. Dr. Dieffenbach suggested that the next meeting feature a discussion of microbicide research and prevention in general. Dr. El-Sadr suggested that we also address how to define the next generation of prevention studies either at the September or January meeting. She thanked the ARAC members and other attendees for their participation.

VII. ADJOURNMENT

The meeting of the Council was adjourned at 4:30 p.m., on Monday, May 18, 2009.

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

-s- **7/1/2009**

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

Date

-s- **6/24/2009**

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.